Образац **4.**

Факултет Фармацеутски

УНИВЕРЗИТЕТ У БЕОГРАДУ

01 број
(Број захтева)

Већу научних области медицинских наука
(Назив већа научне области коме се захтев упућује)

17.10.2024.
(Датум)

З А Х Т Е В

за давање сагласности на одлук**е** о усвајању извештаја Комисије за оцену докторске дисертације и о именовању комисије за одбрану

Молимо да, сходно члану 47. ст. 5. тач. 4. Статута Универзитета у Београду ("Гласник Универзитет", број 186/15-пречишћени текст и 189/16), дате сагласност на одлуку о усвајању извештаја Комисије за оцену докторске дисертације:

КАНДИДАТ **ТУРКОВИЋ (МЕНСУД) ЕРНА**
(име, име једног од родитеља и презиме)

студент докторских студија на студијском програму Фармацеутске науке

пријавио је докторску дисертацију под називом:

„Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова“

из научне области: ФАРМАЦЕУТСКА ТЕХНОЛОГИЈА

Универзитет је дана 28.12.2021.године својим актом под бр. 02-01 број 61206-4875/2-21 дао сагласност на предлог теме докторске дисертације која је гласила:

„Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова“

Име и презиме ментора : - Проф др. Јелена Паројчић, редовни професор, Универзитет у Београду – Фармацеутски факултет;

Комисија за оцену докторске дисертације именована је на седници одржаној 11.07.2024.године одлуком факултета под бр. 01 бр.1650/2 , у саставу:

Име и презиме члана комисије	звање	научна област	Установа у којој је запослен

1. Др сци. Драгана Васиљевић, редовни професор, Универзитет у Београду – Фармацеутски факултет
2. Др сци. Светлана Ибрић, редовни професор, Универзитет у Београду – Фармацеутски факултет
3. Др сци. Франц Вречер, редовни професор у пензији, Универзитет у Љубљани -Фармацеутски факултет (у пензији од 10.04.2024.г.)

Напомена**:** уколико је члан Комисије у пензији навести датум пензионисања.

Датум стављања извештаја Комисије и докторске дисертације на увид јавности: 12.09.2024.године.

Наставно-научно веће факултета усвојило је извештај Комисије за оцену докторске дисертације наседници одржаној дана 17.10.2024.године.

Комисија за одбрану докторске дисертације именована је на седници одржаној 11.07.2024.године

одлуком факултета под бр. 01 број 1650/2, у саставу:

Име и презиме члана комисије	звање	научна област	Установа у којој је запослен

4. Др сци. Драгана Васиљевић, редовни професор, Универзитет у Београду – Фармацеутски факултет
5. Др сци. Светлана Ибрић, редовни професор, Универзитет у Београду – Фармацеутски факултет
6. Др сци. Франц Вречер, редовни професор у пензији, Универзитет у Љубљани -Фармацеутски факултет (у пензији од 10.04.2024.г.)

Напомена: уколико је члан Комисије у пензији навести датум пензионисања.

ДЕКАН ФАКУЛТЕТА

Прилози:
1. Одлука Наставно-научног већа о усвајању извештаја Комисије за оцену докторске дисертације и одлука о именовању Комисије за одбрану докторске дисертације
2. Извештај Комисије о оцени докторске дисертације
3. Примедбе на извештај Комисије о оцени докторске дисертације (уколико их је било) и мишљење Комисије о примедбама

Напомена: Факултет доставља Универзитету захтев са прилозима у електронској форми и у једном писаном примерку за архиву Универзитета

УНИВЕРЗИТЕТ У БЕОГРАДУ
ФАРМАЦЕУТСКИ ФАКУЛТЕТ
11000 - БЕОГРАД
Ул. Војводе Степе 450.
01. број_____
17.10.2024. године

На основу члана 28. Статута и предлога Комисије за последипломске студије – докторске студије, Наставно-научно веће Универзитета у Београду – Фармацеутског факултета на седници одржаној 17.10.2024.године, донело је

О Д Л У К У

ПРИХВАТА СЕ позитиван извештај Комисије за оцену и одбрану завршене докторске дисертације**,** кандидата **маг. фармације Ерне М. Турковић** под насловом: **„Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова“** и упућује Већу научних области медицинских наука на усвајање, а по добијеној писаној сагласности одобрава јавна одбрана пред Комисијом у саставу:

1. Др сци. Драгана Васиљевић, редовни професор, Универзитет у Београду – Фармацеутски факултет
2. Др сци. Светлана Ибрић, редовни професор, Универзитет у Београду – Фармацеутски факултет
3. Др сци. Франц Вречер, редовни професор у пензији, Универзитет у Љубљани -Фармацеутски факултет

Универзитет је дана 28.12.2021.године својим актом бр.: 02-01 бр: 61206-4875/2-21 дао сагласност на предлог теме докторске дисертације.

Кандидат маг. фарм. Ерна Турковић, објавила је резултате из ове докторске дисертације утри рада категорије М21 у међународним часописима са СЦИ листе:

1. **Turković, E**, Vasiljević, I, Parojčić, J. 2024. A comprehensive assessment of machine learning algorithms for enhanced characterization and prediction in orodispersible filmdevelopment. International Journal of Pharmaceutics, 658: 124188.
   IF (2023) = 5,6; Pharmacology & Pharmacy (37/274) M21

2. **Turković, E**, Vasiljević, I, Drašković, M, Parojčić, J. 2022. Orodispersible films - Pharmaceutical development for improved performance: A review. Journal of Drug Delivery Science and Technology, 75: 103708.
   IF (2022) = 4,7; Pharmacology & Pharmacy (75/278) M21

3. **Turković, E**, Vasiljević, I, Drašković, M, Parojčić, J. 2021. An Investigation into mechanical properties and printability of potential substrates for inkjet printing of

orodispersible films. Pharmaceutics, 13(4): 468.
IF (2021) = 7,2; Pharmacology & Pharmacy (30/279) M21

Одлуку доставити: кандидаткињи, Универзитету, члановима комисије, декану, секретару, продекану за последипломске студије, ментору (Проф др. Јелени Пароjчић), Одсеку за наставу и студентска питања, Одсеку за правне и опште послове, пословном секретару, председнику Комисије за последипломске студије – докторске студије (Проф. др Биљана Антонијевић) и архиви.

ПРЕДСЕДНИК
НАСТАВНО-НАУЧНОГ ВЕЋА
ФАРМАЦЕУТСКОГ
ФАКУЛТЕТА

Проф. др Наташа Богавац
Станојевић

НАСТАВНО-НАУЧНОМ ВЕЋУ
УНИВЕРЗИТЕТА У БЕОГРАДУ – ФАРМАЦЕУТСКОГ ФАКУЛТЕТА

КОМИСИЈИ ЗА ПОСЛЕДИПЛОМСКУ НАСТАВУ – ДОКТОРСКЕ СТУДИЈЕ

На седници Наставно-научног већа Универзитета у Београду - Фармацеутског факултета, одржаној 11.07.2024. године, одлука број 1650/2, именовани су чланови Комисије за оцену и одбрану завршене докторске дисертације кандидата маг. фарм. Ерне Турковић, под насловом **Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова.**

Ментор

др сц. Јелена Паројчић, редовни професор, Универзитет у Београду - Фармацеутски факултет

Чланови комисије

др сц. Драгана Васиљевић, редовни професор, Универзитет у Београду - Фармацеутски факултет
др сц. Светлана Ибрић, ванредни професор, Универзитет у Београду - Фармацеутски факултет
др сц. Франц Вречер, редовни професор у пензији, Универзитет у Љубљани - Фармацеутски факултет

Чланови именоване комисије прегледали су приложену докторску дисертацију и подносе Наставно-научном већу Универзитета у Београду - Фармацеутског факултета следећи

ИЗВЕШТАЈ

А. ПРИКАЗ САДРЖАЈА ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

Докторска дисертација под називом **Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова** садржи следећа поглавља: 1. Увод, 2. Циљ, 3. Материјал и методе, 4. Резултати и дискусија, 5. Закључак и 6. Литература. Докторска дисертација укључује сажетак на српском и енглеском језику, као и одговарајуће прилоге: Списак публикованих и саопштених радова који чине део докторске дисертације, Кратка биографија кандидата, и потписане изјаве кандидата о ауторству, истоветности штампане и електронске верзије и коришћењу докторске дисертације (лиценца CC BY-NC-ND).

Дисертација је написана на укупно 173 стране (почевши од Увода, закључно са прилозима) јасним и прегледним стилом и садржи 20 табела, 66 слике/графичка приказа и 272 литературна навода цитирана харвардским стилом.

Увод садржи преглед савремених литературних података о примени, методама израде и карактеризације орално-дисперзибилних филмова (ОДФ) као релативно новог

фармацеутског облика лека са побољшаном прихватљивошћу за пацијенте. У оквиру поглавља 1.2. описане су различите методе које се могу користити за израду ОДФ: изливање дисперзије, електропредење, екструзија растопа, 2Д и 3Д штампање уз сажетак најзначајнијих резултата објављених у литератури и приказ активних и помоћних супстанци које се користе у формулацији ОДФ са нагласком на избор и карактеристике одговарајућих полимера за формирање филмова. У оквиру поглавља 1.3. приказани су и продискутовани различити приступи и постојећи изазови у карактеризацији ОДФ као фармацеутског облика лека. У оквиру поглавља 1.4. наведени су основни принципи примене напредне анализе података, уз приказ најчешће коришћених техника које се могу користити с циљем стицања увида у сложене ефекте фактора формулације и поступка израде од којих зависе критична својства квалитета орално-дисперзибилних филмова.

Циљ истраживања је јасно дефинисан у виду општег и специфичних циљева који су усмерени на испитивање утицаја састава формулације на механичка својства и брзину дезинтеграције орално-дисперзибилних филмова добијених различитим методама израде, као и испитивање могућности предвиђања утицаја испитиваних фактора на критична својства квалитета орално-дисперзибилних филмова, применом савремених техника за напредну анализу података.

У оквиру **Експерименталног дела** дат је преглед коришћених материјала и метода, праћен детаљним приказом и дискусијом добијених резултата. У оквиру прве фазе истраживања испитан је утицај поступка израде на карактеристике филмова израђених применом различитих полимера за формирање филмова, без или уз додатак супердезинтегратора и кофеина, као модел активне супстанце. У оквиру друге фазе истраживања, методом изливања дисперзије израђени су филмови који су садржали различите полимере за формирање филма или комбинацију полимера, уз додатак супердезинтегратора, различитих концентрација пластификатора и изабраних модел лековитих супстанци (атенолол, еналаприл, ибупрофен, карведилол, кофеин, парацетамол и верапамил). Експериментално израђени и испитани узорци, као и резултати детаљне претраге литературних података искоришћени су за формирање две базе података које су анализиране применом метода напредне анализе података. Резултати и дискусија приказани су у оквиру четири потпоглавља која се односе на: евалуацију утицаја методе израде и избора полимера на карактеристике орално-дисперзибилних филмова (поглавље 4.1); свеобухватну евалуацију утицаја различитих фактора формулације на карактеристике орално-дисперзибилних филмова израђених методом изливања дисперзије (поглавље 4.2); формирање и напредна анализа Базе литературних података (поглавље 4.3) и Базе експерименталних података (поглавље 4.4). Резултати су представљени прегледно и систематично и детаљно продискутовани уз реферисање на доступне литературне податке. С циљем визуелизације добијених резултата и упоредне процене испитиваних узорака, конструисани су одговарајући графички прикази.

У оквиру поглавља **Закључак** наведени су најзначајнији налази и одговарајући закључци који произилазе из резултата истраживања и који су у складу са постављеним циљевима рада.

Детаљан приказ формираних база података коришћених за напредну анализу дат је као прилог раду. Прилог I представља База литературних података; Прилог II представља преглед различитих атрибута осећаја у устима од важности за развој ОДФ - *in vivo* и *in vitro* приступи за евалуацију; Прилог III представља детаљна База експерименталних података.

Б. ОПИС ПОСТИГНУТИХ РЕЗУЛТАТА

Резултати спроведених истраживања пружају увид и практично искуство које се односи на предности и недостатке примене различитих метода израде орално-дисперзибилних филмова као релативно новог фармацеутског облика лека, и утицај различитих полимера за формирање филма, са или без додатка изабраних модел активних и помоћних супстанци на критична својства квалитета ОДФ. Такође, спроведена је свеобухватна претрага и напредна анализа базе података формиране на основу резултата истраживања других истраживачких група. У првој фази истраживања, разматран је утицај поступка израде на карактеристике ОДФ израђених применом хидроксипропилцелулозе, поливинилалкохол-полиетиленгликол кополимера, натријум-алгината и малтодекстрина као полимера за формирање филма, појединачно или у комбинацији, без и уз додатак кофеина као модел активне супстанце. Поред најшире примењиваног поступка изливања дисперзије, испитана је и могућност израде филмова методом 2Д и 3Д штампања. Као савремена метода 3Д штампања примењена је техника екструзије получврстог материјала (енгл. *semisolid extrusion*, SSE). Као носачи за 2Д штампање лекова су, поред полимерних филмова израђених методом изливања дисперзије, коришћени и различити типови комерцијално доступних јестивих папира. Израђени узорци су детаљно окарактерисани у погледу уједначености масе и изгледа, порозитета, морфологије површине, унутрашње структуре, садржаја влаге, распадљивости и механичких карактеристика. С циљем процене фактора од којих зависе критична својства квалитета орално-дисперзибилних филмова, спроведена је анализа главних компоненти која је указала на значај поступка израде, с обзиром да су филмови израђени применом различитих метода сврстани у различите кластере са препознатљивим особинама. Добијени резултати су показали да се у зависности од примењене методе израде и избора полимера могу израдити филмови различитих карактеристика. Маса филмова варирала је од 8,4 mg, код танких филмова израђених са малтодескстрином, до 57,1 mg код узорка израђеног са хидроксипропилцелулозом уз додатак натријум-алгината и кофеина као модел активне супстанце. Распадљивост узорака варирала је од 3,5 s код танких филмова израђених са малтодекстрином методом изливања дисперзије до скоро 300 s код филмова израђених методом 3Д штампања који су садржали хидроксипропилцелулозу, уз додатак натријум-алгината или малтодекстрина. Додатак диспергованих полимера (поливинилалкохол-полиетиленгликол кополимера, натријум-алгината или малтодекстрина) резултирао је продуженим временом распадања филмова без обзира на примењену методу израде. Међутим, узорци који су садржали малтодекстрин као полимер за формирање филма нису се могли користити као носачи за 2Д штампање јер је долазило до брзог распадања филма при контакту са течном фазом, дисперзијом за штампање. Дисперзије малтодекстрина и полиетиленгликол-поливинилалкохол кополимера нису била погодне за 3Д штампање методом екструзије получврстог материјала. Испитивања механичких карактеристика показала су да филмови са натријум-алгинатом имају највеће вредности затезне чврстине, Јанговог и комплексног модула, што их чини кртим и мање погодним за руковање. Филмови са хидроксипропилцелулозом окарактерисани су високим вредностима процента елонгације и нижим вредностима Јанговог модула, што указује на њихову флексибилност. Изливање дисперзије препознато је као једноставан поступак који омогућава релативно брзу израду великог броја филмова, уз могућност постизања различитих механичких карактеристика и кратког времена дезинтеграције у складу са циљним профилом квалитета лека.

У складу са налазима прве фазе истраживања, као погодна метода за израду орално-дисперзибилних филмова изабрана је метода изливања дисперзије, која је примењена у

даљим истраживањима утицаја фактора формулације на карактеристике ОДФ. У оквиру друге фазе истраживања израђено је додатних 77 узорака уз варирање врсте и концентрације полимера за формирање филма, додатног диспергованог полимера, пластификатора, супердезинтегратора и модел активних супстанци. Израђени узорци су детаљно окарактерисани и спроведена је њихова упоредна анализа. Добијени резултати су показали да се у зависности од избора основног полимера и додатног, диспергованог, полимера могу постићи различити циљеви у развоју формулације ОДФ. Вредности испитиваних параметара су значајно варирале у оквиру испитиване серије узорака. Маса филмова била је у распону од 44 mg за плацебо филмове са 5% хипромелозе до 180 mg за филмове са малтодекстрином који су садржали ибупрофен и кросповидон, при чему је вредност медијане била 82 mg. Филмови са малтодекстрином и поливинилалкохол-полиетиленгликол кополимером имали су већу просечну масу у поређењу са осталим филмовима. Дебљина филмова је била у распону од 66 μm за узорке са натријум-карбоксиметилцелулозом до 225 μm за филмове са хидроксипропилцелулозом и ибупрофеном, при чему је вредност медијане била 124 μm. Највеће вредности затезне чврстине показали су филмови са натријум-карбоксиметилцелулозом и натријум-алгинатом, док су најниже вредности забележене код филмова са хидроксипропилцелулозом и малтодекстрином. Додатак активне супстанце генерално је доводио до смањења затезне чврстине филмова. Филмови са хидроксипропилцелулозом показали су висок проценат елонгације (преко 250%), што указује на велику склоност ка растезању, док су филмови са поливинилалкохол-полиетиленгликол кополимером окарактерисани знатно мањим вредностима процента елонгације (до 50%). Додатак активне супстанце је код већине узорака довео до смањења процента елонгације. Филмови са натријум-карбоксиметилцелулозом и натријум-алгинатом имали су највеће вредности Јанговог модула, што указује на њихову кртост. Додатак активне супстанце није значајно мењао вредности Јанговог модула код филмова са хидроксипропилцелулозом, док је код филмова са натријум-карбоксиметилцелулозом вредност овог параметра била мања код узорака којима је додата активна супстанца. Распадљивост узорака варирала је у распону од 3 s (код узорака са полиетиленоксидом, PEO N80, уз додатак кроскармелозе-натријум) до 102 s (код узорака са хипромелозом уз додатак натријум-скробгликолата или кроскармелозе-натријум), при чему је вредност медијане била 27 s. Филмови у којима је активна супстанца била суспендована су, генерално, показали краће време дезинтеграције у односу на филмове са раствореном активном супстанцом. Додатак супердезинтегратора није остварио ефекат скраћивања времена дезинтеграције филмова, напротив, време дезинтеграције је, генерално, било продужено додатком супердезинтегратора.

Имајући у виду варијабилност добијених резултата који указују на бројне и сложене утицаје различитих фактора формулације и њихове потенцијалне интеракције, с циљем идентификације и евалуације фактора који утичу на критична својства квалитета ОДФ и развоја модела за њихово предвиђање, формиране су База литературних података и База експерименталних података и спроведена њихова анализа применом метода напредне анализе података. Кластеровањем података било је могуће идентификовати критеријуме (одговарајући параметар и његова вредност) од којих зависе карактеристике испитиваних узорака. Анализом значајности атрибута за различите моделе, идентификовани су кључни фактори који утичу на механичка својства ОДФ: (1) тип полимера као најважнији атрибут од кога зависи проценат елонгације; (2) концентрација активне супстанце као значајан атрибут за предвиђање Јанговог модула; (3) концентрација полимера и пластификатора које имају значајан утицај на комплексни модул и проценат елонгације и (4) молекулска маса коришћеног полимера.

Као најпогоднија метода препозната је метода Случајних шума (енгл. *Random forest*) која је успешно примењена на обе базе података. Иако су алгоритми Случајних шума и Потпорних вектора (енгл. *Support vector machine*) релативно једноставни у поређењу са сложеним алгоритмима Вишеслојних вештачких неуронских мрежа (енгл. *Multi-layer artificial neural network*), они могу пружити драгоцене информације током раних фаза развоја формулације. Ови алгоритми посебно су корисни при избору одговарајућих полимера, који су кључни за постизање жељених механичких карактеристика филмова. С друге стране, алгоритми Вишеслојних вештачких неуронских мрежа пружају значајне предности када је у питању евалуација већих и униформно структурираних база података, али је временски оквир потребан за изградњу ових модела далеко већи, у односу на друга два алгоритма.

В. УПОРЕДНА АНАЛИЗА РЕЗУЛТАТА ДОКТОРСКЕ ДИСЕРТАЦИЈЕ СА ПОДАЦИМА ИЗ ЛИТЕРАТУРЕ

Због бројних предности у терапији и побољшаној адхеренци код различитих, вулнерабилних група пацијената који имају проблеме са гутањем, орално-дисперзибилни филмови су препознати као погодан фармацеутски облик који привлачи велику пажњу истраживача, како у академском окружењу, тако и у фармацеутској индустрији, о чему сведочи велики број публикација објављен у току последњих неколико година. Велики број истраживања усмерен је ка развоју различитих метода за израду орално-дисперзибилних филмова (Elbl и сар. 2023; Khalid и сар. 2021; Łyszczarz и сар. 2021; Musazzi и сар. 2020; Rodríguez-Pombo и сар. 2024; Seoane-Viañoa и сар. 2021). Резултати истраживања спроведених у оквиру ове докторске дисертације у сагласности су са резултатима других аутора који указују на значајан утицај примењеног поступка израде на карактеристике ОДФ, као и предности и недостатке различитих метода.

Избор оптималних полимера за формирање филма и осталих ексципијенаса од којих зависе механичке карактеристике и распадљивост ОДФ су такође предмет интензивног истраживачког рада (Cupone и сар. 2022; Da Silva и сар. 2023; El-Bary и сар. 2019; Kim и сар. 2020; Kittipongpatana и сар. 2022; Musazzi и сар. 2018; Olechno и сар. 2021; Pezik и сар. 2021; Wei и сар. 2023; Yin и сар. 2024). Новија истраживања усмерена су на могућност примене супердезинтегратора и других приступа за постизање брзе дезинтеграције, уз задовољавајуће механичке карактеристике ОДФ и повећање капацитета за инкорпорирање различитих активних супстанци (Onuki и сар. 2018; Steiner и сар. 2019; Steiner и сар. 2022; Takeuchi и сар. 2019; Vlad и sar. 2023). У оквиру ове докторске дисертације испитана је могућност примене различитих полимера и њихових комбинација с циљем оптимизације механичких карактеристика ОДФ. Показано је да додатак супердезинтегратора може допринети оптимизацији механичких карактеристика филмова, али не и повећању брзине распадања, што је у складу са резултатима других истраживачких група.

Утицај карактеристика материјала који улазе у састав ОДФ и поступка израде на њихове фармацеутско-технолошке и биофармацеутске карактеристике је сложен, најчешће нелинеаран и предмет је бројних истраживања, како би се дошло до сазнања која би омогућила моделовање и предвиђање карактеристика препарата у зависности од састава формулације и примењеног поступка израде (Borges и сар. 2016; Gupta и сар. 2021; He и сар. 2021). Савремене технике за напредну анализу података омогућавају екстракцију одређених, претходно непознатих и потенцијално значајних информација из великих база података, њихово класификовање и предвиђање. Ови приступи још

увек нису широко заступљени у фармацеутској технологији иако се очекује да могу значајно допринети развоју и оптимизацији формулације и процеса производње (Vora и сар. 2023). Резултати спроведених истраживања указују на могућност примене напредне анализе података за идентификацију фактора који утичу на критична својства квалитета ОДФ и развој модела за предвиђање који омогућавају развој нових производа у краћем времену из уз смањену потрошњу материјалних ресурса.

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Г. ОБЈАВЉЕНИ И САОПШТЕНИ РЕЗУЛТАТИ КОЈИ ЧИНЕ ДЕО ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

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Д. ЗАКЉУЧАК - ОБРАЗЛОЖЕЊЕ НАУЧНОГ ДОПРИНОСА ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу детаљне анализе приложене докторске дисертације, чланови Комисије закључују да приказани резултати, дискусија и закључци представљају значајан допринос у области развоја и карактеризације орално-дисперзибилних филмова као релативно новог фармацеутског облика лека. У оквиру истраживања је испитан утицај различитих поступака израде, као и врсте и концентрације полимера за формирање филма, додатих фармацеутских активних и помоћних супстанци (пластификатора, супердезинтегратора) на механичке карактеристике и распадљивост који су препознати као критична својства квалитета орално-дисперзибилних филмова. С циљем увида у сложене односе између фактора формулације и поступка израде и њиховог утицаја на критична својства квалитета ОДФ, спроведена је опсежна претрага и критичка анализа доступних литературних података и формирана База литературних података која је обухватила више од 900 узорака преузетих из литературе. Експериментални резултати искоришћени су за формирање Базе експерименталних података која је обухватила 100 узорака ОДФ израђених методом изливања дисперзије који су детаљно окарактерисани у погледу механичких карактеристика и распадљивости. Применом напредне анализе података показано је да је могуће моделовати сложене односе и интеракције између испитиваних фактора и карактеристика узорака. Као најзначајнији атрибут у Бази литературних података идентификована је распадљивост, док су у оквиру Базе експерименталних података највећи значај имале механичке карактеристике (проценат елонгације, Јангов и комплексни модул). Модел развијен применом алгоритма Случајних шума показао је највећи потенцијал за предвиђање карактеристика ОДФ. Резултати спроведених истраживања доприносе даљем раду на развоју и оптимизацији формулација и широј примени орално-дисперзибилних филмова као фармацеутских облика са побољшаним перформансама и прихватљивошћу од стране пацијената.

Ђ. ПРОВЕРА ОРИГИНАЛНОСТИ ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу *Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду* и налаза у извештају из programa iThenticate којим је извршена провера оригиналности докторске дисертације:
Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова, кандидата магистра фармације Ерне Турковић, утврђено подударање текста износи 3%.

Овај степен подударности последица је цитата личних имена, библиографских података о коришћеној литератури, општих места и података, што је у складу са чланом 9. *Правилника*.

На основу свега изнетог, а у складу са чланом 8. став 2. *Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду*, резултати спроведене провере указују на оригиналност докторске дисертације, те се прописани поступак припреме за њену одбрану може наставити.

Е. ПРЕДЛОГ КОМИСИЈЕ ЗА ОЦЕНУ ЗАВРШЕНЕ ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу прегледа докторске дисертације маг. фарм. Ерне Турковић под називом **Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова – могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова**, Комисија закључује да је кандидаткиња испунила постављене циљеве и да резултати приказани у дисертацији представљају оригиналан и значајан научни допринос, што је потврђено њиховим објављивањем у три рада у врхунским међународним часописима. Комисија позитивно оцењује докторску дисертацију маг. фарм. Ерне Турковић и предлаже Наставно-научном већу Фармацеутског факултета Универзитета у Београду да прихвати извештај о завршеној докторској дисертацији и упути га Већу научних области медицинских наука Универзитета у Београду, ради добијања сагласности за јавну одбрану докторске дисертације маг. фарм. Ерне Турковић.

23.08.2024.

Чланови Комисије

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Review article

Orodispersible films — Pharmaceutical development for improved performance: A review

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ABSTRACT

Orodispersible films (ODFs) have recently emerged as innovative dosage form which provides distinct advantages in the patient centric pharmaceutical drug product design due to inherent dosing flexibility and improved patient acceptability. Although their potential advantages in pharmacotherapy are well recognized, there is still a lot of research work to be done in order to explore and understand complex relationships among different formulation factors, film mechanical properties, and their bioperformance. Lack of standardized characterization methods and relevant specifications pose additional limitation for their wider application. In the present study, in-depth review of the available body of data published on ODF development and characterization was performed. In total, 112 papers published between November 2008 and April 2022 were taken into consideration for dataset building. Data collected have been critically evaluated and compiled into the representative dataset formed around three domains, namely: (A) Manufacturing method and composition; (B) ODF characteristics; and (C) ODF sensory attributes. Based on the investigated dataset, an attempt was made to identify the acceptable range of Critical Quality Attributes (CQA) values and propose ODF specific Quality Targeted Product Profile (QTPP) as a foundation which should guide and facilitate pharmaceutical development.

1. Introduction

Orodispersible films (ODFs) have recently emerged as innovative dosage forms which provides distinct advantages in the patient centric pharmaceutical drug product design due to inherent dosing flexibility and improved patient acceptability. ODFs are described as "single- or multilayered sheets of suitable materials, to be placed in the mouth where they disperse rapidly" (Ph. Eur, 2022). It is well documented from a number of studies that ODFs, due to convenient administration, are well accepted in different patient populations, and may significantly improve medication adherence [1–7]. Different polymers and their combinations can be employed as film-forming agents, and interested readers may find detailed information in the excellent review by Borges and coworkers [8]. Although solvent casting is the most widely used method for ODFs manufacture, other methods such as hot-melt extrusion, electrospinning, and, increasingly, different 2D and 3D printing technologies may be employed [9–16]. Investigations in the field of ODFs manufacture are directed towards both small scale, as well as large scale process development [17–19]. It is envisioned that small scale ODF manufacture may take place in the community pharmacy, or hospital pharmacy settings enabling timely, on-demand medicines production in accordance with the specific needs of an individual patient, or patient group [20–23].

Besides safety and efficacy, patient-centricity has emerged as an important drug product attribute contributing to increased medication adherence and improved health outcomes [24]. Patient-centric drug product design refers to a range of issues, from the selection of the route of administration, dosage form shape and size, dosing frequency, to packaging selection [25–27]. It includes all the aspects that contribute to the overall patient experience, and should be incorporated in the Quality Target Product Profile (QTPP) as the basis of design for pharmaceutical product development.

Although, notable progress in the field has been achieved during the last decade, there is still a number of issues which should be further addressed in order to secure effective pharmaceutical development and marketing authorization of ODF products. It is generally perceived that orodispersible film should exhibit: (a) rapid disintegration in oral cavity followed by immediate or, in some cases, modified drug release; (b)

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suitable mechanical properties to withstand handling and packaging, and (c) acceptable appearance and palatability [2,28]. Despite the fact that ODFs are extensively investigated, desirable ranges of the ODF Critical Quality Attributes (CQAs) have not yet been defined. Overview of the available literature data, also, reveals a lack of standardization in characterization methods employed and wide range of values for different ODF quality attributes. Number of studies that investigate different aspects of ODF development is rapidly increasing and therefore review and exploration of available data can be meaningfully applied to answer questions raised during product development.

The aim of the present study was in-depth review of the available body of data published on ODF development and characterization. Data obtained will be employed to identify the acceptable range of CQAs values and propose relevant QTPP as a foundation which should guide and facilitate pharmaceutical development.

2. Dataset development

2.1. Search strategy

Comprehensive data search has been conducted in the PubMed database based on the selected keywords ("orally disintegrating films" OR "oral disintegrating films" OR "orodispersible films" OR "oral soluble films" OR "fast dissolving films" OR "oral dissolving films" OR "fast dissolving oral films" OR "orally disintegrating strips" OR "oral disintegrating strips" OR "orodispersible strips" OR "oral soluble strips" OR "fast dissolving strips" OR "oral dissolving strips" OR "fast dissolving oral strips" OR "strip-films") in singular or plural, according to different terminology found in the literature. Only articles published in English were included. In order to limit survey only to original scientific papers based on experimental work, review articles and articles related to other administration routes (vaginal, sublingual, buccal) were excluded. Additional exclusion criteria were: (i) lack of detailed information on the investigated samples composition (i.e. reports from the clinical or pharmacokinetic studies; studies focused on ODF preparation method development, and studies related to commercial ODF products characterization); (ii) use of non-standardized ingredients (excipients and drug substances), such as different substances of natural origin, and (iii) incomplete samples characterization or lack of parameters relevant for dataset building.

2.2. Data extraction

Collected data have been critically evaluated and compiled into the representative dataset in one of three domains, namely: (A) Manufacturing method and composition; (B) ODF characteristics; and (C) ODF sensory attributes. List of various data categories related to stated domains is presented in Fig. 1. Domain A refers to the applied manufacturing method, and basic information on the drug substance and excipients used. Domain B includes results of ODF characterization related to its mechanical properties, disintegration and dissolution, including basic information on the test setup employed. Under the ODF sensory attributes (i.e. Domain C) *in vivo* disintegration, taste, mouthfeel and handling assessment, which might affect product acceptability, have been reviewed. In order to uniformly present data taken from different studies, relevant adjustments and data transformations have been performed, i.e., reported parameter values were scaled to the same measurement unit, calculated based on the experimental data provided, or extracted from the graphical data via open-sourced online graph-reader (graphreader.com). In addition, availability of pharmacokinetic (PK) data obtained in human or animal *in vivo* studies, and/or through physiologically based pharmacokinetic (PBPK) modeling and simulation has been recorded.

3. Dataset overview

PubMed survey via selected keywords revealed 274 papers related to ODF development, evaluation and characterization published from November 2008 until April 2022. Fig. 2 represents flow of our search results after applying predefined inclusion and exclusion criteria. The dataset established is provided as Supplementary material.

In total, 112 papers reporting on ODF formulation and characterization were taken into consideration for dataset building. Basic information on the manufacturing method and type of the film-forming agent were available in all the papers reviewed, while more detailed data on the formulation composition were provided in 83 papers. It should be noted that in 18 papers data on film size and shape were lacking. Data on ODF *in vitro* disintegration were reported from the majority of studies

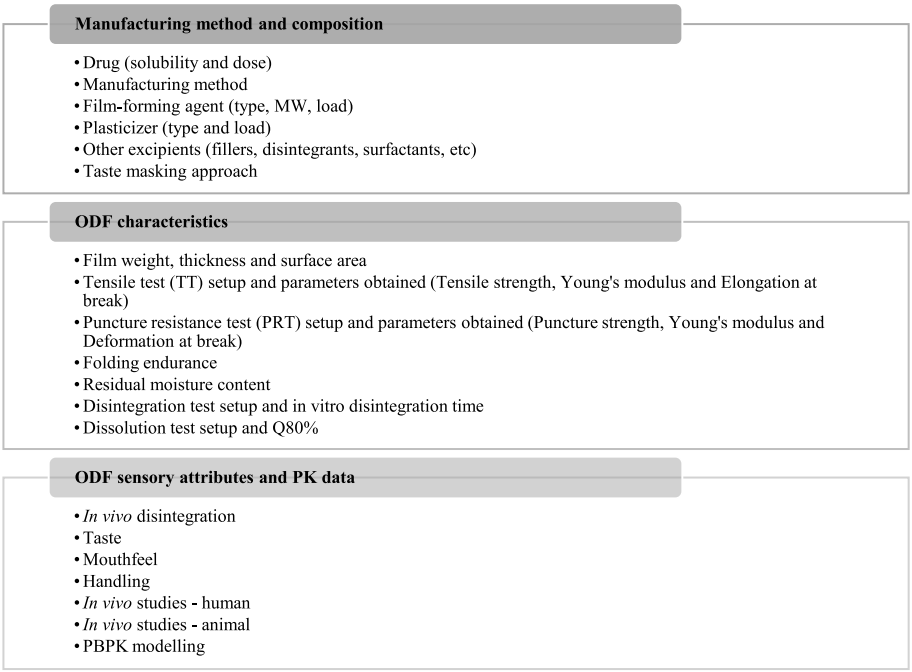

Fig. 1. Overview of the data domains evaluated.

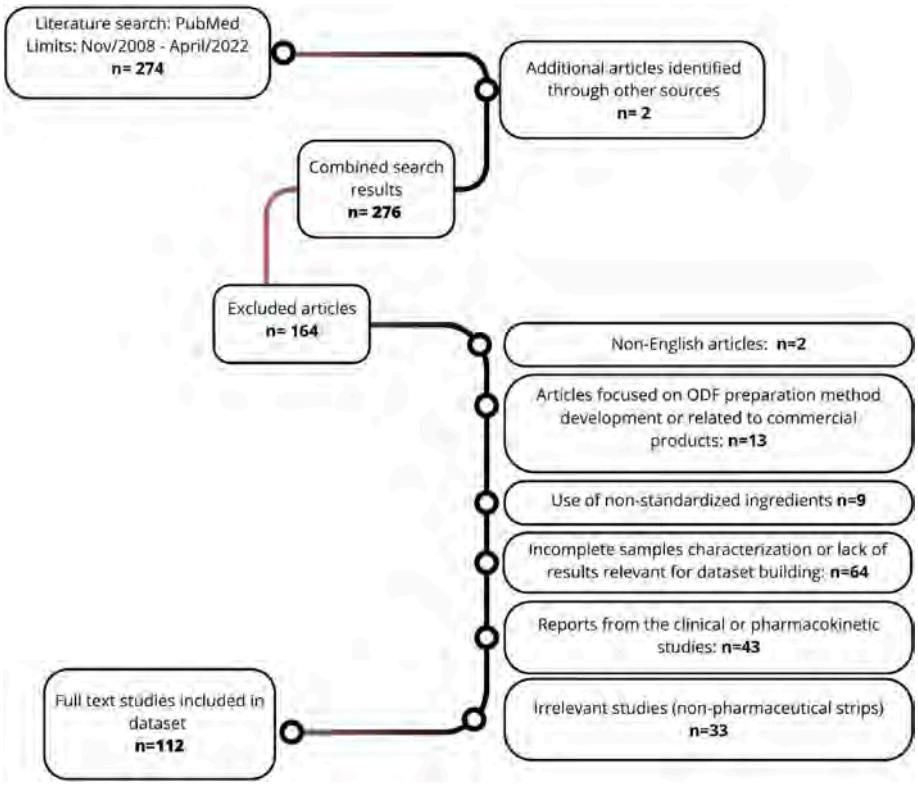

Fig. 2. Flow of search results after applying predefined inclusion and exclusion criteria.

(95/112) while drug dissolution was reported from 77 studies. ODF mechanical characterization was based on the tensile test results in the majority of studies (76/112), followed by puncture resistance test results (12/112), while folding endurance was assessed in 25 studies. *In vivo* or *in vitro* sensory attributes evaluation was reported from the 30 studies. Pharmacokinetic data obtained in human studies were reported in three papers, animal *in vivo* studies were included in nine papers, while PBPK modeling and simulation data were reported in the additional two articles, which have been retrieved from the Google Scholar platform.

Main obstacles encountered during dataset development were lack of quantitative data regarding formulation composition, excipients grades and experimental conditions/setup used for samples characterization.

3.1. Manufacturing method and composition

3.1.1. The most commonly employed manufacturing methods

Methods used for ODFs manufacture include solvent casting, hot-melt extrusion, electrospinning and 2D or 3D printing. Comprehensive review of different technologies used for ODF manufacture can be found in Lee et al. [12] and Musazzi et al. [29].

During dataset development it was noticed that in a number of studies, two or more manufacturing methods have been employed. Review of data collected from the literature indicate that common and most frequently used method for ODF manufacture is solvent casting which was employed in 123 (out of 112) studies evaluated, followed by 2D printing in ten studies, 3D printing in a total of twelve studies, electrospinning in eight, and hot-melt extrusion in two studies (Fig. 3).

3.1.1.1. Solvent casting. Solvent casting (SC) represents widely used method for thin polymer films preparation, using range of polymers with different physicochemical properties. The obtained films may include selected drug substance, or can be prepared as drug-free films to be used as substrates for 2D printing. Although different variations of solvent casting methods can be used, they are based on the same principle

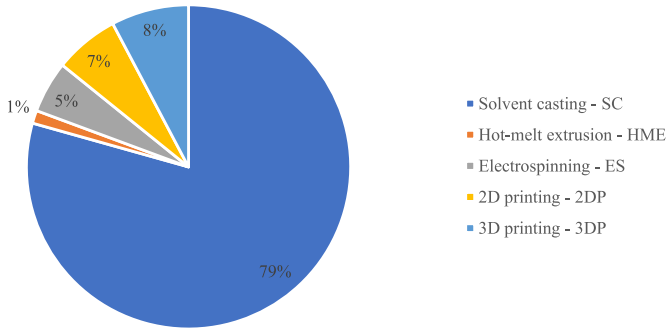

Fig. 3. The frequency of use of different ODF manufacturing methods.

considering: (i) preparation of dispersion containing film-forming agent and other ingredients in the selected liquid vehicle; (ii) casting and (iii) film drying, followed by (iv) cutting into desired shapes, where applicable. This method allows relatively simple casting of both single- and multilayered films [16]. In addition, casting dispersion could be loaded with microparticles or nanoparticles in order to incorporate uniformly higher doses of insoluble active ingredients [30,31]. One of the parameters that have to be taken into account during film casting is way of drying, as well as drying temperature. Despite the fact that slower drying at lower temperature leads to better mechanical properties, drying time has to be properly optimized in order to comply with the requirements of both large-scale industrial production and on-demand film preparation in pharmacy [32]. Freeze-drying was investigated as alternative method for casted dispersion drying with the aim to increase drug stability [33] or improve drug dissolution rate [34]. It was reported that freeze-dried samples exhibited higher porosity and consequently faster disintegration, with impaired mechanical properties, while the effect on drug substance stability and dissolution rate was not so obvious [33,34].

Viscosity of casting dispersions is also shown to be noteworthy factor

that can affect final dosage form performance [22,35]. Centkowska et al. [35] pointed out that highly viscous dispersions are disadvantageous due to problems with deaeration and uneven distribution of dispersion on the casting plate. Opposite, Visser et al. [36] encountered problem with lower viscosity values that led to formation of non-peelable films, evidencing the need for viscosity optimization. In the suspension-type systems containing insoluble drug, viscosity optimization is necessary in order to slow down sedimentation and provide uniform drug distribution [35]. Film-forming agent molecular weight has been identified as good predictor of dispersion viscosity [37]. The increase in polymer fraction leads to viscosity increase, irrespective of the type of polymer used [38]. Based on the investigated dataset, casting dispersion viscosity ranging from 0.7 to 25.8 Pas would be recommended for preparation of homogeneous films [22,35,38].

3.1.1.2. Hot-melt extrusion. Hot-melt extrusion (HME) is recognized as an emerging approach for ODF manufacture which, being a solvent-free method, may offer certain advantages over solvent casting in the case of drugs sensitive to water. This technology utilizes high temperature and shear force which lead to drug substance and polymer melting and blending, followed by extrusion and solidification of the molten mass. Pregelatinized hydroxypropyl pea starch [14] and maltodextrin [39,40] have, so far, been used as film-forming polymers in hot-melt extrusion.

3.1.1.3. Electrospinning. Electrospinning (ES) is a method used to produce ultrafine fibers by jetting electrostatically charged polymer solution through metal needle onto a collector surface. The solvent evaporates rapidly resulting in formation of the non-woven fiber mats onto collector. According to the literature data available, polyvinyl alcohol [1,41–43] and povidone [44–47] were extensively investigated as the base for preparation of electrospun fibers. The main advantage of films prepared in this manner is highly porous structure and increase in surface area leading to almost instant disintegration upon contact with saliva and fast drug dissolution.

3.1.1.4. 2D and 3D printing. There is an increasing research interest for the use of different printing technologies as novel ODF manufacturing approach. 2D printing (2DP), also referred to as inkjet printing, is a non-contact approach that enables deposition of small droplets of ink onto suitable substrate. Although different substrates may be used, solvent-casted thin films are most often employed [6,16,19,20,23,48,49]. In this case, film mechanical properties are particularly important as it should withstand additional wear and tear during printing. 3D printing (3DP) is additive technology which enables manufacture of three-dimensional physical objects by successive material deposition and fusing based on a predesigned digital model. According to the presented dataset, only extrusion-based 3D technology is utilized for ODF printing, including fused deposition modeling (FDM) and semisolid extrusion (SSE). Extrusion-based 3D technology is based on the construction of layer-by-layer design either from the prefabricated filaments or by direct extrusion of semi-solid mixture. FDM involves preparation of drug and polymer mixture, with the addition of plasticizers, which is extruded to form filaments that are used to produce thin films by targeted deposition onto the building platform. In the case of personalized ODFs fabrication, priority was given to the SSE approach, as it eliminates the need for prefabrication since the starting material is semi-solid and can be directly printed with the syringe-based tool-head nozzle [6,13,50–54].

Comparative analysis on different manufacturing approaches is quite limited, which makes it difficult to adequately assess benefits and shortcomings of the proposed methods. Comprehensive assessment of 2D and 3D printed ODFs based on hydroxypropyl cellulose revealed, despite samples similarity regarding thickness and size, notably lower mechanical resistance and elongation followed by somewhat faster disintegration and dissolution rate of 3D printed samples that could be attributed to slightly wavy surface, and thus increased surface area, produced during 3D printing [6]. However, both methods provided high drug content uniformity of the prepared units. Jamroz et al. [10] reported remarkably faster drug dissolution from samples prepared by FDM in comparison to solvent-casted samples due to stabilization of the amorphous drug state and higher surface area. Abdelhakim et al. [1] conducted comparative analysis of the sensory attributes and the end-user acceptability of electrospun and solvent-casted samples containing the same film-forming agent. The obtained results revealed equal acceptability in all the examined criteria indicating suitability of electrospun films application in practice. Electrospun films exhibited additional benefit regarding disintegration and drug dissolution when compared with casted samples, due to pronounced porosity and increased surface area [43]. Łyszczarz and co-workers [55] backed up these finding as they showed that electrospun films showed highest wettability, which is reflected in fast disintegration in comparison to casted and 3D printed films from the same polymer. The main obstacle in this study for electrospun films was inconsistency in mechanical properties and drug recrystallization during dissolution studies, while casted and 3D films showed prolonged disintegration which affects the patient acceptability. Cilurzo and co-workers [39] investigated feasibility of hot-melt extrusion approach for ODF preparation. The obtained results revealed better performance of casted samples in terms of *in vitro* and *in vivo* disintegration time and patient acceptability compared to hot-melt-extruded films. Even placebo samples prepared via hot-melt extrusion were considered as unacceptable due to unpleasant sensation caused by microcrystalline cellulose residues.

3.1.2. Composition

3.1.2.1. Film-forming agents. ODF formulations include usually one or a mixture of appropriate film-forming agents in which drug substances and other excipients, such as plasticizers, soluble and insoluble fillers, superdisintegrants, surfactants and taste-masking agents are incorporated. A range of hydrophilic polymers have been used for ODF preparation, including: hydroxypropyl methylcellulose (HPMC); hydroxyethyl cellulose (HEC); hydroxypropyl cellulose (HPC); methylcellulose (MC); carboxymethylcellulose (CMC); maltodextrin (MDX); pregelatinized hydroxypropyl pea starch (PHPS); granular hydroxypropyl starch (GHPS); pullulan (PUL); polyvinyl alcohol (PVA); polyvinyl alcohol – polyethylene glycol graft copolymer (PVA-g-PEG); polyvinyl alcohol – polyethylene glycol graft copolymer with polyvinyl alcohol (PVA-g-PEG with PVA); povidone (PVP); polyethylene oxide (PEO); pectin (PT); high methoxyl pectin (HMPT); gelatin (GEL); hyaluronic acid (HYA); sodium alginate (SA); chitosan (CS); polyacrylic acid (PAA). Although usually only one film-forming agent is employed for ODF preparation, sometimes additional polymers, such as carbomer (CBM), wheat starch (WS), carboxymethylcellulose sodium salt (CMC-Na), trehalose (THL) and dextran (DXT) are included in order to: (a) provide better spreadability of prepared dispersion [32]; (b) improve mechanical properties of the obtained samples [34,48]; (c) increase stability of the incorporated drug substances [33] or (d) reduce film stickiness [56]. In Fig. 4, an overview of the frequency of different film-forming agent application in association with different manufacturing methods used, based on the investigated dataset analysis is presented.

The most often used polymers for ODF preparation, irrespective of the manufacturing method employed, are cellulose derivatives, especially HPMC. Different HPMC grades that vary in the degree of substitution, i.e. the number of methoxyl and hydroxypropyl groups attached to the ring, exhibit remarkable differences in the molecular weight (MW 10–410 kDa) leading to the pronounced variation in disintegration and mechanical properties. HPMC type E having lower hydroxypropoxyl/methoxyl ratio [8] proved to be, according to the presented dataset, the most often applied film-forming agent suitable for solvent casting, inkjet

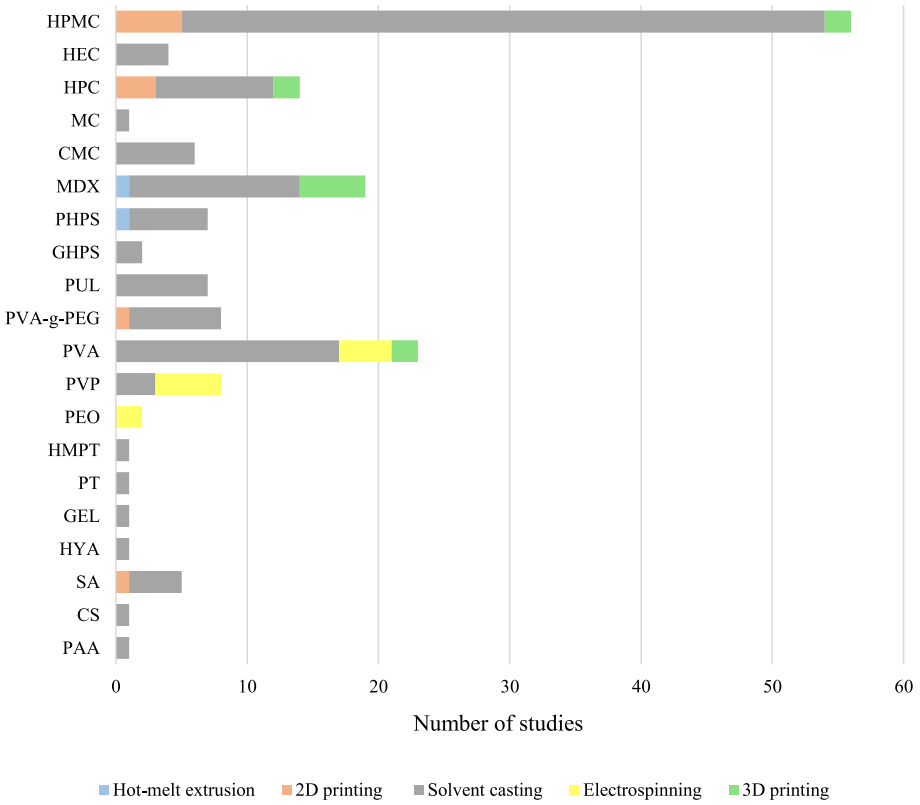

Fig. 4. The frequency of different film-forming agents use, and the associated manufacturing method.

or 3D printing [22,32,36]. PVA, water soluble synthetic polymer differing in terms of hydrolysis degree, is second most often used polymer employed for solvent casting, electrospinning and 3D printing. Processability improvement and exemption of plasticizer was reported for ODF containing pegylated PVA derivative, PVA-g-PEG [57]. Modified starches, such as MDX and PHPS are extensively investigated as film-forming agents for solvent casting and hot-melt extrusion, while MDX was additionally applied for ODF preparation by 3D printing. Lower values of MDX dextrose equivalent lead to formation of stronger, somewhat stiffer and less ductile ODFs designated as samples with better mechanical characteristics [58,59]. MDX films prepared by hot-melt extrusion disintegrated slower in comparison to the casted films, and dissolution time was notably prolonged [39]. Polymers utilized for electrospinning were PVP, which was used in 4 (out of 7) studies, and PVA which was used in 3 (out of 7) studies. Although both polymers enabled formation of films with very fast disintegration and dissolution due to porous structure and high surface area, mechanical properties are yet to be explored, due to limited data. Liew and coworkers (2014) reported that PVP has to be combined with other polymers due to disability to form flexible films. Despite the fact that majority of the listed polymers might be applied for different manufacturing methods, PEO was exclusively investigated only for 3D printing [60,61].

Selection of the film-forming agent and its content represent the main formulation factors which should be carefully optimized to achieve the balance between mechanical resistance necessary to withstand manipulation, and desired fast disintegration. Although polymers with lower molecular weight (from 10 kDa) are preferable for ODF preparation [8], film-forming agents with molecular weight up to 1300 kDa were, also, successfully employed for ODF development [46,62]. However, higher molecular weight related to polymer entanglement due to longer chains is possibly associated with higher viscosity and prolonged ODF disintegration [63].

It should be noted that, besides hydrophilic polymers, certain hydrophobic polymers such as polyvinyl acetate, methacrylate-based copolymer and shellac might be used for ODF preparation [64].

3.1.2.2. Plasticizers. Addition of plasticizer notably affects ODF mechanical properties. Liew et al. [65] postulated that higher flexibility and shorter film disintegration time governed by facilitated polymer movements might stem from plasticizer interpose between polymer chains and the effect on intermolecular bonding. Commonly used plasticizers include glycerol (GLY), polyethylene glycol (PEG) of various grades (200–4000), propylene glycol (PG) and sorbitol (SOR), which were used, respectively in 65, 23, 7 and 7 (out of 112) studies included in the investigated dataset. Xylitol, D-α-Tocopherol polyethylene glycol 1000 succinate, triacetin, triethyl citrate and citric acid were also employed in some cases, as well as amino acids such as glycine, proline and lysine [21,66]. It was reported that addition of glycine and proline resulted in reduced elastic modulus (about 50%) and tensile strength (about three times) and, therefore, increased ductility of the ODFs based on maltodextrin [66]. Although triethyl citrate was employed as plasticizer in several studies, it cannot be considered as appropriate for ODF formulation due to sensation of bitter taste [18]. Presence of poloxamers and copovidone acting as plasticizers and stabilizers increase feasibility of FDM 3D printing by optimization of printing conditions [60,61].

3.1.2.3. Fillers and disintegrants. Other excipients which may affect ODF mechanical properties and/or disintegration include different soluble and insoluble fillers (such as mannitol, lactose, starch, microcrystalline cellulose – MCC, low-substituted hydroxypropyl cellulose – L-HPC, polyvinyl acetate, calcium carbonate, calcium silicate and silica) and disintegrants (sodium starch glycolate – SSG, crospovidone – CP, croscarmellose sodium – CCS, sodium alginate – SA, carboxymethyl starch sodium – CMSS). Considering the data presented, influence of disintegrant addition on film disintegration is not completely clarified. Although in several papers (16/112) impact of disintegrants was investigated, the lack of corresponding samples without disintegrants prevent more in-depth understanding of the phenomena involved. In

addition, studies in which corresponding samples were available, revealed absence of any effect, or even ODF disintegration prolongation [67–69]. The opposite, Zhang et al. [31], reported that addition and increase in SSG or CCS load in HPMC-containing films significantly decreased disintegration time. However, although presence of SSG enhances disintegration of PVA or HMP based ODFs, further increase in superdisintegrant load resulted in the prolonged disintegration time [70]. Having in mind diversity in samples composition reflected primarily in the film-forming agent selection (MDX, HPC, PVA-PEG, PVA or HMP) it might be postulated that disintegration is affected by combined effect of polymer characteristics and properties of the selected superdisintegrant. Insoluble and soluble fillers were evaluated as disintegration enhancers in ODFs formulation in 23 out of 112 studies. Although the results obtained are somewhat arguable due to complex formulation, Takeuchi and co-workers [71] conducted comprehensive study to investigate not only the type of different insoluble excipients, but also the influence of their characteristics, including particle size and shape, on ODF disintegration. They reported that increase in particle size and load of insoluble excipients was accompanied with disintegration improvement, possibly due to reorganization of the structure of polymer molecular chains. This hypothesis was confirmed based on the observed mechanical properties deterioration represented by significant decrease in film tensile strength. When compared to particle size, the shape of the particles had less effect on the film characteristics [71]. Despite the fact that ODF disintegration enhancement was confirmed by Ref. [71]; in the majority of other studies, the impact was not so obvious [39,71,72]. Citric acid was extensively [39,61,73] investigated (in 14 out of 112 papers) as saliva stimulating agent or pH modifier, alone or in combination with sodium citrate in order to accelerate disintegration, enhance drug solubility and improve drug dissolution. Franceschini et al. [66] evaluated the impact of nanosized polyvinyl acetate as insoluble filler on mechanical reinforcement of maltodextrin films. The obtained results revealed that presence of nanofiller in the range of 3–5% (w/w) notably improved tensile strength and elastic modulus of the investigated samples, without any impact on film disintegration [66]. Hence, for adequate ODF disintegration and mechanical properties optimization, presence of additional excipients would have to be carefully assessed case-by-case.

3.1.2.4. Thickening agents. Addition of thickening agents such as hydroxyethyl cellulose, alginate, tragacanth, xanthan gum or arabic gum was investigated in several studies [17,38,40,50,74,75]. The obtained results revealed that addition of various grades of HEC contributed to uniformity of excipients distribution during 3D printing leading to formation of flexible and easily removable films with smooth surface [50]. Inclusion of different natural gums did not exhibit any additional advantage regarding ODF manufacture and formulation optimization in comparison to samples without gums [38]. Krull et al. [74] reported that, despite the fact that increase in the xanthan gum concentration led to higher dispersion viscosity, any improvement of drug distribution was lacking while drug dissolution was, even, prolonged.

3.1.2.5. Surfactants. It was reported from a number of studies that in the case of starch derivatives, such as pregelatinized hydroxypropyl starch, maltodextrin or pullulan, addition of surfactants (lecithin, sorbitan oleate or polysorbate 80) is necessary in order to improve spreadability of prepared dispersion onto the casting plate and facilitate dried film removal [33,39,58,66,76–79]. Besides acting as anti-adherents, surfactants, also, facilitate film wetting, disintegration and drug dissolution, and contribute to casting dispersion uniformity preventing drug nano- or microparticles aggregation.

3.1.2.6. Taste masking. In order to enhance ODF palatability and patient adherence, different approaches to taste masking have been employed. In the majority of studies, taste masking was based on the addition of different sweeteners and aromas [14,34,58,65,76,80–83]. In some cases, it was reported that increased content of certain film-forming agents such as maltodextrin resulted in improved formulation taste [81,84]. Other taste masking approaches, such as preparation of inclusion complexes with β-cyclodextrins [46,85,86], development of microparticles containing polymer with pH dependent solubility [87] or preparation of drug-ion exchange resin complexes [88] have also been employed. It was shown that inclusion complexes with β-cyclodextrins proved to be, also, suitable approach for drug solubility improvement, prevention of drug recrystallization, improved stability and increased drug release rate [46,85,86]. Cilurzo et al. [39] reported that propylene glycol adversely affected ODF palatability. However, it should be noted that taste masking might not been an issue in the case of certain low soluble drug substances due to, generally, low drug load, and short residence time in the mouth. In order to improve film appearance, different colorants, as well as opacifier titanium dioxide were used [17,21,69,89].

3.1.2.7. Drug load. Low drug load has been generally perceived as the main limiting factor for wider ODF application. Therefore, at present, ODF development is limited to highly potent drugs, while novel formulation approaches are focused on drug load increase. In order to perform comparative analysis of the amounts of drug substance incorporated, doses reported from different studies were transformed and presented in the dataset as drug amount per unit film surface (mg/cm^2). Relevant values ranged from 0.01 mg/cm^2, in the case of solvent-casted films containing poorly soluble cholecalciferol and inkjet printed caffeine, to 20.83 mg/cm^2 in the case of solvent-casted films with highly soluble pyrazinamide, with 2.08 mg/cm^2 as the median value estimated for the investigated dataset. In general, higher drug load was obtained with highly soluble drugs [90–92] and in the case where more advanced manufacturing approaches such as 3D printing [21] or consecutive solvent casting were employed [36,93]. In the case of polymer films used as substrates for inkjet drug printing, addition of mesoporous fumed silica resulted in the increased film porosity which was associated with the increased drug load [20]. Increased porosity and consequently drug load has been achieved by manufacturing structured orodispersible film templates. Their structured matrix is obtained by dispersing additional polymer in the HPC polymer solution and formation of open-pore top layer which enables higher ink sorption [92,94].

3.2. ODF characteristics

Analysis of the developed dataset revealed that investigated ODFs differ significantly regarding size, thickness and weight. Size of the prepared films ranged from 0.25 to 10.6 cm^2 in order to provide adequate dosing of diverse model drugs employed. Although film thickness, in the majority of the presented studies, ranged between 13 and 710 μm, values above 1000 μm were, also, observed. Thickness higher than 450 μm was, in general, associated mainly with the presence of drug-loaded microparticles governing modified drug release [60,73].

3.2.1. Mechanical properties

Mechanical properties are critical for the achievement of proper ODF handling and stability [78]. It is stated that, during ODF manufacture measures need to be taken to ensure suitable mechanical strength to resist handling without being damaged (Ph. Eur, 2022). However relevant specifications have not been established. In addition, standardized methodologies for ODF mechanical properties assessment are still under development. The most often employed approach includes tensile testing based on the standardized test for determination of tensile properties for films and sheets (DIN EN ISO 527–3) [22,32,67,95]. Hence, in the majority of published papers mechanical properties of thin polymeric films are assessed based on tensile strength, elongation at break and Young's modulus values calculated from stress-strain curves

derived after sample stretching until break. Considering that ODFs are expected to be flexible, stable and easy to handle [2], targeted mechanical properties might include high tensile strength and elongation at break and low Young's modulus [96]. It should be noted that evident differences with regards to sample dimensions (width to thickness ratio) and speed used for longitudinal sample movement/stretching have been recorded within the investigated dataset. Based on the published data, it is also worth noting that films containing PVA have been associated with both the highest and the lowest tensile strength values within the investigated dataset (120 MPa versus 0.001 MPa). The highest tensile strength was observed for the thin sample (around 40 μm) containing high MW PVA type (160 kD), while the lowest value was determined for very thick ODFs (around 700 μm) based on PVA with low MW (9–10 kD), indicating that polymer grades, as well as sample thickness may greatly influence ODF mechanical properties [42,97]. Investigation of the developed dataset revealed that, regardless of the employed film-forming agent, increased polymer load in ODF formulation results with increased sample resistance to fracture [10]; Kevadiya et al., n. d.2018; [98–100]. However, samples containing starch derivatives (such as MDX and PHPS) exhibited low tensile strength irrespective of the amount of polymer [39,59,78,101]. Although the investigated samples exhibited notable differences with respect to the resistance to fracture, their handling was not compromised, indicating that tensile strength might not be considered as ODF CQA. Fig. 5 represents the range of TS values observed with respect to the manufacturing method and polymer used (relevant data were extracted from the database based on the availability of tensile strength values reported; 2D printed films were excluded, as they are essentially solvent casted to be further used for active ingredient deposition). Relatively wide range of TS values observed for solvent casted HPMC films should be interpreted taking into account the number of studies dealing with this polymer/-manufacturing method combination, and the fact that different additional excipients are usually included in the formulation. On the other side, range of TS values reported for 3D printed films was narrow and more consistent irrespective of the polymer type (MDX, PVA or PEO). It appears that 3D films had low mechanical strength, but small number of included studies must be taken into consideration. The impact of manufacturing method was most prominent in the case of PVA based films, where highly uniform TS values in the range of 5.8–28 MPa have been observed in the case of solvent casted films, and 6–9 MPa for 3D printed films, while PVA films obtained by electrospinning exhibited great variability with regards to TS values observed (6.1–120 MPa).

Puncture resistance is another parameter used for ODF mechanical properties characterization [72,73,96,102]. Puncture resistance test is performed by fixing ODF sample within a holder followed by moving probe downward with the predefined speed until film rupture. In order to accurately calculate relevant parameters, information on cross sectional area of the probe pushing the samples is needed. However, it was noticed that different research groups have used various probe sizes, shapes and movement speed. The use of a cylindrical probe with flat-faced surface might be advantageous in comparison to spherical probe, as the area directly affected by the strain can be easily defined and used for parameters calculations [103]. Puncture strength, Young's modulus and deformation at break (elongation-to-puncture) are the most commonly discussed parameters when puncture resistance test is performed. Results obtained by the puncture resistance test were generally lower in comparison to those determined by tensile test, due to different ways of sample deformation [68].

Folding endurance (FE) is another parameter affected both by tensile strength and elongation at break that can be used for additional ductility/brittleness and flexibility evaluation [45,99]. Authors usually express FE as a number of times a film can be folded in the same place until it breaks or visible cracks appear. Different approaches can be seen, as films are folded manually [81] or by automatic measurement system [82,99]. Takeuchi and co-workers developed in-house apparatus for FE determination, reported remarkably high values for ODF FE (above 4400), while in the case of manual evaluation those values usually did not exceed 300. Results of ODF folding by hand are highly dependent on the way it is performed by different individuals which might be the reason for observed variability in the presented dataset where folding endurance ranged from 1 to 1200 times [99].

Moisture content can significantly affect ODF mechanical properties and is recognized as critical factor for ODF shelf life and storage conditions determination [78], although certain level of residual moisture is necessary to maintain proper ductility upon storage [84]. Based on the investigated dataset (34/112 papers), moisture content generally did not exceed 15%, however, Takeuchi et al. [99] reported moisture content higher than 30% for HPMC-based ODF with high glycerol load. Increased residual moisture content might lead to pronounced film stickiness which negatively affects product handling [67]. It was observed that ODFs made with higher molecular weight film-forming agents generally exhibited lower moisture content [37,67]. Samples plasticized with hydrophilic compounds like glycerol, are prone to higher water absorption. Borges et al. [28] reported that addition of glycerol may cause increased moisture adsorption. It may be noted from the developed dataset that films containing glycerol had higher moisture

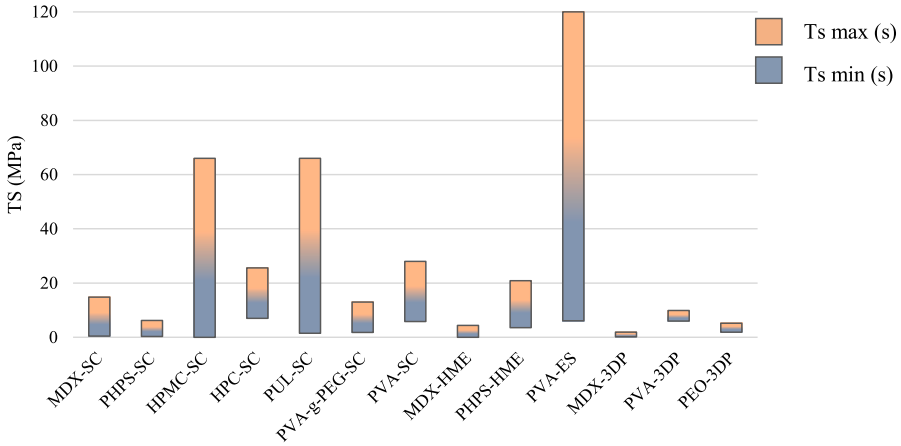

Fig. 5. Visual representation of the experimentally obtained range of tensile strength (TS) values for ODFs prepared using various polymers and different manufacturing methodsYoung's modulus reflects film rigidity i.e., film resistance to permanent deformation, accordingly, high values are related to extreme sample stiffness/rigidity. Within the investigated dataset, high Young's modulus values, up to 5500 MPa, were observed for PVA-containing samples [105], while the lowest values were reported for MDX-based films [39, 59]. Elongation at break, indicator of film ductility, ranged from 0.36, up to 1000%. For the majority of investigated ODFs, elongation at break did not exceed 100% [35]. reported that too high elongation at break values (260–340%) determined for ODFs containing combination of PVA and PVP disable proper film packaging or cutting into single-dose units due to extensive flexibility. Nevertheless, it was shown in another study that, although samples containing only PVA exhibited elongation at break between 313 and 745%, their mechanical properties were considered as acceptable [86]. In addition, handling difficulties were not reported in the case of MDX-based films having elongation at break values up to 1000%, although due to low tensile strength, high risk of breaking might be expected [21,39,58].

content (0.6–36%) compared to films containing sorbitol (0.6–3.5%) or PEG 400 (2.2–6.6%). Although it might be expected that residual moisture content depends on the manufacturing method employed, including drying conditions, review of the investigated dataset did not show any evident influence of the manufacturing method employed. It is noted that electrospun films had significantly lower values for moisture content, compared to 3D and casted films with similar formulation and might be resulting from the increased surface area [55].

3.2.2. ODF disintegration and drug dissolution

Disintegration is considered as the key ODF quality attribute. Although there is a number of commercially available pharmaceutical products and dietary supplements in the form of ODF, compendial methods for their characterization and relevant requirements are not fully defined. Careful review of the ODF dataset revealed various approaches for disintegration testing regarding: (i) test medium volume ranging from 0.1 to 900 ml; (ii) medium type (mainly purified water, phosphate buffer or various simulated salivary fluids); (iii) temperature (25 or 37 °C); (iv) agitation (none or continuous or occasional shaking (60–300 rpm), immersion (28–30 dpm) or 90° inversions); and (v) mechanical force implementation (by attaching the 0.72–5 g weight). In the majority of tests, disintegration end-point is not well defined which poses additional obstacle as ODFs containing different film-forming agent exhibit different behavior upon contact with medium [96]. Having in mind above mentioned differences between the proposed methods, all disintegration approaches might be classified in one of the following categories: (i) compendial method for solid dosage forms disintegration testing; (ii) adapted compendial method aiming standardization of film position with or without simulation of tongue force; (iii) drop or slide frame method with limited media volume, with or without mechanical force; (iv) film disintegration in suitable container, with or without mechanical agitation and (v) others. The frequency of use of different disintegration methods based on the proposed classification is presented in Fig. 6.

In order to standardize disintegration end-point assessment and facilitate ODF characterization, different modifications of the official approach have been introduced, including: (i) utilization of the arm for ODF positioning that operates under the same conditions as the official apparatus [22]; or (ii) addition of suitable holders enabling more precise assessment of disintegration end-point [96,104]. In addition, Preis et al. [96] evaluated the impact of tongue force by attaching the weight on the bottom side of the film, during testing. The total weight of 3 g was chosen based on the reported findings that minimal force detected during tongue licking over the probe is 0.03 N [96]. Disintegration end-point is indicated by dropping down of the clipped weights. Garsuch and Breitkreutz [95] proposed a simple ODF disintegration/dissolution test with one drop of medium (Slide frame method/Drop method). Film is framed and positioned on Petri dish and one drop of medium is added. The time taken for the drop to dissolve the film and form the hole within it is defined as disintegration end-point. End-point was assessed also as the time needed for drop to fall on the bottom of the disintegration assembly [63]. Steiner and coworkers (2019b) adjusted slide frame tester by adding the ball of defined weight (4 g) in order to better mimic conditions in oral cavity and facilitate disintegration end-point observation (Slide frame and ball method). The most diverse category of disintegration approaches includes assessment of ODF disintegration time in different types of containers (Petri dish, beaker, vessel, glass vial) after medium addition, with or without agitation. Additional obstacle that prevents direct data comparison represents lack or clear disintegration end-point. In different methods, end-points are defined in different manners: the moment film starts to break, film disintegrates into small parts or completely dissolves. Comprehensive literature overview revealed that disintegration methods utilized in several papers couldn't be categorized in any of the proposed categories, and were assigned as "other". Interested readers may find additional information in Refs. [96,97,105]. Although, adapted compendial methods, as well as different modifications of drop method provide clear end-point determination, Petri dish method and similar, poorly standardized procedures are more widely used for ODF characterization. Review of the published data (ODF dataset) revealed great divergence in the obtained disintegration times, regardless of the method applied, ranging from 1 to 4900 s. It is interesting to note that both values were determined in ODFs having the similar composition (HPMC, glycerol and MCC) differing only in the casting height and MCC content. However, remarkable difference might be attributed to different disintegration approaches employed [72]. Considering high variability of factors affecting film disintegration, such as type and concentration of the film-forming agent, addition of superdisintegrants, plasticizers or different fillers, and diversity in film size and thickness, direct comparison of the obtained data is hard to accomplish. Nevertheless, based on the papers reporting concomitant use of different disintegration testing approaches, several assumptions can be made: (i) longer disintegration times are observed in methods with poor hydrodynamic mixing and smaller medium volume (e.g. Slide frame vs Petri dish method) [49,69,86,106]; (ii) remarkably longer disintegration time was observed when end-point is defined as complete film dissolution [72,95]; (iii) adapted compendial methods with weights provide shorter disintegration time in comparison to compendial method due to clear end-point and mechanical force impact [72,104] and (iv) in case of methods simulating tongue force rapid disintegration is observed when higher medium volume was employed [107]. According to the presented dataset, it is clearly evident that ODFs manufactured by electrospinning possess highly porous structure that disintegrates within few seconds, despite pronounced film thickness (>300 μm) [45,47].

Despite the fact that various approaches are developed in order to mimic conditions in the oral cavity, lack of correlation between *in vitro* disintegration time and *in vivo* ODF behavior is clearly evident. There are several papers reporting on the comparative *in vivo* and *in vitro*

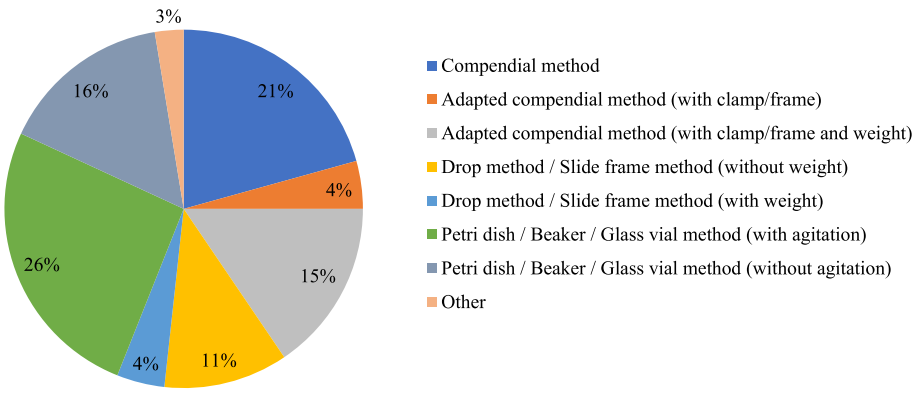

Fig. 6. The frequency of use of different ODF disintegration methods.

disintegration assessment [14,34,39,46,63,65,82,85,91,104]. Saab et al. [104] investigated applicability of four *in vitro* disintegration methods including: (i) compendial method; (ii) compendial method with frame (iii) cell method (comparable to slide frame and ball method) and (iv) adapted compendial disintegration test with sample holder and weight, for *in vivo* disintegration time prediction. Strong positive correlation between the *in vitro* and *in vivo* determined results was established ($r > 0.97$), irrespective of the method applied. Disintegration times determined by compendial method were quite longer in comparison to those determined by methods with weight, but the obtained data were comparable to the *in vivo* observed disintegration times. Similar findings were also reported by Refs. [34,65,82]. Establishment of quantitative correlation between *in vitro* and *in vivo* disintegration time is of the utmost importance in order to confirm applicability of the proposed methods. Based on the investigated dataset, ratio between the *in vivo* and *in vitro* disintegration times ($R_{DT\ in\ vivo/in\ vitro}$) reported from different studies using various disintegration methods were calculated. Data obtained are presented in Fig. 7 where each bar represents average value of the $R_{DT\ in\ vivo/in\ vitro}$ calculated for formulations investigated within one study.

Data reported from 7 studies were taken into consideration. The employed disintegration testing included compendial method for solid dosage forms disintegration time assessment [34,65,82,104] adapted compendial method with sample holder and weight; slide frame and ball method [104] and different Petri dish methods [14,46,82,85]. The number of panelists involved in the individual studies ranged from 6 to 16 [65,82], while the number of formulations tested ranged from one [14,46,85] to 14 [82]. In the majority of studies HPMC was used as film-forming agent [34,65,82,85,104]. Interestingly, values of the ratio between the *in vivo* and *in vitro* disintegration time were close to unity for the *in vitro* data obtained using compendial disintegration apparatus [34,65,82]. The highest ratio value (4.56) was obtained for the adapted compendial disintegration test with sample holder and weight [104], while results obtained using the Petri dish model were variable, with the relevant ratio between the *in vivo* and *in vitro* data ranging from 1.04 in the case of solvent-casted ODF containing HPMC [85] to 2.96 for electrospun fibers prepared with PVP [46].

High variability of disintegration times (DT) observed might be attributed to different testing conditions employed. However, contribution of the impact of film-forming polymer and manufacturing method should also be considered. In Fig. 8 relevant data were extracted from the database based on the availability of DT values for the same polymers as presented in Fig. 5, also, 2D printed films were excluded, as they are essentially solvent casted to be further used for active ingredient deposition. It can be seen that HPMC-based ODFs prepared by solvent casting exhibit wide range of DT values. As discussed for TS values, this observation may be attributed to the number of studies dealing with HPMC as film-forming agent, and the fact that addition of other excipients impact film disintegration. MDX-based films exhibited rather fast and uniform disintegration irrespective of the manufacturing method employed (SC, HME or 3DP).

Orodispersible films are usually designed with the goal to achieve immediate drug release after administration, followed by rapid therapeutic effect onset. However, in order to reduce the frequency of dosing, there were attempts to develop modified release products. Based on the investigated dataset, modified drug release from ODFs was accomplished by preparation of: (i) drug-ion exchange resins [88]; (ii) lipid or polymer dispersion coated microparticles [59,108]; (iii) matrix particles [73]; or by utilization of successive casting (layered structure) [109] or hot-melt extrusion [39]. Musazzi et al. [59] used maltodextrin ODF as a platform for innovative delivery system combining free drug and solid lipid microparticles providing sustained drug release, for at least 5 h.

Although dissolution testing may provide valuable information about the influence of different formulation factors and process parameters on pharmaceutical product performance, relevant methodology and specifications for ODF characterization are not established. As stated above, different approaches to evaluate drug release from ODFs were reported from 71 (out of 112) studies. Compendial dissolution apparatuses, i.e., the rotating basket, rotating paddle and flow-through cell apparatus employing various testing conditions were employed in 64 studies, while various non-compendial methods aimed to more closely simulate conditions in the oral cavity, were employed in 13 studies. One of the advantages of the rotating basket apparatus is sample positioning within the basket, however, adhesion to the basket mesh and clogging may occur affecting negatively drug release [110]. In order to provide standardized film positioning, various types of holders [61,67,88,108] or film adhesion onto suitable carriers [5,42,55,88,111,112] have been proposed. Different non-compendial dissolution assemblies included the use of glass cylinder, vials, beakers or Petri dish positioned on a laboratory shaker using different agitation intensity (10–150 rpm) with the media volume ranging between 5 and 300 ml. Krampe et al. [93] proposed new dissolution assembly simulating biorelevant conditions in the oral cavity. The proposed setup, designated as the Punch & Filter Method is based on the paddle apparatus with the addition of a device which consist of a sample holder – frame with the filter, and the 14 g punch which imitates tongue force. In order to optimize the testing conditions Krampe et al. [93] investigated drug dissolution in the compendial rotating paddle apparatus and novel Punch and Filter method in which prolonged drug dissolution was observed. Regardless of the dissolution method applied, dissolution time for 80% drug released ($Q_{80\%}$) varied between few seconds [58] to 40 min [77] for immediate release ODF preparations. It is interesting to note that both lowest and highest $Q_{80\%}$ values were determined for formulations containing maltodextrin as the film-forming agent. The difference observed

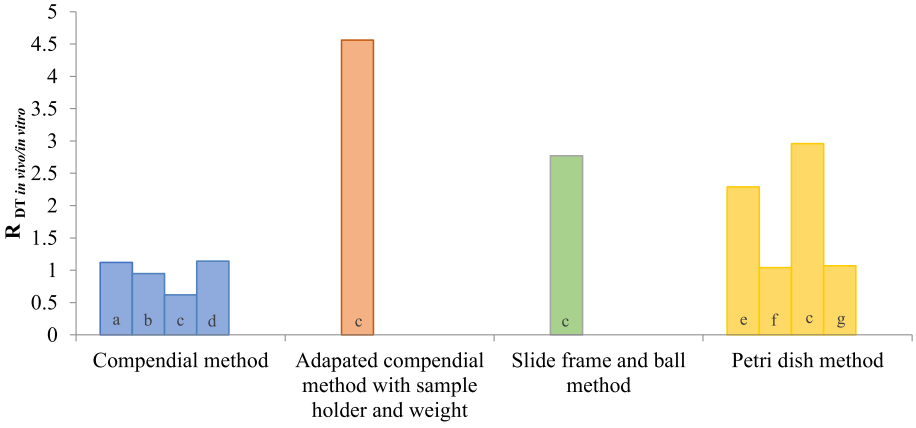

Fig. 7. Review of *in vivo/in vitro* disintegration times ratio obtained for different disintegration methods (*letter in brackets refers to relevant study: a* – Liew et al. [65]; b – Liew et al. [34]; c - Saab et al. [104]; d – Liew et al. [82]; e – Pimparade et al. [14]; f – Khan et al. [85] and g - Samprasit et al. [46].

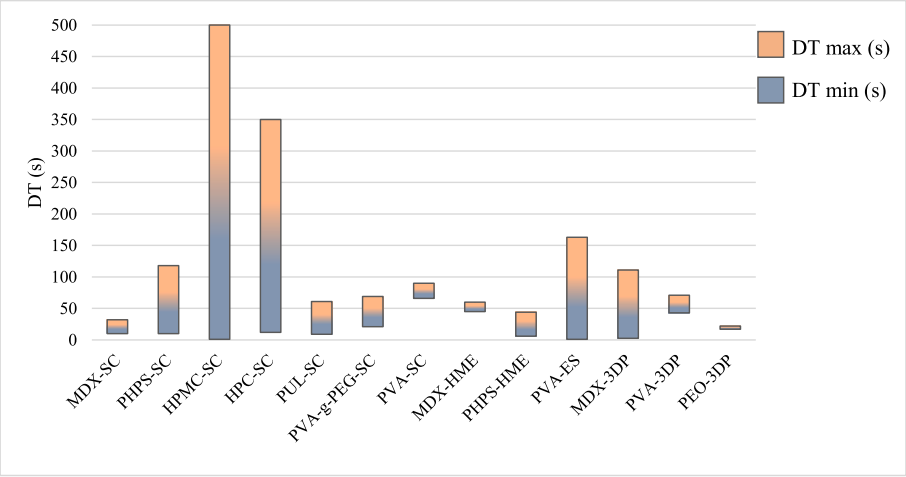

Fig. 8. Visual representation of experimentally obtained ranges of disintegration time values for ODFs prepared using various polymers and different manufacturing methods.

might be attributed to drug substance solubility, since highly soluble nicotine and poorly soluble quercetin have been used as model drugs in the fast and slow dissolving ODF formulations, respectively [58,77]. Such findings are in line with the findings reported by other authors [45,67,71]. However, in the case of highly soluble drug substances, drug particle coating or incapsulation is often used as taste masking approach which may negatively affect drug release [87,88]. Solid dispersions preparation [55,60,61] or drug nanonization (Kevadiya et al., n.d.2018 [37,62,74,91,98,113,114]; have been investigated as ways to enhance poorly soluble drug dissolution. However, based on the analysis of the investigated dataset, drug release from ODFs is affected mainly by the type and content of the film-forming agent [37,38,55,62,69,81,84,115–119]. Polymer content, molecular weight and swelling properties can be identified as critical factors affecting drug release from ODF. Despite the influence of formulation constituents, it was also noted from the investigated dataset that ODF samples prepared by 3D printing [6,13,47,54] generally exhibited faster drug dissolution than samples prepared by solvent casting, probably due to higher porosity and surface area.

3.3. Sensory ODF attributes

Considering that ODFs reside in the oral cavity until complete disintegration, and paediatric and elderly patients as target populations, ODF palatability has been recognized as important factor that can markedly affect patient adherence (EMA, 2013, 2017). Sensory attributes designated as palatability include pharmaceutical product appearance, smell, taste, mouthfeel and aftertaste [120]. It is of the utmost importance to identify formulation properties affecting the end-user acceptability, as well as, to develop *in vitro* methods for quantitative estimation of palatability attributes and prediction of ODF sensation [63]. There are several *in vitro* methodological approaches for solid dosage forms taste assessment, including utilization of taste-sensing system (electronic tongue), or evaluation of in situ drug dissolution by UV spectroscopy [121]. Based on the investigated dataset, it appears that in the majority of publications efficiency of the applied taste masking approach was evaluated *in vivo* through the human taste panel or animal taste preference tests [14,34,46,65,81,82,85,87,122]. Feasibility of electronic tongue application was, also, assessed and the obtained results indicate great ability of this device to differentiate between drug-free samples, formulations without the applied taste-masking approach and taste-masked samples [58,76,86,88]. However, for proper taste evaluation, it is inevitable to prepare large volume solutions which do not correspond well with the *in vivo* conditions after ODF administration and brings into question the reliability of the approach proposed.

In vitro assessment of mouthfeel, as physical sensation that is created in the mouth by drug product, is hard to accomplish. Above all, overall perception which is subject to change over time, arises from complex interactions between conditions in the oral cavity (especially presence of saliva), and administered drug products [123]. Considerable effort is focused on determination and selection of parameters which are indicative on the *in vivo* sensation and would decrease variability due to personal preferences [123]. Overview of the presented dataset revealed that key mouthfeel attributes associated with ODF administration include: intraoral disintegration time, roughness/grittiness, stickiness/adhesiveness, swallowability/comfort/ease of administration, and astringency [1,36,39,46,58,63,65,84,97,122]. Astringency, as it is more related to API properties, was successfully evaluated using the electronic tongue equipment, so it might be assigned more to taste, then to mouthfeel assessment [58]. Detailed overview of different mouthfeel attributes of importance for ODF development, as well as the applied *in vivo* and *in vitro* approaches for their evaluation are summarized in Table 1.

There are several studies reporting on the investigation of sensory perception and convenience of ODF disintegration *in vivo* [1,39,63,117]. However, only [1,63] related *in vivo* determined disintegration time with the subjective experience of drug administration. The obtained results revealed that ODF *in vivo* disintegration time between 1 and 3 min was perceived as somewhat uncomfortable, while fast disintegration (time less than 1 min) was evaluated as comfortable to extremely comfortable, irrespective of other film properties [63]. In support [1], reported that majority of panellist, also, perceived ODF disintegration time lower than 1 min as somewhat comfortable. Interestingly, in the study performed by Ref. [63]; only molecular weight of PVA or CMC used as film forming agents was found to influence both *in vivo* disintegration time and perception of ODF disintegration, and not the polymer type. Having in mind that limited product acceptability might be associated with poor patient adherence, acceptable specification for ODF disintegration time should be considered carefully. According to the available *in vivo* data, targeted disintegration time to fulfil patient expectation should be set to less than 1 min.

There are only three reports on the *in vivo* assessment of comfort after ODF administration related to overall convenience of administration and suitability of pharmaceutical form to be taken without water [39,65,84]. In addition, despite the fact that reported *in vivo* disintegration time was around 60 s, overall convenience of pregelatinized hydroxypropyl pea starch based ODFs administration was rated as high [84]. It was

Table 1
Overview of ODF mouthfeel attributes and *in vivo* and/or *in vitro* methods for their evaluation.

ODF mouthfeel attribute	*In vivo* assessment (No of human panellists)	*In vitro* evaluation	*IVIV* relationship reported	Ref.
Disintegration time	Five point hedonic scale (from extremely uncomfortable to extremely comfortable) + *in vivo* disintegration time recording (n = 24)	*Drop method* (framed sample, 0.2 ml deionised water (37 °C); end point – fall of the drop to the apparatus base located 1 cm away of the sample) *Petri dish method* (2 ml deionised water (37 °C) under gentle shaking; end point – start of breaking	The drop method provided results that better agreed with the *in vivo* determined disintegration time	[63]
	Five point hedonic scale (from extremely uncomfortable to extremely comfortable + *in vivo* disintegration time recording (n = 50)	n/a	n/a	[1]
Roughness/grittiness	Four point scale (from very satisfied to not at all satisfied) (n = 6)	n/a	n/a	[39, 84]
	Roughness versus smoothness (n = 6)	n/a	n/a	[46]
	Five scores (from gritty and irritating to very smooth) (n = 16)	n/a	n/a	[65]
	n/a	*Light interferometric microscopy* for surface roughness quantification *(*Sa value*)*	Comparing Sa results with a roughness detection threshold of a tongue – 200 nm	[55]
	Preliminary investigation with only few panellists (n = 3)	*Atomic force microscopy* for ODF topography evaluation	Maximum roughness of 5 μg might be considered as low	[35]
Stickiness/ adhesiveness	Five point hedonic scale (from extremely uncomfortable to extremely comfortable) (subjective assessment of *ODF stickiness intensity* and *stickiness perception*) (n = 50)	n/a	n/a	[1]
	Five point hedonic scale (from extremely uncomfortable to extremely comfortable) (n = 24)	*Adhesive force* measurements by texture analysis (sample was wetted with 0.2 ml of warm water (37 °C); a force of 2.308 N was applied to the sample and maintained for 12 s, before the probe was withdrawn at 0.4 mm/s *Adhesive force* measurements by dynamic mechanical analysis – DMA (sample was wetted with 0.45 ml of warm water (37 °C); clamps were broth together and the force of 2.649 N was applied to the sample before the clamps was withdrawn at predefined rate) + *area under the curve of the adhesive force versus time plot*	Results of DMA were in agreement with the perceived stickiness evaluated *in vivo (*values lower than 0.01 N/mm^2 are acceptable)	[63]
	Three-point scale (good, moderate and bad) (n = 5)	n/a	n/a	[36]
	n/a	*Bioadhesive strength measurements* (chicken skin humidified with 0.1 ml phosphate buffer pH 6.75, 0.5 mm/s to contact to chicken skin for 10 s (force 1 N) and the ascent rate was fixed at 1 mm/s)	n/a	[125]
Swallowability/ comfort/ease of administration	Five point hedonic scale (from extremely uncomfortable to extremely comfortable) (perception of *ODF size* and *thickness in the mouth*) (n = 24)	n/a	n/a	[63]
	Five point hedonic scale (from extremely uncomfortable to extremely comfortable) (perception of *ODF size* and *thickness in the mouth* and *saliva thickening effect*) (n = 50)	n/a	n/a	[1]
	Four point scale (from very satisfied to not at all satisfied) (perception of *convenience of administration, quickly of disintegration* and *suitability of pharmaceutical form for taking without water*) (n = 6)	n/a	n/a	[39]
	Four point scale (from very satisfied to not at all satisfied) (perception of *convenience of administration* and *suitability of pharmaceutical form for taking without water*) (n = 6)	n/a	n/a	[84]
	Five scores (from very poor to very good) (perception of *acceptance*) (n = 16, n = 12)	n/a	n/a	[34, 65]

reported, based on the *in vivo* assessment, that ODF size up to 6 cm^2 and thickness up to 350 μm was perceived as comfortable [1,63,65].

Considering relatively large ODF surface area (up to 10.6 cm^2) which comes into contact with tongue and upper palate, roughness, defined as degree of drug product surface irregularity [123] may impair end-user acceptance. Although in several *in vivo* studies panellist assessed formulation roughness, through overall subjective feeling of palatability, correlation between relevant physical features of polymer films and roughness sensation was not established [39,46,65,84]. [46] examined palatability of electrospun nanofiber mats and reported that smooth film surface (confirmed by scanning electron microscopy) provided lack of roughness sensation *in vivo*. Having in mind that ODF may incorporate poorly soluble drugs, sensation of roughness might be also associated with the presence of insoluble drug particles. The results obtained by Ref. [55] utilizing light interferometric microscopy, indicate that preparation of solid dispersions contributes not only to faster

drug dissolution, but also to lower roughness. An interesting approach for roughness estimation was proposed by Takeuchi and co-workers [99] who determined film roughness based on the difference between the measured and ODF thickness calculated based on the results of true density analysis. Atomic force microscopy was, also, successfully applied in order to assess roughness of ODF samples [35]. The same group conducted preliminary *in vivo* study with three participants to establish correlation between sample roughness and panellist sensation. The obtained results indicate that maximum determined roughness of 5 μm (although the investigated formulation contained approximately 40% of incorporated microparticles) was not perceived as rough [35]. Liew et al. [65]investigated *in vivo* disintegration time and palatability of donepezil ODFs prepared using different taste masking approaches. Interestingly, it was found that addition of sucralose as a sweetener contributed to mouth sensation of, otherwise, almost identical ODF samples.

ODF stickiness might be considered from three points of view: (i) potential influence on the manufacturing process [2,103,124]; (ii) ability to be properly handled [58,63] and (iii) the effect on the mouthfeel sensation [1,36,63]. The perceived product stickiness in combination with slow disintegration may impact adherence in patients suffering from dry mouth syndrome [1,63]. Opposite, higher stickiness might be favourable in order to accomplish therapeutic goals in non-cooperative patients [36,125]. Abdelhakim and associates (2020) investigated stickiness perception (related comfort/discomfort), as well as the intensity of stickiness. The absence of any correlation between these results was reported, indicating the presence of strong subjective and multifactorial influence on stickiness perception [63]. presented comparable trend between the *in vitro* measured parameter, such as adhesive force, and *in vivo* perceived stickiness, following ODF administration. Adhesive force was measured utilizing two different approaches: texture analysis and dynamic mechanical analysis with the instrumental parameters set up to mimic biorelevant conditions and enable methods comparison. It was shown that dynamic mechanical analysis provided better discrimination of the investigated samples. According to the presented data, adhesive force lower than 0.01 MPa and fast disintegration deemed to be optimal in order to avoid stickiness sensation *in vivo*. The same group reported that stickiness perception was mainly affected by the type of film-forming agent and its molecular weight [63]. It is interesting to note that among various investigated ODF sensory attributes, statistically significant difference between participant reported outcomes in terms of stickiness, disintegration time and thickness was observed indicating that those attributes determine to a large extent ODF acceptability in healthy, young adults, which merits further consideration in pharmaceutical development [63].

ODF sensory attributes include also the overall film appearance and handling properties which are associated with the ease of administration and patient acceptability. These parameters have been estimated based on visual inspection, ease of handling [65,78,83], size and thickness acceptability [63] and stickiness [21,78]. Overview of the approaches employed for ODF ease of handling evaluation is depicted in Table 2.

[78] reported that handling difficulties may be associated with: (i) brittle films, which exhibit low elongation at break, high Young's modulus and pronounced tensile strength and (ii) sticky films, which exhibit low Young's modulus, low film strength and high elongation at break. Moreover, samples with lower elongation at break values exhibited brittleness and tendency to break easily [78]. Hence, to facilitate handling, it is expected for films to be flexible, with suitable tensile strength and without observed adhesion to packaging material or patient fingers. It was reported that, besides the type of film-forming agent, increase in the plasticizer content resulted in the increased film stickiness [21]. In order to standardize assessment of film stickiness, method based on the measurement of the film detachment force following application of the constant force for the specified period of time was applied [39,58,97].

3.4. PK data

ODFs are primarily designed to rapidly disintegrate in the oral cavity and be easily swallowed in order to provide drug release and absorption from the gastrointestinal tract. It is, however, arguable if drug absorption may also occur via oral mucosa, as certain amount of drug may dissolve even during the short ODF residence in oral cavity. In order to predict *in vivo* drug absorption and facilitate formulation development, physiologically based pharmacokinetic (PBPK) modeling and simulation might be utilized. The Oral Cavity Compartmental Absorption and Transit (OCCAT) model, combined with the Advanced Compartmental Absorption and Transit (ACAT) model (GastroPlus™ software, Simulations Plus Inc.) has been developed as a tool to simulate pharmacokinetic profiles and the fraction and rate of intraoral drug transit/absorption Up to date, OCCAT™ model was used mostly for assessing the bioperformance of buccal and sublingual intraoral dosage forms i.e., sublingual tablets [126,127], buccal tablets [128], buccal films [129,130], and only two studies investigated the absorption routes of drugs incorporated in ODFs [67,89]. The main outcomes indicated that the rate and extent of drug absorption via oral mucosa depend mostly on the drug physicochemical properties, including its molecular weight, solubility, ionization constant and partition coefficient, as well as the product residence time in the oral cavity, while saliva flow rate did not affect drug absorption. The results obtained indicate that, due to short residence time in the mouth, majority of drug absorption occurs in the gastrointestinal tract and that amount of drug absorbed via oral mucosa may be considered as negligible [67,89]. In order to evaluate the applicability of the PBPK model developed [89], conducted *in vivo* study in Beagle dogs, which confirmed good agreement between the *in vivo* and *in silico* data. This publication is also a confirmation that rather good *in silico* predictions of drug (intraoral) absorption can be made not only in humans, but also in animals. However, more *in vivo-in silico* studies are needed to evaluate the possible drug absorption via oral mucosa after ODF administration.There are few more reports on the ODF bioavailability studies conducted *in vivo* in humans [131] and animals (rats, rabbits or dogs) [41,84,89,117,132]; Kevadiya et al., n.d.2018; [69,75]. As the reference formulations in these studies, marketed tablet formulations are usually employed and the results obtained indicate

Table 2
Overview of approaches employed for ODF handling assessment.

ODF handling	Assessment approach	Ref.
Stickiness	*In vitro* (texture method usually used for the measurement of the tack of pressure sensitive adhesives; constant force of 0.05 N was applied onto the sample for 5 s after which, the probe was removed at the constant velocity of 5 mm/s)	[39,58]
	In vitro (texture method; force of 500 g was applied onto film followed by probe removal at constant rate of 0.5 mm/s)	[97]
	Tactile (five-point hedonic scale, from extremely uncomfortable to extremely comfortable)	[63]
	Tactile (thumb tack test; the thumb was pressed lightly on sample for a short time followed by quick withdrawn; three-point scale, from no sticky to very sticky)	[21]
Ease of handling	Five scores (from very brittle to very ease to handle)	[65]
	Five-point hedonic scale (From extremely uncomfortable to extremely comfortable)	[1]
	Five-point hedonic scale (from extremely uncomfortable to extremely comfortable)	[41,63]
	(Organoleptic assessment of size and thickness on handling)	

Table 3
Quality target product profile.

QTPP element	Target	Justification
Drug load	Up to 120 mg	Limited by ODF size and tendency of drug to recrystallize
Film-forming agent	Various, mostly hydrophilic polymers (MW 10–1300 kDa)	Polymer selection depends on manufacturing method; In order to achieve rapid disintegration, lower content of polymers with high MW should be employed
Plasticizer	Glycerol PEG 400 Sorbitol	Although the presence of plasticizer is necessary for mechanical properties optimization, content of plasticizer has to be properly optimized in order to avoid high moisture content, pronounced stickiness and preparation instability
Dimensions	Size 1–6 cm^2 Thickness <350 μm	Very small ODF may be considered unacceptable regarding film handling, while sizes higher than 6 cm^2 might attribute to poorer patient acceptability
Mechanical properties	Young's modulus 100–1500 MPa	Specific, mainly, to the polymer type
	Elongation at break <100%	High film elongation at break values are generally associated with handling difficulties and inaccurate dosing
Moisture content	<10%	Higher values might be associated to pronounced stickiness and handling difficulties
Disintegration time (*in vitro*)	<60 s (<20 s)	In order to assure patient comfort *in vivo* disintegration time should be set to less than 1 min, If compendial method is used, disintegration time should not exceed the same time frame, while in the case of methods with limited media amount and tongue force influence this time might be shortened to 20 s.
Palatability	Acceptable taste	Inclusion of different flavours, aromas and sweeteners in order to improve patient adherence
	Acceptable mouthfeel	It is based mainly on the lack of stickiness perception (*in vitro* determination of adhesive force under biorelevant conditions)

comparable plasma level-time profiles [117,132]. Furthermore, in the majority of presented publications improved bioavailability was observed following administration of drug nanoparticles loaded films in comparison to commercially available tablets [131], comparable ODF formulation [133] or oral suspension (Kevadiya et al., n.d.2018).

4. Concluding remarks

Quality by Design approach in pharmaceutical development entails identification of targeted drug product characteristics which should be reached in order to meet the patient needs in terms of drug efficacy, safety and acceptability, designated as Quality Targeted Product Profile (QTPP). There are limited data available on ODF quality attributes of interest for the targeted drug product profile [32,78]. proposed desired range for disintegration time, dissolution time, and certain mechanical properties of placebo prepared films containing pregelatinized hydroxypropyl pea starch or hydroxypropyl methylcellulose. However, these assumptions were based on the relatively small number of experimental data obtained for formulations containing the same film-forming agents [28]. defined acceptable values for CQAs through detailed study of several commercially available samples, which might serve as a guide for strategic drug development. However, it may be argued that ODF CQAs should include, besides disintegration time and mechanical properties, also relevant sensory attributes which may affect patient acceptability and readiness to take the drug.

Further research and increased body of knowledge is necessary in order to identify meaningful Critical Process Parameters (CPPs) for innovative manufacturing methods which are mainly used for ODF manufacture. Current review indicates that information about the process parameters employed are often missing or poorly described in relevant publications. Given the differences between the manufacturing methods which are still evaluated in terms of their applicability and usefulness for ODF manufacture, method specific CPPs would have to be further elaborated and defined.As concluding remarks, based on the comprehensive analysis of the investigated dataset, an attempt was made to propose ODF specific QTPP as a framework and guidance which may facilitate pharmaceutical development. The proposed QTPP is presented in Table 3.

CRediT authorship contribution statement

Erna Turkovic: Conceptualization, Data Curation, Visualization, Writing - original draft. **Ivana Vasiljevic:** Writing - review & editing. **Milica Drašković:** Conceptualization, Data Curation, Visualization, Writing – original draft. **Jelena Parojčić:** Conceptualization, Draft review, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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A comprehensive assessment of machine learning algorithms for enhanced characterization and prediction in orodispersible film development

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ABSTRACT

Orodispersible films (ODFs) have emerged as innovative pharmaceutical dosage forms, offering patient-specific treatment through adjustable dosing and the combination of diverse active ingredients. This expanding field generates vast datasets, requiring advanced analytical techniques for deeper understanding of data itself. Machine learning is becoming an important tool in the rapidly changing field of pharmaceutical research, particularly in drug preformulation studies. This work aims to explore into the application of machine learning methods for the analysis of experimental data obtained by ODF characterization in order to obtain an insight into the factors governing ODF performance and use it as guidance in pharmaceutical development. Using a dataset derived from extensive experimental studies, various machine learning algorithms were employed to cluster and predict critical properties of ODFs. Our results demonstrate that machine learning models, including Support vector machine, Random forest and Deep learning, exhibit high accuracy in predicting the mechanical properties of ODFs, such as flexibility and rigidity. The predictive models offered insights into the complex interaction of formulation variables. This research is a pilot study that highlights the potential of machine learning as a transformative approach in the pharmaceutical field, paving the way for more efficient and informed drug development processes.

1. Introduction

Orodispersible films (ODFs) are recognized as innovative dosage forms that can facilitate personalized patient treatment through customizable doses. Their ability to rapidly disintegrate in the oral cavity without the need for water makes them especially suitable for patients with swallowing difficulties, such as the elderly and children (Patel et al., 2015; Christmas and Rogus-Pulia, 2019). These films can be tailored to individual needs by adjusting the dosage through size customization, and by combining different active pharmaceutical ingredients (APIs), highlighting their potential in personalized therapy (Morath et al., 2022). Also, the interest in ODFs as extemporaneous preparations highlights their value in personalized therapy, enabling the precise modification of doses, formulation components, especially flavours to improve patient compliance (Visser et al., 2017). While ODFs have certain limitations, such as low drug loading capacities, suited primarily for APIs with low effective doses, advancements in manufacturing techniques like inkjet and 3D printing have expanded their application range (Ferlak et al., 2023, Tian et al., 2023; Carou-Senra et al., 2023a; Salawi, 2022). The mechanical properties of ODFs, including elongation at break, Young's modulus, and complex modulus, are crucial to their performance, but standardized testing and specifications are currently lacking in the European Pharmacopoeia (Ph. Eur. 11, 2023; Turković et al., 2022). Elongation at break is essential for assessing the flexibility of ODFs, ensuring they can endure physical stresses during handling and storage without breaking. Young's modulus is critical for ensuring that the films can stretch and revert to their original shape and the complex modulus is vital for maintaining structural integrity until proper application, ensuring the films withstand pressures encountered during packaging and handling (Turković et al., 2022).

A large amount of data generated over the years has not resulted with a clear explanation of how different formulation factors influence ODF critical quality attributes. Therefore, it seems necessary to bridge this gap by using previously obtained experimental data to predict future performance-related ODF characteristics. The employment of machine learning algorithms can help bridge this gap and enhance the development process (Alpaydın, 2014; Sarker, 2021). Machine learning

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algorithms have become increasingly important in data analysis, particularly due to their ability to gain insights from data by learning from previous experience. These algorithms have the ability to recognize the complex patterns in data that can be used to classify or predict outcomes in a variety of contexts (Alpaydın, 2014). Their application spans a wide range of tasks including, but not limited to, improving prediction accuracy in classification problems, refining financial models through regression analysis, improving market segmentation through data clustering, optimizing feature selection in feature engineering, reducing data complexity through dimensionality reduction, and improving decision-making processes through reinforcement learning. However, the performance of machine learning algorithms depends on the quality of the input data and the complexity of the algorithmic design (Sarker, 2021). Clustering, a machine learning technique, is the process of organizing data into several groups (K), ensuring that elements within each group share a high degree of similarity, while minimizing the similarity between different groups (Jain et al., 1999). Nowadays, automatic clustering is predominantly employed, which autonomously identifies the number and structure of clusters within a dataset, without requiring prior knowledge about the attributes of the data (Ezugwu, 2020). The k-means clustering algorithm, known for effectively assigning samples to clusters, has limitations like random centre initialization affecting convergence and the need to predetermine cluster numbers, often based on *ad hoc* decision and influenced by data complexity. The x-means algorithm, addressing these issues, uses the Bayesian Information Criterion (BIC) to automatically determine the optimal number of clusters by evaluating model scores across different initializations. Beyond clustering, various machine learning algorithms excel in classification and prediction within large datasets (Jain et al., 1999; Pelleg and Moore, 2000; Hamerly and Elkan, 2002; Ahmed et al., 2020). Apart from clustering, a variety of machine learning algorithms exist that are capable not only of classifying but also predicting values within large datasets. The Support Vector Machine (SVM) is an advanced method for classification, later extended to vector regression for predicting outcomes. As a kernel-based algorithm, SVM utilizes kernel functions and adapts to various applications, optimizing a hyperplane that maximizes the margin between data points (Fig. 1). The closest points, termed support vectors, define the hyperplane's position and direction. These points, based on data features, classify each observation, allowing the hyperplane to accurately label new data (Alloghani et al., 2020; Pisner and Schnyer, 2019).

The Random Forest (RF) algorithm, used for classification and regression, creates multiple decision trees to improve prediction accuracy (Fig. 2). By aggregating these trees, RF outperforms single tree models, dividing data based on criteria like mean square error for regression until a termination condition is met, and then averaging these tree-based predictions (Breiman, 2001; Scornet, 2016; Schonlau and Zou, 2020). Deep learning (DL), based on a multilayer feedforward artificial neural network, is mimicking biological neurons, to establish complex relationships between inputs and outputs (Fig. 3). Its architecture comprises input, hidden (processing data non-linearities), and output layers (delivering predictions). DL model multilayer feedforward artificial neural network training involves stochastic gradient descent,

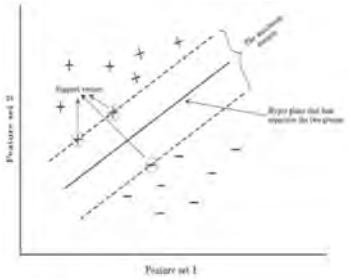

Fig. 1. Support vector machine.

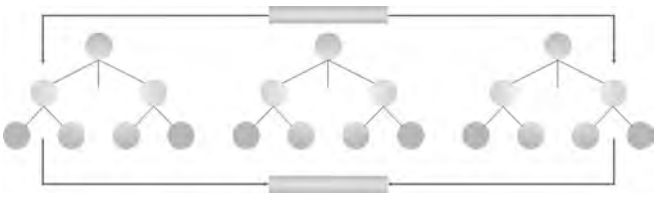

Fig. 2. Random forest algorithm.

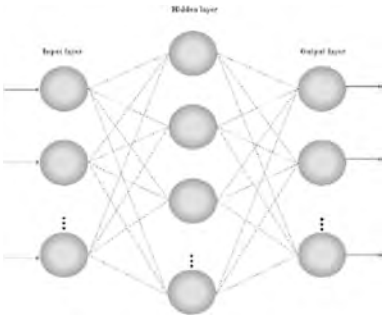

Fig. 3. Deep learning algorithm.

minimizing loss by adjusting per data example, and backpropagation, calculating gradients to refine accuracy (Marini et al., 2007; Candel and LeDell, 2021). RF and SVMs are known for accurate predictions and managing large datasets with low overfitting risk. Their effectiveness across many applications has established them as capable general-purpose algorithms (Biau, 2012). Multi-layer feed-forward artificial neural network algorithms are much more complex and have the advantage over traditional machine learning algorithms because they perform better when learning from large datasets (Svozil et al., 1997). Recent studies have demonstrated the effectiveness of machine learning in accelerating the development of orodispersible films, highlighting its potential to enhance formulation optimization and predictive analysis (O'Reilly et al., 2021, Carou-Senra et al., 2023b).

This work aims to explore the integration of machine learning algorithms in the analysis of experimental data for ODFs, with the goal of uncovering the underlying factors that influence ODF performance. Specifically, it examines how SVM, RF, and DL algorithms can be effectively utilized to predict ODF characteristics critical to performance, based on data derived from sample clustering. This approach aims to provide valuable insights and guidance for pharmaceutical development, leveraging the predictive power of machine learning to enhance the formulation and optimization of ODFs.

2. Materials and methods

2.1. Materials

Eight hydrophilic polymers were investigated as film-forming agents: (1) hydroxypropyl cellulose (HPC, Klucel® GF, Ashland™, USA), (2) hypromellose (HPMC, Pharmacoat 606, Shin-Etsu Chemical Co., Japan); (3) carboxymethylcellulose sodium salt (CMC-Na, Fluka Chemie AG, Switzerland), (4) polyethylene glycol–polyvinyl alcohol graft copolymer (PVA-PEG, Kollicoat® IR, BASF, Germany), (5) maltodextrin (MDX, Glucidex IT12, Roquette, France), (6) sodium alginate (SA, Fisher Scientific, USA), (7) poly(ethylene oxide) polymers (PEO N10, POLYOX™ WSR N10, DuPont, U.S.) and (8), poly(ethylene oxide) polymers (PEO N80, POLYOX™ WSR N80, DuPont, U.S.). Glycerol (Gly), 85 % (w/w) (Ph.Eur) was used as plasticizer, and magnesium aluminometasilicate (NUF, Neusilin UF, Fuji Chemical Industries Co, Japan), croscarmellose sodium (CCS, Primellose®, DFE Pharma, Germany), crospovidone (CP, Polyplasdone™ XL-10, Ashland™, USA),

sodium starch glycolate (SSG, Primojel®, DFE Pharma, Germany), calcium silicate (CaS, RxCIPIENTS® FM1000, Huber Engineered Materials, USA) were used as disintegrants (D). Active pharmaceutical ingredients (APIs) ibuprofen (IBU), paracetamol (PAR), caffeine (CAF), enalapril (EN), verapamil (VP), atenolol (AT), carvedilol (CAR) (Ph. Eur) were used as model substances. Purified water (Ph. Eur) was used as solvent.

2.2. Methods

2.2.1. Sample preparation

Samples were prepared by solvent casting method. Formulation components were used in a predetermined ratio based on the literature data and preliminary experiments. HPMC polymer was used in concentrations of 5 and 10 %. PVA-PEG and CMC-Na were also used at a concentration of 5 % and PVA-PEG at a concentration of 7 %, as were the other polymers. Samples were prepared with the addition of glycerol (Gly) as plasticizer in concentrations of 0.25–1 %, and in some formulations various disintegrants were also added. The concentration of the disintegrants was constant at 0.5 %. The aim was to include a relatively wide range of concentrations and combinations of constituents and perform their characterization using the same methodology. For the preparation of polymer casting dispersions, relevant polymer was dissolved in water and glycerol mixtures with or without addition of the selected active ingredient and/or disintegrant. The dispersions were stirred on a magnetic stirrer (IKA RCT standard, Germany) and casted on unit-dose plexiglas plates. Equal mass of dispersion was casted for each formulation, so that the thickness of the wet dispersion is the same for each sample. The obtained films were dried for 24 h under ambient conditions, cut into pieces of defined size (2.5 × 2.5 cm), packed and stored in a desiccator.

2.2.2. Weight and thickness

Weight and thickness of the prepared samples were assessed. For the assessment of weight, a total of ten samples were weighed, with the variation among them being reported in the form of a mean value to provide a concise summary of the collective weight data.

In the case of thickness measurements, a micrometre screw (IP65, Kern & Sohn GMBH, Germany) was employed to determine the thickness of another set of ten samples. These measurements were taken at five distinct points across each sample, including the centre and the four corners, to ensure a comprehensive understanding of the sample's uniformity in thickness and the results were presented as mean value.

2.2.3. Mechanical properties

Mechanical properties were investigated using the Precision universal tester (Shimadzu EZ-X, Shimadzu Corporation, Japan). Bone-shaped samples (Fig. 4) were clamped with the extension grips which moved at a speed of 5 mm/min until sample breakage. Applied test generated a stress–strain graph, which showed how material reacted when the force is being applied. Tensile strength (TS), Young's modulus (YM) and elongation at break (EB) were calculated using equations (1–3).

Oscillatory rheometry (RheometerRheolab MC 120, PaarPhysica, Germany) was used to assess viscoelasticity of the investigated samples, based on the complex modulus (CM) values. Linear viscoelastic region was determined for the investigated samples (amplitude sweep) after which all the measurements were performed at the constant strain (1 %) within frequency range 0.1–10.0 Hz. Complex modulus is calculated using the equation (4) (Drašković et al., 2020).

$$TS\ (MPa) = F/A \tag{1}$$

F represents maximal applied load and A is the cross-sectional area

$$EB\ (\%) = 100 \times (\Delta L_0)/L_0 \tag{2}$$

ΔL0 is the change in the specimen length and L_0 is the specimen original length

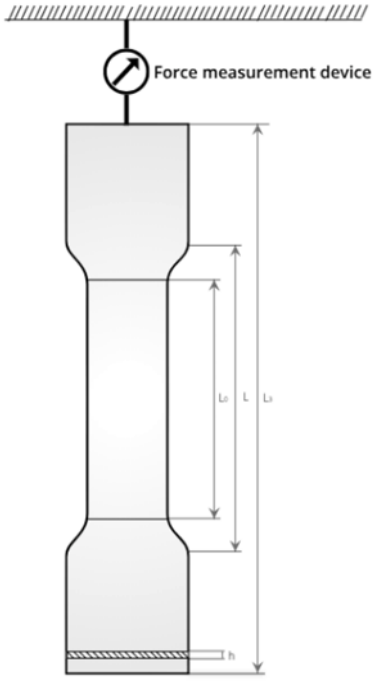

Fig. 4. Bone-shaped specimen.

$$YM = (\sigma 2 - \sigma 1)/(\varepsilon 2 - \varepsilon 1) \tag{3}$$

σ2 − σ1 is the applied stress over strain ε1 and ε2.

Additionally, L is the initial distance between grips, h is thickness and L_3 overall length.

$$|G^*| = \sqrt{((G')^2 + (G'')^2)} \tag{4}$$

G* Complex modulus, G′ storage (elastic) modulus and G″ loss (viscous) modulus.

2.2.4. Disintegration time

The disintegration time (DT) of the investigated samples was measured employing a modified disintegration method, as outlined by Preis et al. (2014). In this procedure, films were securely clamped in place using a film holder, with a 3-gram weight attached to the film's underside. This setup aims to simulate the force exerted by the tongue within the oral cavity. The endpoint for disintegration was defined as the moment when the weight fell to the bottom of the vessel, signifying complete film disintegration. To ensure reliability, each sample was tested in triplicate, and results were reported as mean values, providing a comprehensive overview of the disintegration behaviour of the films.

2.2.5. Data mining

2.2.5.1. Dataset preparation. In order to provide comprehensive and uniform input data, dataset was built using results obtained in the present study, as well as from the previous study conducted by our group (Drašković et al., 2020). The outlier operator was employed to detect the number of outliers and eliminate them from the dataset. The applied operator was detecting distance-based outliers measuring the distance of a point from its k^{th} nearest neighbour. Each point was rated based on its distance to k^{th} nearest neighbour and the top n points were declared to be outliers (Ramaswamy et al., 2000).

2.2.5.2. Data clustering. Different machine learning models were developed, and their clustering and predictive power were evaluated for

the generated dataset. RapidMiner 9.10.011 software (RapidMiner Studio, USA) was used for model development. RapidMiner is an open-source interactive machine learning and data mining software implemented in Java. It provides complex nested operator chains for a wide range of learning problems. RapidMiner uses XML to describe the operator trees that model knowledge discovery processes. RapidMiner has flexible operators for data input and output in various file formats. It includes more than 100 learning schemes for classification, regression and clustering tasks (Naik and Samant, 2016).

The preprocessing tasks, including normalization of data were included into data and loaded into the software which then clustered data using x-means algorithm. Values are scaled using normalization to provide attributes a uniform scale for unbiased comparison. The true value of K is estimated in an unsupervised way and only based on the dataset itself. K_{max} and K_{min} as upper and lower limits for the possible values of X were set as recommended (Zendrato et al., 2020). K_{min} is set to the lowest number 2 and K_{max} is set to 20. Based on the threshold values, a decision tree was automatically generated by software to explain which data points are part of each cluster.

2.2.5.3. Predictive models development. Data was filtered and some film properties were chosen to be target attributes in additional modelling based on the clustering results.

The development of the models began with dividing the dataset into training and testing groups with 70:30 split, a crucial step to ensure the models' ability to generalize to new data, as emphasized by Pisner and Schnyer (2019). To maintain consistency across the dataset, stratified sampling was utilized, ensuring that each subset mirrored the overall distribution of classes within the dataset. Some missing values were presented for one attribute (complex modulus), which were addressed by calculating the average of the available values for complex modulus and using this average to fill in the gaps. This approach was deemed reliable as the outlier detection algorithm, employed in the pre-processing stage, confirmed that these missing values did not significantly impact the dataset's overall integrity, showing no extreme values that could tilt the average. During the tuning phase, cross-validation was employed as a key strategy. This involved systematically dividing the dataset into several folds, training the model on a subset of these folds, and validating it on the remaining fold. This cross-validation process was repeated multiple times, cycling through all folds, to optimize the model's hyperparameters. For the Random Forest model, hyper-parameters such as the number of decision trees and their maximum depth were adjusted. In the case of Support Vector Machines, the focus was on tuning the penalty parameter (C) and the kernel coefficient (gamma). The performance of each model was evaluated to assess the predictive quality of the models. For regression tasks, coefficient of determination (R-squared) values were calculated to measure the proportion of variance explained by the model to ensuring a balance between predictive power and the ability to generalize to unseen data.

3. Results and discussion

3.1. Dataset preparation

The dataset consisted of a total of one hundred ODF samples of which seventy-four were prepared within the present study, and twenty-six were included from the previous study published by our group (Draskovic et al. 2020). Overview of the Dataset structure and range of values related to the investigated samples composition and their characteristics is presented in Table 1. Detailed information is provided in the Supplementary data. Representation of different polymers and model active pharmaceutical ingredients in the dataset is visualised in the Fig. 5.

Majority of samples (28 %) were prepared with HPMC as the most commonly used polymer for ODF, which is consistent with trend observed in the literature (Turković et al., 2022), while IBU was the most commonly used active ingredient (15 % of samples represented in the Dataset). Model active ingredients were dissolved or dispersed in the liquid phase and categorically linked to this information, with 0 indicating no active ingredient, 1 indicating dissolved, and 2 indicating dispersed. Plasticizer was set as the ID (identification) attribute, i.e., it serves as an identifier for the dataset and is not utilized in the data modelling.

The weight of the investigated ODF samples varied between 46 and 180 mg and their thickness ranged from 66 to 358 μm. The HPMC-based films had the lowest weight at a polymer concentration of 5 %. The samples prepared with MDX polymer at a concentration of 7 % had noticeably higher weight compared to the other samples. Formulation of the MDX-based films was not particularly different, so the difference in weight cannot be attributed to differences in formulation factors. The thickness was predominantly in the limits of 350 μm, which is considered comfortable for patient acceptance (Liew et al., 2012, Scarpa et al., 2018, Abdelhakim et al., 2020). The initial wet mass thickness was the same for all films, but different film compositions, especially the presence of dispersed API and/or disintegrants, resulted in different behaviour during drying and the formation of uneven surface. HPMC-based films with a polymer concentration of 5 % showed the lowest thickness values, which corresponds to the lowest sample weight. HPC-based films with the addition of API showed higher thickness values, similar to PVA-PEG samples, also, with the addition of API.

The mechanical properties of the evaluated samples showed a range of values for tensile strength (Fig. 6) from 0.1 to 83 MPa, elongation at break from 0.7 to 272 %, Young's modulus from 0.3 to 5381 MPa and complex modulus with values ranging from 0.02 to 180 MPa (Figs. 7-9). The lowest values for tensile strength were obtained for the MDX-based samples, which is consistent with the literature data indicating that films prepared with starch-based films have lower strength values (Cilurzo et al., 2008, Manda et al., 2018, Musazzi et al., 2019). CMC-Na films exhibited the highest tensile strength values, which decreased significantly with the addition of API. SA and CMC-Na based samples exhibited the highest Young's modulus values, indicating brittle structure susceptible to cracking, which was also evident when handling the samples. With the exception of HPC-based samples, which showed noticeably higher values from 6.7 % to 272.9 %, Elongation at break was generally low for rest of examined samples (i.e., ranging from 0.7 % to 33.8 %).

The dataset contained only complex modulus attribute with missing data, which was attributed to the inability of samples formulated with MDX and PEO polymers to withstand the test's high-pressure conditions, leading to their damage during the process. Despite this, results from the intact samples were included to enrich the dataset and potentially offer deeper insights into the film's structural properties. Disintegration time is critical quality attribute for ODFs (Borges et al., 2017). To remove subjectivity from the test, a modified disintegration test was conducted with the addition of a magnet (3 g), the fall of which was designated as the clear test endpoint. The results obtained indicate that the majority of films disintegrated for the time shorter than 60 s (Fig. 10), which is often considered to be comfortable for the patients, but some samples had disintegration time longer than 1 min, which can be perceived as uncomfortable for the patients (Scarpa et al., 2018). However, there are still no precise guidelines regarding the disintegration time of ODFs. The European Pharmacopoeia (2023) specifies that orodispersible films should disintegrate quickly in the mouth, but it doesn't specify the maximum value for disintegration time or even the proper technique for obtaining it. The 180 s disintegration time required for orodispersible tablets by Ph. Eur. 11.0. (2023) is sometimes cited as the disintegration time recommended for films, despite the fact that two dosage forms are entirely different.

3.2. Data clustering

Within the examined dataset, sample containing paracetamol as a model drug, CP as a disintegrant, and MDX as the film-forming polymer

Table 1
Overview of collected data for the dataset.

Film forming polymer			Active pharmaceutical ingredient		Disintegrant		Plasticizer		ODF Characteristics						
type	MW (kDA)	C (%)	type	C (%)	type	C (%)	type	C (%)	W (mg)	TH (μm)	YM (MPa)	TS (MPa)	EB (%)	CM (MPa)	DT (s)
MDX	15.4	7	IBU PAR	1.5	NUF CP	0.5	Gly	2.5	140–180	124–221	1.54–228.95	0.08–1.62	0.98–14.33	n/a	16–27
PVA-PEG	45	5, 7	IBU CAF CAR AT VP	1.5, 2, 3	CP CCS SSG	0.5	Gly	0.25–1	91–112	156–264	47.91−530.00	1.83−13.31	2.35−33.80	0.73−180	27–68
HPC	370	7	IBU CAF EN	1, 1.5	CP CCS SSG	0.5	Gly	0.25–1	72–136	102−358	0.32−373.55	0.10−7.20	6.70−272.91	0.58–148.00	24–104
HPMC	13	5, 10	VP IBU	1, 2	CP CCS SSG	0.5	Gly	0.5, 1	45–140	66−152	92.96−2199.35	7.90−47.01	1.11–13.86	1.06−19.52	13–102
SA	400	7	CAR	2	CP CCS SSG	0.5	Gly	1	85–128	78–130	3498.00−5381.15	41.02–63.71	0.88–2.50	1.37–90.35	21–74
CMC-Na	260	5	CAF	1	CP CCS SSG	0.5	Gly	0.5, 1	70–90	75–100	2371.58−5001.15	21.50–83.27	0.68−4.24	0.02−42.71	22–52
PEO N10	100	7	/	/	CP CCS SSG	0.5	Gly	1	79–90	133–149	57.81−150.91	0.44−1.35	0.91−1.49	n/a	6–10
PEO N80	200	7	/	/	CP CCS SSG	0.5	Gly	1	54–81	96–144	92.40−231.91	0.76−2.30	1.15–1.63	n/a	3−7

MW – molecular weight; C – concentration; YM – Young's modulus; TS – tensile strength; EB – elongation at break; CM − complex modulus; W – weight; TH – thickness; DT – disintegration time, HPC − hydroxypropyl cellulose, HPMC − hypromellose, CMC-Na − carboxymethylcellulose sodium salt, PVA-PEG − polyethylene glycol–polyvinyl alcohol graft copolymer, maltodextrin − MDX, SA − sodium alginate, PEO N10 and PEO N80 − poly(ethylene oxide) polymers Gly – Glycerol, NUF − magnesium aluminometasilicate, CCS − croscarmellose sodium, CP – crospovidone, SSG − sodium starch glycolate, CaS − calcium silicate, IBU – ibuprofen, PAR − paracetamol, CAF − caffeine, EN − enalapril, VP − verapamil, AT − atenolol, CAR − carvedilol.

Fig. 5. Distribution of the used polymers and active ingredients in the investigated samples.

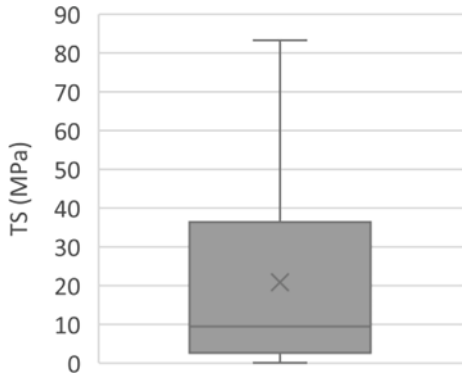

Fig. 6. Tensile strength value distribution in dataset.

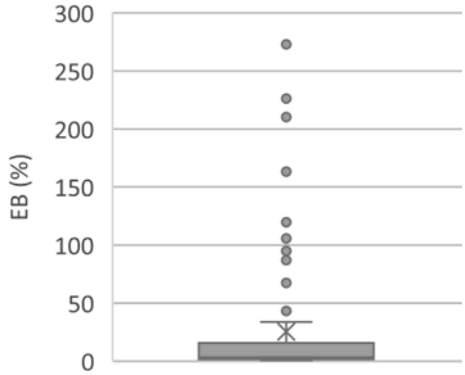

Fig. 7. Elongation at break value distribution in dataset.

was identified as outlier, disturbing dataset uniformity. Upon its removal, the uniformity requirement was fulfilled.

When dealing with attributes across varied units and scales, normalization is crucial to align values within a specific range. This process led to identifying three optimal clusters for presented dataset:

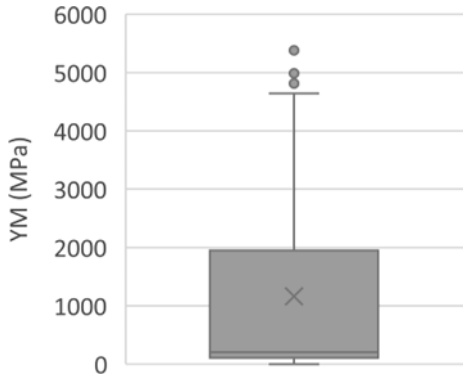

Fig. 8. Young's modulus value distribution in dataset.

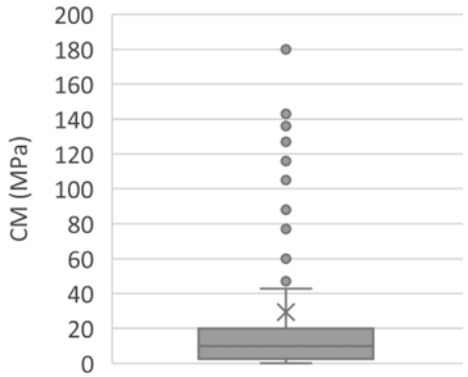

Fig. 9. Complex modulus value distribution in dataset.

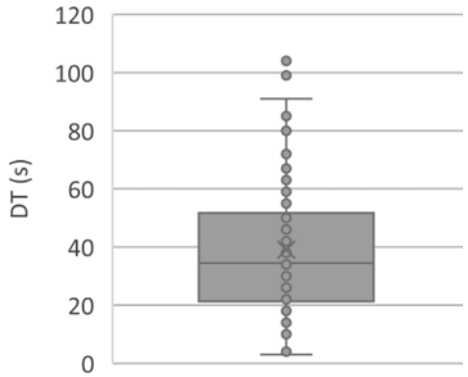

Fig. 10. Disintegration time value distribution in dataset.

Cluster 0 with 51 elements, Cluster 1 with 24, and Cluster 2 with 25. Cluster 0 is characterized by significantly lower values in elongation at break, complex modulus, and polymer concentration, over 50 % smaller than those in the other clusters. Cluster 1 exhibits lower elongation at break values but polymer and API concentrations are over 70 % higher. Conversely, Cluster 2 shows the highest elongation at break and complex modulus values, but its Young's modulus is nearly 90 % lower compared to the others, illustrating distinct clustering based on attribute significance (Fig. 11).

The decision tree in Fig. 12 serves as a visual aid, illustrating how data attributes influence clustering by displaying threshold values. Elongation at break is decisive attribute, with values above 38.55 % guiding data to Cluster 2. Data with elongation at break $\leq$ 38.55 % undergo further division based on complex modulus (>or $\leq$ 58.355 MPa) sample weight and polymer molecular weight. Attributes like thickness, polymer concentration, Young's modulus, and the addition of

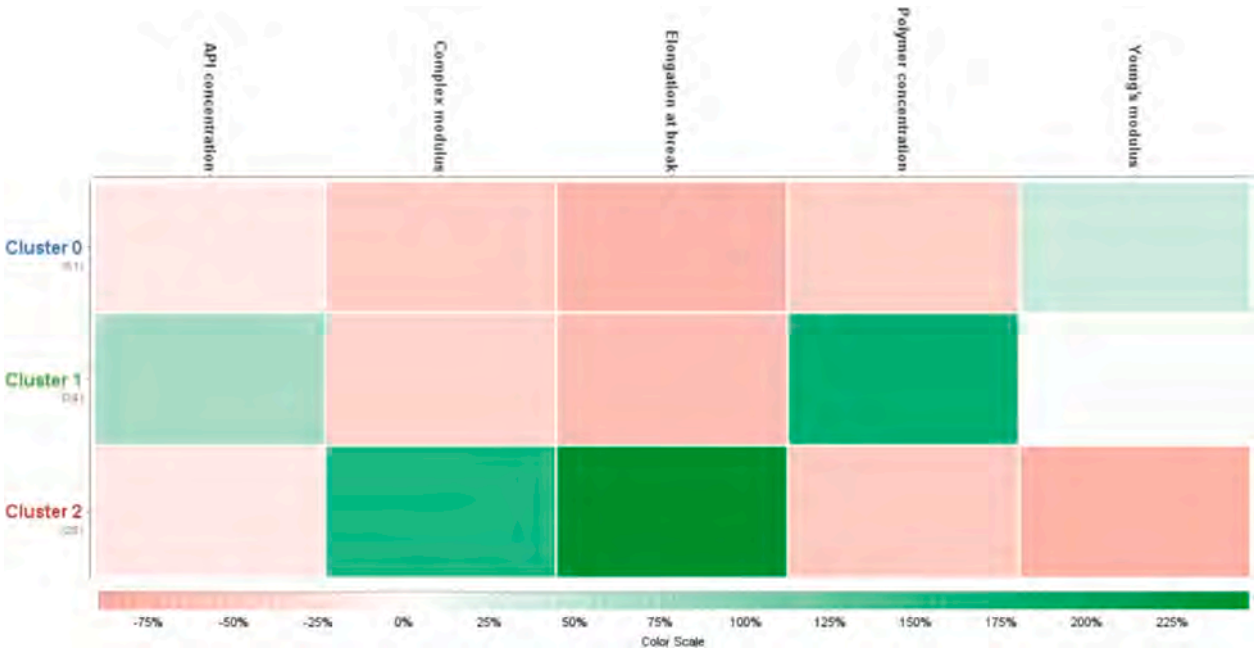

Fig. 11. Heatmap of attribute values by cluster: darker green shades denote greater values, lighter green shades lower values, and rose-coloured shades the reverse. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

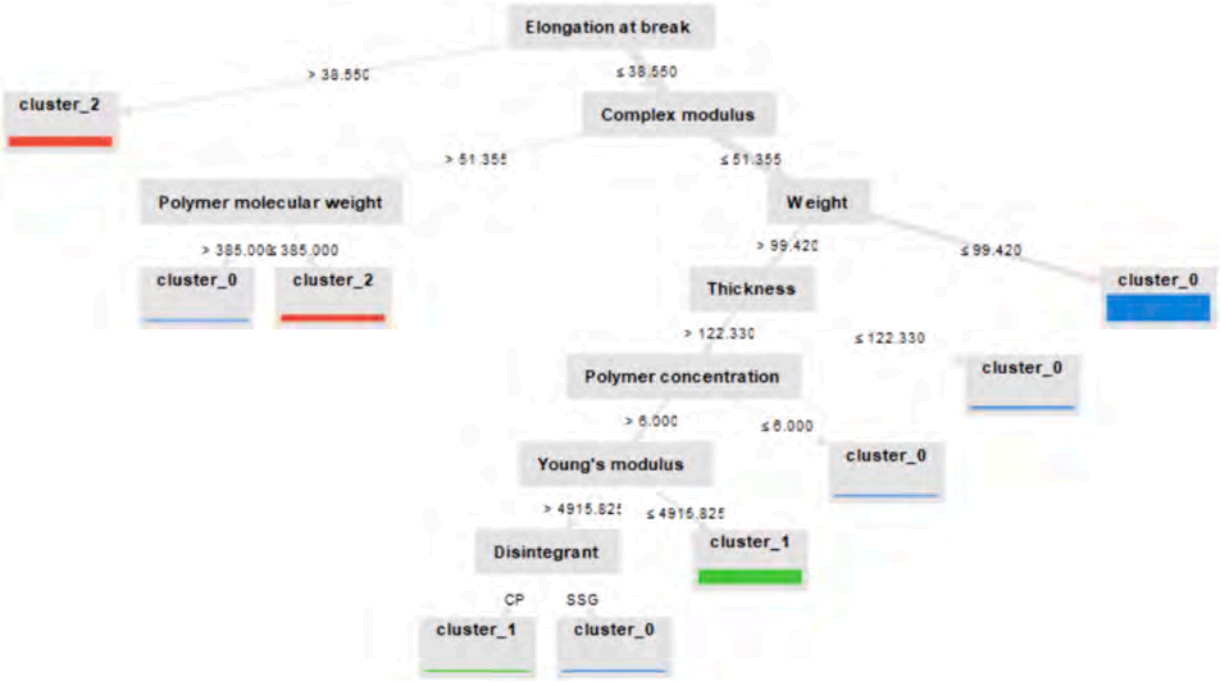

Fig. 12. Explanatory decision tree generated by RapidMiner Studio.

a disintegrant delineate the allocation into Clusters 0 or 1, offering a clear graphical interpretation of the clustering logic and the impact of various film characteristics.

3.3. Predictive model development

To enhance the predictive analysis of orodispersible films three different predictive models, i.e. Support vector machine (SVM), Random forest models (RF) and Deep learning (DL) were developed. These models focus on crucial attributes—Elongation at Break (EB), Young's Modulus (YM), and Complex Modulus (CM)—identified as key differentiators in ODF characteristics. Three attributes were selected by the algorithm as the most important for distinguishing ODFs and consequently their predictive models could potentially facilitate future ODF development. Each model showed good correlation between the predicted and actual data (Table 2). For model development, target attributes were selected based on their importance for clustering the data.

In the SVM predictive model, a Radial Basis Function kernel is used because the model must handle nonlinear problems. SVM models were developed by choosing gamma and C values before data training, which are considered as tuning parameters (Guenther and Schonlau, 2016). In Fig. 13 model performance is evaluated using accuracy and F1-score as

Table 2
Comparative overview of coefficients of determination for evaluated modeling techniques.

	Correlation values for the developed models		
Attributes	SVM	RF	DL
EB	0.96	0.97	0.90
YM	0.92	0.97	0.97
CM	0.81	0.93	0.88

the primary metrics. These metrics were chosen to provide a comprehensive assessment of model precision and robustness under varying configurations of C and gamma. The contour lines in the plot represent constant values of accuracy and F1-score, visually depicting how adjustments to C and gamma influence the model's predictive capabilities. The gamma parameter plays a critical role in determining the shape and flexibility of the decision boundary. The regularization parameter C controls the trade-off between increasing the space between data points and reducing the prediction error on the training dataset. The optimal values were chosen by measuring the model performance by calculating the cross-validation mean squared error, guiding the selection of optimal C and gamma parameters for the SVM model to achieve precise predictions. For the elongation at break, gamma 0.05, and C 1000. In the case of Young's modulus, gamma 5 and C 1000, and for complex modulus, 0.005 and 10, for the gamma and C, respectively.

The RF were constructed to have the lowest possible error rate, i.e., good model performance, as low values of the error rate indicate that the model makes fewer incorrect predictions (Breiman, 2001). In the tuning process of the RF model, the error rate was determined by evaluating the out-of-bag error, which is an internal error estimation method intrinsic to the RF algorithm. Error rate was lowered by fine-tuning the maximum depth and number of decision trees. Maximum depth was limited between 2 and 7 to avoid overfitting, as deeper trees increased errors. The optimal count of decision trees is detailed in Table 3.

DL models were trained to forecast values adhering to a Gaussian distribution, ensuring that the model outputs align with the characteristics of a normal distribution, as outlined by Lippmann (1988). To optimize model performance, the quadratic loss function was employed, quantifying the model's accuracy by calculating the average of the squares of the differences between predicted and actual values. The architecture of the predictive models proved crucial in enhancing data analysis, structured with an input layer that initially receives the dataset, followed by two hidden layers adept at processing and interpreting complex patterns. The final output layer efficiently delivers precise predictions. This configuration facilitates effective data processing and ensures accurate predictions of key orodispersible film characteristics. Furthermore, each model incorporates highly significant data points from the dataset, emphasizing their essential role in predicting outcomes.

Fig. 14 depicts the attribute importance as determined by machine learning models, illustrating the impact of various attributes on predicting characteristics of orodispersible films. The figure was generated using RapidMiner's feature importance tool, which calculates and normalizes the influence scores for each attribute based on their contribution to model accuracy.

Polymer type emerged as a critical factor across all predictive models. For the DL, the only exception was the complex modulus, where the importance was slightly lower. When analysing the dataset, it might be noticed that HPC-based films have higher elongation at break values compared to the other samples. Only HPC-based samples exceed elongation at break values above 100 %, which is considered a value above which materials are able to handle excessive loading without failure (Palomba et al., 2014). In contrast, films made with other polymers display markedly lower elongation at break values, often around 5 %, and with some CMC-Na samples the values were close to 0 %, which is typically associated with brittle and fragile materials (Palomba et al., 2014). Interestingly, variations in polymer, disintegrant, and plasticizer concentrations appear to have minimal impact on elongation at break predictions, suggesting that elongation at break values remain stable even with significant changes in polymer concentration, as evidenced by HPMC-based samples where doubling the concentration from 5 % to 10 % did not notably alter elongation at break values. This might indicate that the fundamental characteristics of the materials, rather than changes in formulation, play a more significant role in determining how flexible the sample is. The highest values for Young's modulus were obtained for samples containing either SA, CMC-Na or HPMC as film-forming polymer. Young's modulus, or modulus of elasticity, is the parameter that is correlated to the material stiffness, i.e., it indicates the extent to which film samples can be physically deformed and still recover their original shape. Samples prepared with these polymers showed a distinct range for this parameter, with CMC-Na having values between 2300 and 5000 MPa, SA between 3500 and 5000 MPa, and HPMC between 700 and 2000 MPa. API concentration attribute was important in predicting the Young's modulus. Placebo samples, i.e., samples with a numerical value of 0 % for ATP concentration, had higher Young's modulus values compared to the same polymer samples with an API concentration of 1 to 3 %. This suggests that API incorporated into the polymers results in less stiff samples and a change in mechanical properties. For the SVM model, disintegrant and plasticizer concentration are important attributes for prediction, implying that perturbations to the film structure caused by the addition of various excipients could contribute to the change in stiffness and mechanical properties. Comparing the prediction models to the elongation at break models, the attributes with lower importance are not as distinctive.

Table 3
RF model evaluated parameters.

Models	Maximal depth	Number of trees
EB	7	60
YM	7	140
CM	4	140

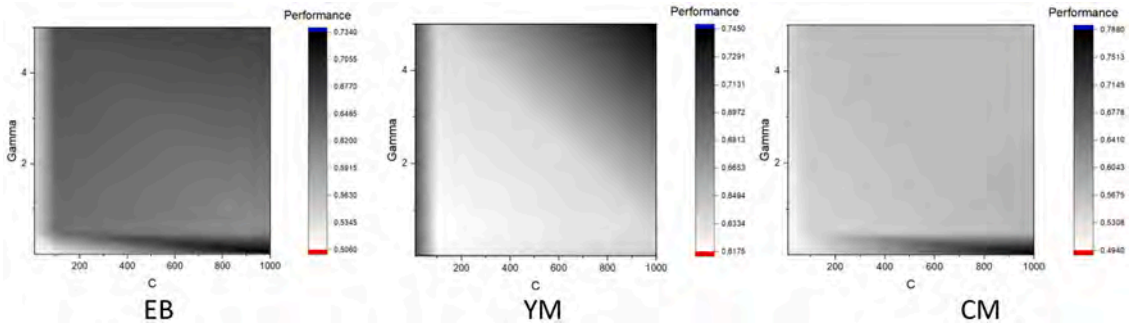

Fig. 13. Contour plot of model performance as a function of tuning parameters C and gamma for each of the evaluated output parameters.

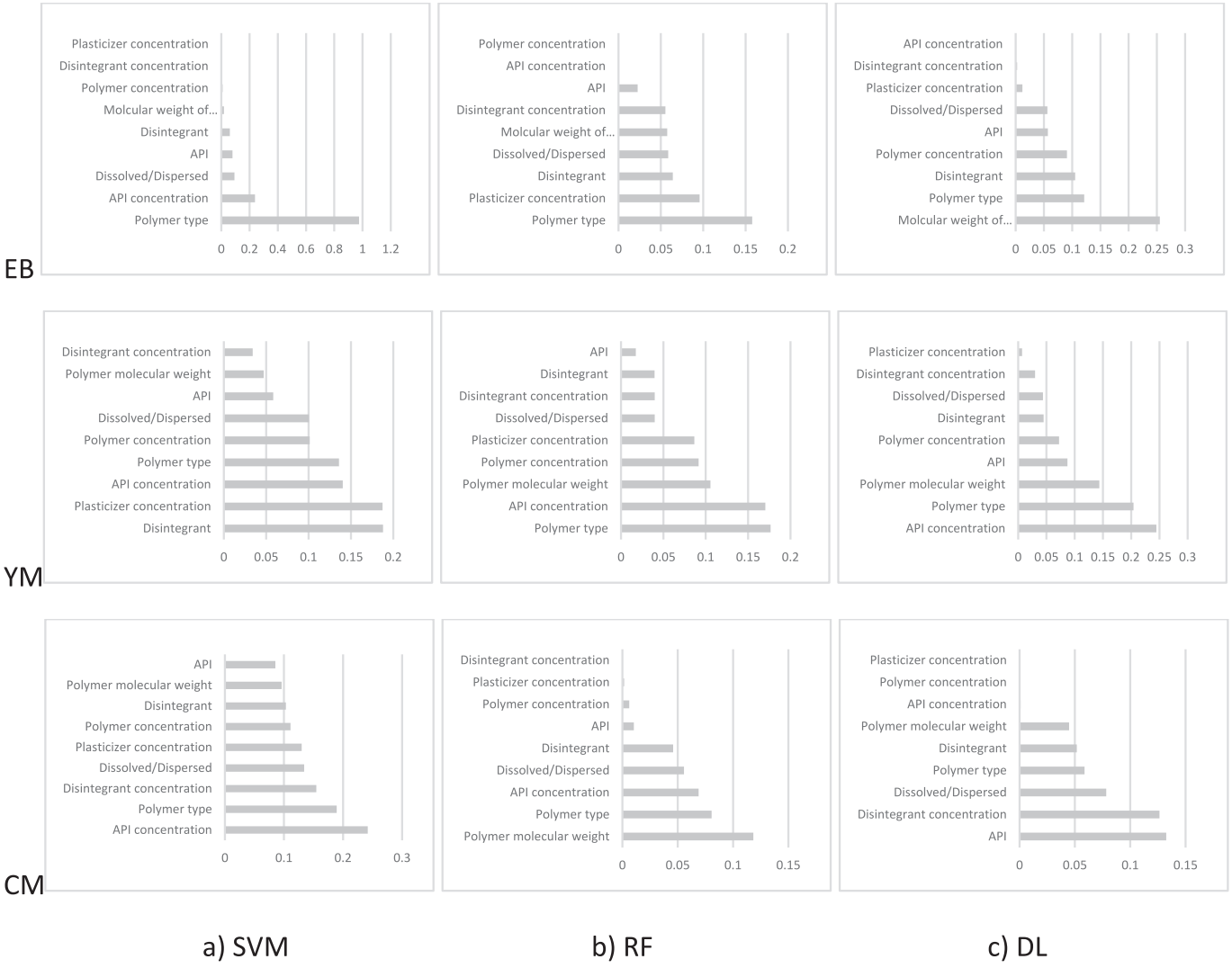

Fig. 14. Attribute weight for the created models.

Interaction between the attributes could not be disregarded for the Young's modulus and therefore all attributes contribute to model performance. The complex modulus values were not impacted by the type of polymer, unlike the Young's modulus values, and the complex modulus range of values was not as broad. Complex modulus and Young's modulus parameters have been previously linked, as more rigid structure is indicated by higher complex modulus and Young's modulus values, which is an indicator of system's overall resistance to strain (Drašković et al., 2020). Interestingly, the highest values were obtained for the samples with the lowest plasticizer concentrations, but the models did not estimate plasticizer concentration as an important attribute. Each model that was built to predict complex modulus rated different attributes as more important and were not comparable in terms of attribute importance.

Models that were built have validated several well-established facts in the field of ODF development. The models confirmed the critical role of polymer type in influencing the mechanical properties of ODFs, a finding consistent with current literature. This validation underscores the reliability of modeling approach and aligns with established formulation principles, such as the influence of polymer molecular weight and concentration on film strength and flexibility.

Beyond validating existing knowledge, the models unveiled new insights that could advance ODF formulation strategies. The analysis revealed that certain combinations of polymers and plasticizer, previously underexplored, significantly affect the mechanical properties of the films. These novel findings suggest potential pathways for formulating ODFs with optimized performance and mechanical strengths, tailored to specific pharmaceutical requirements. Moreover, the models identified unexpected patterns in the data, such as the minimal impact of disintegrant concentration on certain film properties, prompting need for further investigation. The presentation of these two aspects confirms the dual value of the machine learning approach: Confirming known formulation factors and uncovering new avenues for research and development in ODF technology. This extended discussion not only addresses the gap between machine learning insights and domain knowledge, but also emphasises the need for future empirical studies to explore these new insights.

The analysis highlighted the intricate relationships among different components in orodispersible film formulations, emphasizing the challenge of optimizing their properties. Distinct predictive models demonstrated varied priorities in attributes, showcasing the complex influence of formulation elements on the film mechanical behaviors. This diversity in model emphasis underscores the elaborate dynamics of film formulation and its crucial role in determining the sample mechanical properties.

4. Conclusion

In this research a range of machine learning techniques were employed, including X-means clustering, Random forest, Support vector machine, and Deep learning, to develop models for predicting orodispersible film performances based on the formulations.

The findings underscore the significance of polymer type as a predominant factor across all predictive models, particularly highlighting the role it plays in dictating the mechanical robustness and flexibility of orodispersible films. The models revealed that, while HPC-based films exhibit exceptional elongation at break values, indicating superior stress tolerance, films made from other polymers showed markedly lower elongation at break values, pointing to their brittle nature. This distinction emphasizes the material inherent characteristics over formulation modifications as the key determinant of film flexibility.

Moreover, the study highlights the minimal impact of variations in polymer, disintegrant, and plasticizer concentrations on elongation at break values, suggesting a degree of stability in film characteristics despite changes in composition. In contrast, the analysis of Young's modulus through these predictive models provided insights into the stiffness of samples, revealing how the incorporation of active ingredients could lead to less rigid films, thereby altering their mechanical properties. The application of RF, SVM, and DL algorithms has further revealed the complex interplay between different formulation components and their collective impact on sample performance. RF and SVM algorithms, although relatively simple when compared to DL multilayer feedforward artificial neural network algorithms, may provide sufficient information to guide early phase of pharmaceutical development, indicating polymer selection in accordance with targeted mechanical properties. Deep learning algorithms would be advantageous in evaluation of bigger datasets leading to identification of more complex patterns within dataset and design the optimal formulation. This study serves as a screening study, closely aligned with the goal of utilizing machine learning for the advancement of pharmaceutical development, specifically in the realm of orodispersible films. By conducting a preliminary investigation into the impact of various factors on film performance, this research can be seen as a groundwork for employing machine learning algorithms as a predictive instrument in orodispersible films development. These algorithms have emerged as a valuable resource in forecasting the important attributes for orodispersible films, facilitating more strategic approaches to their formulation and optimization.

CRediT authorship contribution statement

Erna Turkovic: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ivana Vasiljevic:** Writing – review & editing, Investigation, Data curation. **Jelena Parojcic:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Erna Turkovic reports financial support was provided by Republic of Serbia Ministry of Education Science and Technological Development. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2024.124188.

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An Investigation into Mechanical Properties and Printability of Potential Substrates for Inkjet Printing of Orodispersible Films

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Abstract: Inkjet printing is novel approach in drug manufacturing that enables dispensing precise volumes of ink onto substrates. Optimal substrate properties including suitable mechanical characteristic are recognized as crucial to achieve desired dosage form performance upon administration. Identification of relevant quality attributes and their quantification is subject of intensive scientific research. The aim of this work was to explore applicability of different materials as printing substrates and explore contribution of the investigated substrate properties to its printability. Substrates were characterized with regards to uniformity, porosity, disintegration time, mechanical properties and drug dissolution. Experimentally obtained values were mathematically transformed and the obtained results were presented as relevant radar charts. It was shown that structurally different substrates may be employed for orodispersible films inkjet printing. Main disadvantage of single-polymer films was low drug load, and their printability was dependent on film flexibility and mechanical strength. Structured orodispersible film templates exhibited favorable mechanical properties and drug load capacity. Wafer edible sheets were characterized with high mechanical resistance and brittleness which somewhat diminished printability, but did not hinder high drug load. Obtained results provide insight into application of different materials as printing substrates and contribute to understanding of substrate properties which can affect printability.

Keywords: inkjet printing; printing substrates; mechanical properties; orodispersible films; structured orodispersible film templates; wafer edible sheets

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1. Introduction

Inkjet printing (IJP) is a commonly used digital fabrication technique which allows processing and precise deposition of various liquid materials onto suitable substrates. It is recognized as a novel promising technology for medicine manufacture providing patient-centric drug delivery, and individualization of therapy through flexible dosing of multiple, usually high potency active pharmaceutical ingredients (API) in accordance with the patient specific needs [1,2]. The principle of IJP is that the ink, which contains active pharmaceutical ingredient/s, is precisely transferred onto the selected substrate. In order to obtain targeted drug product profile, both ink formulation, as well as substrate properties should be carefully considered [3–5].

Iftimi et al. defined the ideal printing substrate as a uniform, edible and flexible porous open-pore carrier that could be produced in large sheets [6]. They qualitatively summarized specific substrate properties that are needed in order to obtain optimal printing substrate. The importance of substrate mechanical stability was highlighted as it ensures printing of high volumes of the API-containing ink. Morphology, water penetration rate,

low hygroscopicity, porosity, swelling index and fast dissolution were also evaluated as factors that can affect substrate printability [6]. Mechanically stable substrates enable film printing, distribution and administration without final dosage form damaging, i.e., they should be flexible enough, but still resistant enough to ensure maintenance of dosage form integrity during printing and handling steps [7]. Methodology for printing substrate mechanical properties evaluation and relevant specifications are subject of intensive investigation. Visser et al. [8] quantified mechanical properties of polymer films and reported that tensile strength higher than 2 MPa, elongation at break higher than 10% and Young's modulus lower than 430 MPa can be considered as optimal for drug-free films handling, however, these boundaries should be further evaluated with respect to their applicability for characterization of polymer films intended for use as printing substrates.

Apart from the mechanical strength which reflects the substrate flexibility/rigidity, it is recognized that the important characteristic for effective printing onto the thin films is porous structure which facilitates penetration of the API-containing ink [9]. Furthermore, printing substrates should be relatively thick as opposed to conventional oral strips to enable printing of higher drug doses, and prevent disintegration upon contact with the ink [6]. Thus, the main challenge for orodispersible films printing substrates is to prevent disintegration, rupturing, tearing or winding during printing, while maintaining rapid disintegration required for orodispersible dosage forms [10].

The most common substrates used for IJP are orodispersible thin films prepared using different film-forming polymers. It was shown that API printing onto placebo orodispersible thin films, may overcome certain limitations related to film casting in terms of product thickness and content uniformity, the associated dose variation, and unacceptable material waste [9,11]. It was noted that orodispersible thin films need to be improved in order to further increase the amount of API absorbed and prevent ink leakage through backside of the printing substrate [7]. Enhanced film porosity was associated with better control of ink deposition and the ability to entrap higher amount of inkjet-printed API inside the matrix, although mechanical properties might be somewhat diminished [10].

Structured orodispersible film templates (SOFTs) have been recently introduced as highly porous substrates which enable increased drug load without compromising its mechanical properties. Steiner et al. [12] prepared SOFTs by casting dispersion of hydroxypropyl methyl cellulose in hydroxypropyl cellulose ethanolic solution in order to form a rougher film surface with open pore structure on the top side enabling API-containing ink to be filled into the pores, and the closed bottom side to circumvent leakage. Open pore structure is crucial for ink penetration, as closed pore structure with a continuous film on its surfaces restricts ink penetration [13].

Apart from the casted substrates such as orodispersible thin films or SOFTs, commercially available edible papers, which are often used in the food industry to decorate baked goods and other food products, might be, also, used as printing substrates. Wafer edible sheets and rice papers have been previously used as printing substrates for API-containing inks due to their porous structure and the ability to absorb relatively high amounts of liquid [14–17].

The aim of this study was to explore applicability of different orodispersible thin films, structured orodispersible film templates and wafer edible sheets as printing substrates for IJP. Additionally, printability of substrates was evaluated with respect to porosity, thickness, drug load capacity and the ability of orodispersible thin films to withstand mechanical stress and deformation when passing through printer rollers, expressed as relevant mechanical properties, including film tensile strength, Young's modulus, elongation at break and complex modulus.

2. Materials and Methods

2.1. Materials

Four hydrophilic polymers were investigated as single film-forming agents or polymer blends for printing substrates preparation: (1) hydroxypropyl cellulose (HPC, Klucel®

GF, Ashland™, Wilmington, DE, USA), (2) polyethylene glycol–polyvinyl alcohol graft copolymer (PVA-PEG, Kollicoat® IR, BASF, Ludwigshafen, Germany), (3) maltodextrin (MDX, Glucidex IT6, Roquette, Lestrem, France) and (4) sodium alginate (SA, Fisher Scientific, Waltham, MA, USA), as well as three commercially available wafer edible sheets (Easy Bake, UK, Edible print supplies, Birstall, The United Kingdom). Ink formulation contained caffeine anhydrous (CAF, Sigma-Aldrich Chemie GmbH, Munich, Germany) as the selected model drug, dissolved in the 7:3 mixture of ethanol (≥99.8%, Honeywell, Charlotte, NC, USA) and glycerol, 85% (*w/w*) (Ph. Eur.).

Simulated salivary fluid pH 6.75 [18] prepared with sodium chloride, potassium phosphate monobasic, disodium hydrogen phosphate, hydrochloric acid (Sigma-Aldrich Chemie GmbH, Munich, Germany) and purified water (Ph. Eur.) was used as drug release media.

2.2. Methods

2.2.1. Printing Substrate Preparation

Single-polymer casting dispersions were prepared by dispersing relevant polymer in water heated to 50 °C (in the case of PVA-PEG, SA and MDX) or 70 °C (followed by rapid cooling, in the case of HPC). Dispersions were stirred on the magnetic stirrer (IKA RCT standard, Staufen, Germany) until homogenization.

Polymer blend casting dispersions were prepared by dispersing PVA-PEG, SA or MDX in HPC ethanolic solution followed by continuous stirring on the magnetic stirrer for one hour.

Prepared dispersions were casted on a unit-dose plexiglas plates as described by Drašković et al. [19]. The films were left to dry under ambient conditions during 24 h, cut into pieces of defined size (2.5 by 2.5 cm), packed and stored in a desiccator. Commercial wafer edible sheets were manually cut into 2.5 by 2.5 cm individual films.

2.2.2. Ink Formulation Preparation

Based on the preliminary studies (data not shown), ethanol:glycerol mixture (7:3) has been selected as liquid vehicle for inkjet printing. Then, 10 mg/mL of CAF was dissolved in the solvent mixture. Hydrosoluble food dye containing water, propylene glycol, E 124 and E 122 (Aroma, Krusevac, Serbia) was added in order to facilitate visualization of the printed patterns. Further details on ink characterization are presented in the Table S1 and Figure S1 from the Supplementary Material.

2.2.3. Drug Printing

Thermal inkjet printer Canon® IP 1300 (Canon, Tokyo, Japan) was used. Cartridges were adapted by cutting the top cap, removing the ink sponges and pads and rinsing the empty cartridges with absolute ethanol and purified water. Rectangular printing pattern (2.5 by 2.5 cm) was designed in Microsoft® Office Word 2019 (Microsoft Inc., Albuquerque, NM, USA). In the preliminary study (data not shown), best print quality was obtained using black cartridge (BC-3e BK) solely, therefore, the selected pattern was painted black. Printer settings were adjusted to the following option: High print quality/glossy photo paper/grayscale printing. Printing process consisted of five printing cycles, with 15 min drying step between each cycle. Plain paper was used as a support for individually casted substrates in order to accomplish precise printing. Paper was preprinted with designed pattern and substrates were attached onto paper with an adhesive tape.

2.2.4. Printing Substrate Characterization

Uniformity

Film uniformity was assessed based on the individual films weight, thickness and printed pattern appearance. Thickness was measured at five positions (four corners and one central point) using micrometer screw Insize 3203-25 A (Insize, Suzhou, China). Film weight and thickness are presented as mean values (±SD) of ten replicate measurements.

Printed pattern appearance was assessed by visual inspection of the uniformity of color and edges definition, after five printing cycles. Uniformly distributed color without smearing was considered as acceptable appearance (marked with "+"), while visible splashes of color indicated poor appearance (which was denoted as "−"). The same marking system was used to denote printed patterns edges definition.

Porosity

Porosity was determined as a relative weight difference of the investigated samples following 24 h immersion in the paraffin oil as described by Khorasani et al. [20]. Measurements were performed in triplicate and presented as the mean value (±SD).

Additionally, porosity was investigated using the ImageJ software package 1.51k (National Institutes of Health, Stapleton, NY, USA). Micrographs obtained by trinocular microscope (SZM-168-TL, Motic, Barcelona, Spain) were converted to 8-bit images and the threshold was adjusted to color empty space within the structure, while solid parts remained black. The software was used to calculate fraction of pores in the investigated sample. Relationship between the experimentally determined porosity values and those estimated by image analysis was explored using linear regression analysis.

Image Analysis

Trinocular microscope (SZM-168-TL, Motic, Barcelona, Spain) and scanning electron microscope-SEM (JEOL, JSM-6390 LV, Akishima, Japan) were used to visualize the drug-free samples surface morphology. SEM sample preparation included cutting samples into small pieces and fixing them to the sample holder with double-adhesive carbon tape. After that, samples were coated with gold alloy on sputter coater (Baltec SCD 005, Baltec, Buffalo Grove, IL, USA) to improve their conductivity during recording. Smile Shot^{TM} software was used for obtaining images.

Polarized microscopy (Olympus BX51-P polarized microscope, Olympus, Tokyo, Japan) was employed to detect presence of CAF crystals in the printed samples. For polarized light microscopy a Sony DXC-950P digital camera (Sony, Tokyo, Japan) was used with CellSens Entry 3.1 software (Olympus, Tokyo, Japan).

Disintegration

Disintegration time (DT) of the investigated samples was recorded before and after five printing cycles. Disintegration test for orodispersible dosage forms developed by Preis et al. [21] was employed using 500 mL of the simulated salivary fluid heated to 37 ± 0.5 °C in the compendia disintegration apparatus (Erweka ZT52, Langen, Germany). Individual films were fixed with a holder attached to the upper part and the magnet (3 g) attached to its bottom side. Disintegration endpoint was determined as the time when the magnet attached to the investigated sample dropped down. Six samples were tested, and the results are reported as mean value (±SD). Paired t-test was used for comparison of disintegration time values before and after printing.

Mechanical Properties

Mechanical properties of the investigated printing substrates were evaluated using the Precision universal tester (Shimadzu AG-X plus, Shimadzu Corporation, Kyoto, Japan). The test was performed according to the ISO 527-3 regulation [22]. Samples were cut in the bone shaped specimens, clamped with the film extension grip which moved at a speed of 1 mm/min until sample breakage. The measurements were performed in triplicate. Sample tensile strength (TS), elongation at break (EB) and Young's modulus (YM) were calculated according to the Equations (1)–(3).

$$TS\ (MPa) = F/A \quad (1)$$

where F is maximal applied load and A cross-sectional area.

$$EB\ (\%) = 100 \times (\Delta L_0)/L_0 \quad (2)$$

where ΔL_0 is the extension and L_0 is the original length

$$YM = (\sigma_2 - \sigma_1)/(\varepsilon_2 - \varepsilon_1) \quad (3)$$

where $\sigma_2 - \sigma_1$ represents the applied stress over strain ε_1 and ε_2.

Viscoelasticity of the investigated samples was evaluated based on the complex modulus (G*) values determined by oscillatory rheometry (RheometerRheolab MC 120, PaarPhysica, Stuttgart, Germany) using the parallel plate measuring system MP50 (diameter 12.5 mm, gap 50 μm) with samples placed into frames to prevent drifting.

Oscillatory measurements were performed to determine linear viscoelastic region of the investigated samples (amplitude sweep). After linear viscoelastic region was determined and all the measurements were performed at the constant strain (1%) within frequency range 0.1–10.0 Hz to estimate the impact on the change in storage (elastic) modulus (G′) and loss (viscous) modulus (G″) values.

G* is calculated using the following equation [23]:

$$|G^*| = \sqrt{((G')2 + (G'')2)} \quad (4)$$

Measurements were performed in triplicate and the results expressed as mean value (±SD).

Drug Load

Drug load achieved after five printing cycles was determined by dispersing individual film in 10 mL of purified water on the laboratory shaker (KS 260 basic, IKA VR-Werke GmbH, Staufen, Germany) at 250 rpm. Obtained samples were filtered through a 0.45 mm filter (Millipore, Bedford, MA, USA), properly diluted and assayed for CAF at 273 nm using UV-spectroscopy (UV spectrophotometer EvolutionTM300, Thermo Scientific, Waltham, MA, USA). Reference measurements were done with drug-free substrates used as a blank in order to eliminate interference of substrate components. Test was performed in triplicate.

In Vitro Drug Dissolution

CAF dissolution from the printed samples was studied in the small volume dissolution setup consisting of 100 mL laboratory glasses immersed in the temperature-controlled shaker (LSB Aqua Pro18, Grant, Shepreth, UK) agitated at 110 rpm. Investigated samples were attached to the bottom of the glass with the printed side facing up, and 50 mL of simulated salivary fluid (pH 6.75, 37 ± 0.5 °C) was carefully added. Then, 2 mL samples were withdrawn manually at the pre-determined time intervals. CAF concentration was determined using UV spectrophotometer (EvolutionTM300, Thermo Scientific, Waltham, MA, USA) at 273 nm (drug-free substrates were used as blank). The test was performed in triplicate, and the results are expressed as the mean values (±SD).

Printability Evaluation

Experimentally obtained results for porosity (POR), thickness (TH), EB, TS, YM, G* and drug load (DL) were mathematically transformed onto the 0–100% scale in order to perform comparative evaluation of the investigated substrates printability. Estimated printed pattern appearance (PPA) was assigned with the value 0, 5 or 10 if the sample scored none, one or two pluses, respectively. PPA values were, also, transformed onto the 0–100% scale and value 100% was considered as favorable, as it indicated both the uniformity and precision of drug distribution. Furthermore, high porosity and substrate thickness were recognized as factors that contribute to higher drug load [6,12]. Mathematical transformation of experimentally obtained mechanical characteristics was based on the boundary

values recommended by Visser et al. [8]. Accordingly, the target value for tensile strength was set to 2 MPa or higher, while in the case of elongation at break it was equal or higher than 10%. Young's modulus was considered more satisfactory in the case of lower values, while values higher than 400 MPa were unfavorable. Complex modulus might be useful in prediction of substrates resistance to deformation. Hence, higher values are favorable, as they can indicate substrates ability to withstand repeated printing cycles [19]. Factors affecting substrate printability are represented as radar charts which provide multivariate data visualization, where larger chart area indicates better printability.

3. Results and Discussion

3.1. Printing Substrate Preparation

Ten printing substrate samples were prepared or purchased from the market. Sample subset I included four polymer films prepared using HPC, PVA-PEG, SA and MDX as single film-forming agents in the concentration of 7%, except in the case of MDX samples where, due to film sticking, polymer concentration was set to 5%. The subset II included three samples prepared as structured orodispersible film templates containing polymer blends in which HPC was used as binder with the addition of PVA-PEG, SA and/or MDX as particulate matrix material. The subset III included three wafer edible sheets purchased from the market. Composition of the investigated samples is presented in Table 1.

Table 1. Sample composition.

		Constituents (% *w*/*w*) *					
Subsets	**Samples**	**HPC**	**PVA-PEG**	**SA**	**MDX**	**Purified Water (up to)**	**Absolute Ethanol (up to)**
I	S1	7.0				100.0	
	S2		7.0			100.0	
	S3			7.0		100.0	
	S4				5.0	100.0	
II	S5	7.0	5.0				100.0
	S6	7.0		5.0			100.0
	S7	7.0			5.0		100.0
III	S8	Corn starch, olive oil, water					
	S9	Corn starch, olive oil, water					
	S10	Corn starch, olive oil, maltodextrin, water					

* 1% glycerol was added to samples S1–S7; HPC—hydroxypropyl cellulose, PVA-PEG—polyethylene glycol–polyvinyl alcohol graft copolymer, SA—sodium alginate, MDX—maltodextrine.

3.2. Uniformity

Weight, thickness and the estimated printed pattern appearance of the investigated samples are presented in Table 2. The subset I samples were characterized with lower thickness (ranging from 69 to 124 μm), and film weight when compared to the subset II samples which exhibited higher and more variable thickness (ranging from 309 to 481 μm) due to the presence of dispersed polymer particles on top of the HPC base which resulted in rough and uneven film surface. The commercial wafer edible sheets (sample subset III) also varied in composition and thickness, which ranged from 264 to 502 μm.

Substrate S5 exhibited high level of uniformity with regards to color deposition after five printing cycles. Occasional splashes of ink were seen on the surface of samples S1, S7 and S8. Well defined edges of the printed patterns indicate that ink was not smeared and removed by printer roller. Inconsistency in printed pattern color deposition and edges definition was observed for substrates S1 and S3, hence they were marked as "poor".

Table 2. Printing substrate characteristics.

Subsets	Sample	Weight (mg/cm^2)	Thickness * (μm)	Drug Load * (μg)	Porosity *(Experimental) (%)	Porosity (Image Analysis) (%)	Printed Pattern Appearance (Color Uniformity/Edges Definition) ***	
I	S1	13.2 ± 1.1	124 ± 5	197.5 ± 0.2	1.3 ± 0.1	2.5	−	−
	S2	16.2 ± 0.6	121 ± 2	181.5 ± 0.4	1.8 ± 0.2	3.1	+	+
	S3	13.6 ± 0.4	78 ± 4	54.2 ± 2.6	0.8 ± 0.1	0.5	+	−
	S4	8.4 ± 0.4	69 ± 4	n/a **	0.8 ± 0.1	0.3	n/a **	
II	S5	31.1 ± 0.7	396 ± 22	437.1 ± 2.5	8.2 ± 0.5	31.8	+	+
	S6	26.5 ± 0.7	309 ± 12	97.8 ± 4.9	3.0 ± 0.6	9.8	−	+
	S7	30.9 ± 1.0	481 ± 18	294.2 ± 0.0	6.3 ± 0.5	31.5	−	+
III	S8	8.6 ± 0.0	264 ± 6	217.3 ± 4.1	6.9 ± 0.2	33.8	−	+
	S9	12.4 ± 0.2	369 ± 6	333.2 ± 1.0	9.7 ± 0.2	41.1	+	+
	S10	18.6 ± 0.2	502 ± 7	151.0 ± 5.6	6.1 ± 0.4	30.4	+	+

* mean ± standard deviation; ** n/a—not applicable—sample disintegrated upon contact with ink during printing and *** + acceptable, − poor.

3.3. Porosity

Experimentally obtained and calculated substrate porosity values are presented in Table 2. Orodispersible thin films (i.e., subset I) exhibited poor oil absorption capacity and porosity values were in the range from 0.8 to 1.8%. Porosity values estimated by image analysis were consistent with the experimentally determined results and ranged from 0.3 to 3.1%. The subset II samples exhibited diverse experimentally determined porosity values ranging from 3% (which is close to the determined values for orodispersible thin films) in the case of S6 sample, to more than 6% (which is comparable to wafer edible sheets) for the samples S5 and S7. Sample S6 contained SA polymer as a particulate matrix material characterized with good swelling and gelling properties. It can be anticipated that the reason for a more compact top layer being associated with lower porosity of the SA containing sample (S6) when compared with samples S5 and S7 containing, respectively, PVA-PEG and MDX as particulate matrix material might be polymer swelling and gelation during the film casting and drying, as discussed by Shi et al. [24].

Commercial wafer edible sheets (i.e., the subset III samples) exhibited high porosity values, ranging from 6.1 to 9.7% as estimated based on the oil absorption capacity, and 30.4 to 41.1% estimated by image analysis. However, linear regression analysis indicated high correlation between experimentally and ImageJ determined porosity ($y = 4.88x - 3.44$, $R = 0.98$).

3.4. Image Analysis

Photomicrographs of the investigated samples obtained by the trinocular microscope are presented in Figure 1. While the subset I samples (Figure 1a) reflected the image of transparent material, without any inner structure, photomicrographs of the subset II and III samples (Figure 1b,c) showed notable differences with respect to their inner structure and pore distribution.

Open pores which allow light transition were visible in the samples S5 (HPC-PVA-PEG SOFT) and S7 (HPC-MDX SOFT), with more uniform pore distribution evident for the sample S5. Such structure is in accordance with relatively high porosity of these samples. Sample S6 (HPC-SA SOFT) exhibited compact inner structure without any transparent sections which is in accordance with low porosity value obtained for this sample. Commercial wafer edible sheets exhibited uniform distribution of open pores which is consistent with their high porosity values. In addition, in contrast to the subset II samples, subset III samples enabled intensive light transition, probably due to the lack of closed bottom side which is attributed to SOFTs.

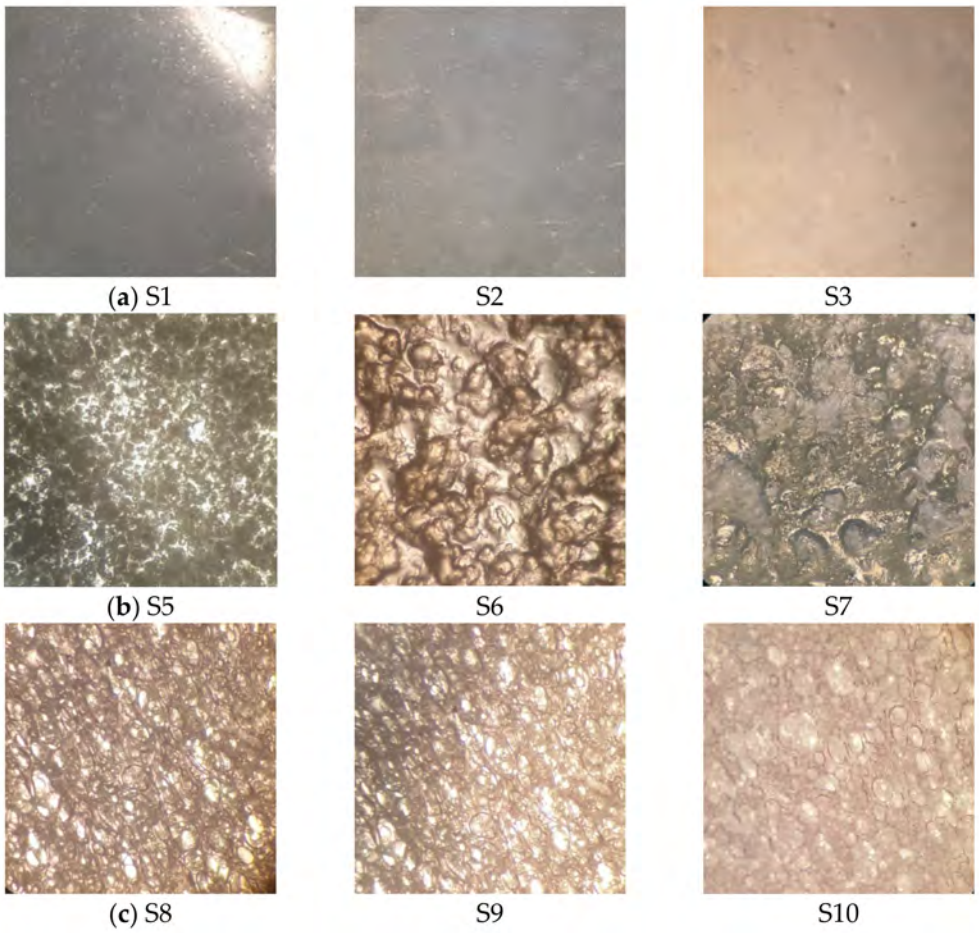

Figure 1. Photomicrographs (50×) of the investigated printing substrates obtained by trinocular microscope: (**a**) subset I; (**b**) subset II and (**c**) subset III (for the sample composition refer to Table 1).

The cross-sectional structures of the samples were assessed using SEM (Figure 2). Subset I samples appeared dense with no inner pores, but there were differences in microstructure. Sample S1 had completely smooth cross-sectional surface while S2 had wrinkled appearance with higher surface area. S3 had small cracks throughout cross sectional area which might indicate stiff structure. Sample S5 exhibited uniformly distributed pores and formed wrinkled structure. Sample S6 cross section appeared homogeneous and similar to orodispersible thin films, which was in agreement with the estimated porosity values. In the case of sample S7 porous inner structure was observed, but pores were irregular and sporadically distributed. Similar composition of subset III samples resulted with similar microstructure with noticeable layers. High porosity might be due to an open space between layers.

Polarized light photomicrographs of the evaluated printed films are presented in Figure 3. The obtained photomicrographs provide insight into the presence of needle-shaped CAF crystals only in the sample S3 (SA) while crystals were not visible in other investigated samples. Crystallization of CAF at the surface of the S3 substrate might be associated with the poor drug adhesion onto the printing substrate and incorrect dosing. It was previously assumed that HPC polymer has the ability to inhibit drug recrystallization [10], which might explain why CAF crystals were not observed in the samples containing HPC. Additionally, it was reported that penetration of ink into the porous printing substrates is associated with altered crystallization behavior compared to printing on nonporous substrates [25]. Hence, it might be assumed that CAF entrapped into the porous substrate will not recrystallize. This is in accordance with the absence of visible CAF crystals in the subset II and III samples.

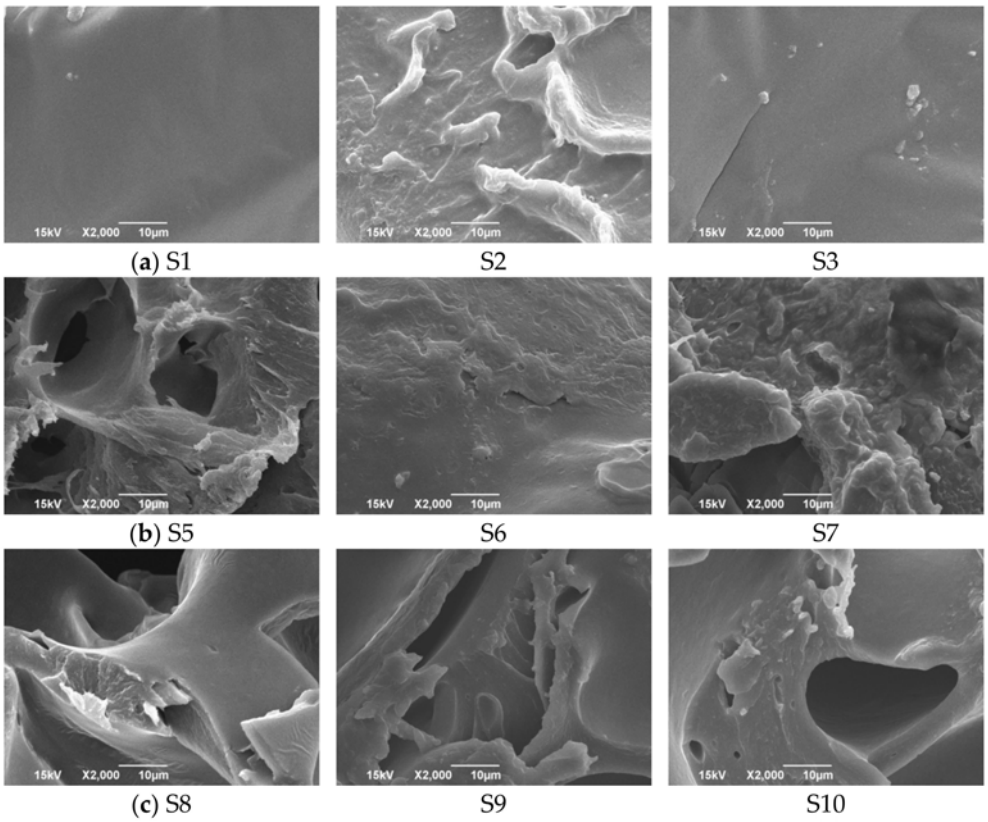

Figure 2. SEM Photomicrographs of the investigated substrates: (**a**) subset I; (**b**) subset II and (**c**) subset III.

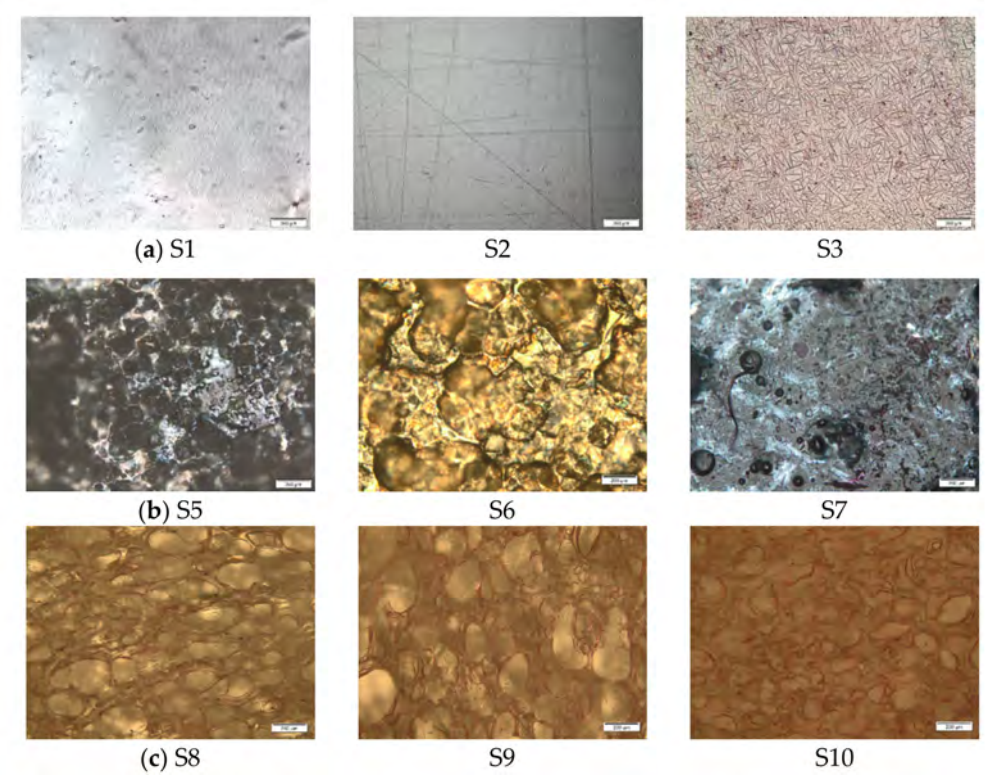

Figure 3. Photomicrographs of the printed samples obtained using polarized light microscopy (200 μm): (**a**) subset I; (**b**) subset II and (**c**) subset III.

3.5. Disintegration

Disintegration times of the drug-free and printed samples are presented in Table 3. Sample S4, prepared from single-polymer dispersion, ruptured upon first contact with the ink and was eliminated from further evaluation. Five printing cycles had no significant influence on disintegration time of the other investigated samples ($p = 0.75$ for paired samples *t*-test). Additionally, all samples fulfilled pharmacopeial requirement for orodispersible tablets disintegration [26].

Table 3. Investigated samples disintegration before and after five printing cycles.

		Disintegration Time					
Subsets	**Samples**	**Before Printing ***			**After Printing ***		
I	S1	27.0	±	2.0	26.7	±	1.0
	S2	32.5	±	0.8	2.2	±	1.8
	S3	41.7	±	0.9	41.5	±	2.0
	S4	3.5	±	0.5	n/a **		
II	S5	28.2	±	1.9	28.8	±	1.6
	S6	52.5	±	1.4	53.1	±	1.6
	S7	46.0	±	1.3	46.5	±	2.1
III	S8	17.2	±	1.2	17.0	±	0.9
	S9	20.8	±	0.7	20.5	±	1.0
	S10	129.3	±	2.5	129.3	±	1.4

* mean ± standard deviation and ** sample disintegrated upon contact with ink during printing.

Although films prepared from polymer blends dispersion (i.e., subset II samples) were thicker than the single polymer film samples (subset I) this was not associated with prolonged disintegration. Similar disintegration was observed for S1 and S5, which might be attributed to higher porosity of the sample S5, in which the open pore side enabled rapid water penetration. Samples S6 and S7 exhibited somewhat longer disintegration time possibly due to lower porosity and, consequently, slower water penetration through the top side of the samples.

The results obtained revealed that S8 and S9 samples, which contain highly porous structure with both sides open, exhibited shortest disintegration times. On the other hand, sample S10 exhibited the longest DT. Highly porous structure with both sides open was associated with very fast disintegration, while multidimensional inner structure and higher film thickness might be the reason for somewhat different behavior of the sample S10.

3.6. Mechanical Properties

Mechanical properties of the evaluated drug-free samples, including tensile strength, elongation at break, Young's modulus and complex modulus are presented in Table 4. Elongation at break is described as the capacity of film to stretch before it breaks. Therefore, if the elongation at break is high, sample structure might be considered as flexible and ductile [27]. The obtained results revealed the highest EB value (272.9%) for the sample S1 which contained hydroxypropyl cellulose as the single film forming polymer. Although some level of flexibility is required for the substrate to be able to fold when it passes through the printer, extensive flexibility might cause sample stretching leading to erroneous drug disposition [28]. On the contrary, low EB determined for samples S3 and wafer edible sheets (S8–10) indicate potential rupturing during film folding due to pronounced brittleness. Elongation at break values for samples S5 and S7 were comparable (i.e., around 11%), while the sample S6 exhibited somewhat higher flexibility. The subset II samples were characterized with flexible structure, but when compared to S1 substrate it can be assumed that addition of particulate matrix material greatly reduced film flexibility. The obtained EB values indicate that the subset II substrates can fold multiple times during printing without dose disruption. The subset III samples exhibited low EB values which could potentially

lead to problems during multiple printing cycles, as their lack of flexibility limits folding without breaking.

Table 4. Mechanical properties of the investigated printing substrates

Subsets	Sample	EB * (%)			TS * (MPa)			YM * (MPa)			G* (MPa)		
I	S1	272.91	±	0.00	0.43	±	0.00	2.99	±	0.00	0.58	±	0.06
	S2	21.14	±	1.07	8.26	±	0.36	146.25	±	0.07	0.73	±	0.12
	S3	2.50	±	0.37	53.63	±	6.67	3498.00	±	173.09	90.35	±	4.34
II	S5	11.31	±	1.66	1.52	±	0.16	182.67	±	8.95	433.12	±	15.34
	S6	28.77	±	8.43	1.07	±	0.13	111.86	±	13.33	642.98	±	16.12
	S7	11.27	±	0.52	4.11	±	0.31	403.67	±	36.18	467.63	±	28.98
III	S8	1.86	±	0.21	3.81	±	0.66	300.45	±	0.64	0.35	±	0.06
	S9	1.49	±	0.31	1.14	±	0.53	105.49	±	16.84	2.65	±	0.07
	S10	0.67	±	0.18	1.66	±	0.38	290.20	±	22.77	601.29	±	0.08

* mean ± standard deviation. EB—elongation at break, TS—tensile strength, YM—Young's modulus and G*—complex modulus.

Tensile strength is defined as the maximum load force used to break the sample. Hard and brittle substrates demonstrate very high mechanical resistance [29]. Generally, somewhat higher TS is preferred in the case of printing substrates in order to avoid tearing which could result from the constant stress induced by the printing rollers. High flexibility of the sample S1 was accompanied with lower mechanical resistance compared to the other subset I samples. Sample S3 containing sodium alginate exhibited extreme brittleness and the highest strength among all the investigated samples, which might cause certain problems during repeated printing cycles. Considering that HPC presents the base polymer in the subset II samples, all substrates exhibited more flexible and less brittle structure compared to thin orodispersible films. Commercially available, edible sheets (subset III) exhibited lower TS values, which is in accordance with the literature data reported by Vakili et al. [16].

Young's modulus is associated with film stiffness and capacity to undergo elastic deformation under applied stress [29]. Strong positive correlation between YM and TS values was established ($R^2 = 0.98$), indicating that more mechanically resistant substrates are also stiffer. YM, also, represents parameter that can serve as reliable indicator of substrate durability during printing and further handling. The obtained results revealed great diversity in YM values in the subset I (i.e., single polymer films) confirming pronounced impact of polymer characteristics. Sample S1 prepared with HPC exhibited the lowest (2.99 MPa) while sample S3 prepared with SA exhibited the highest determined YM value (3498 MPa), which was in accordance with the other investigated mechanical properties. As it was previously reported, presence of MDX in the sample S7 might be related to the increased film hardness and stiffness, without affecting film flexibility as discussed by Cilurzo et al. [30]. According to the presented results, all the investigated samples, except sample S3, had YM in line with recommendation, i.e., lower than 430 MPa [8].

Complex modulus is defined as a measure of total resistance of the system to strain. It is noted that systems that have increased fraction of the dispersed phase are characterized with higher G* values, as a result of the particle–particle interaction and more rigid structure [19,31]. Low values of G*, which were determined for samples S1 and S2 indicate greater flexibility, while the highest complex modulus value observed for S6 might be related to stiffer and less flexible structure. Although Young's modulus values of the subset III samples were comparable, substrate S10 had very high G*, probably due to higher thickness and more complex inner structure (as presented in Figure 2).

3.7. Drug Load

Determined drug load of the investigated orodispersible films, after five repeated printing cycles, are presented in Table 2. The obtained results revealed great inconsistency

of CAF load in the investigated samples, ranging from 54.2 to 437.1 µg. In the subset I samples, lower amounts of drug were incorporated indicating that thin orodispersible films could hold ink only on the top of the surface. The only exception was evident in the sample S3 (prepared with SA), where CAF recrystallization caused facilitated removal of printed drug during successive printing cycles. Within the subset II, the highest drug content was incorporated in the sample S5 (437.1 µg), which is in accordance with the highest porosity and uniform distribution of open pores observed (Figure 2a). Commercially available edible substrates (subset III) are produced with intention to reach high sorption capacity for edible inks. It was noticed that level of porosity affects the amount of drug incorporated. According to the presented results it might be assumed that substrate porosity is the main indicator of the drug load capacity, so the sample S5 with uniform and high porosity and the highest drug content incorporated can be considered as favorable among the presented samples.

3.8. In Vitro Drug Dissolution

The cumulative percentages of CAF released from different orodispersible films as a function of time are presented in Figure 4. There were no remarkable differences in dissolution profiles of the investigated samples during the first five minutes. Printed CAF was predominantly deposited on the surface of orodispersible thin films, thus drug dissolved almost immediately upon contact with dissolution media (Figure 4a). Interestingly, more than 80% of CAF was released within 10 min from all the subset I samples and subset III samples S8 and S9 indicating that, despite differences in structure, thickness and porosity, both sides open structure enables, also, fast drug release (Figure 4a,c). Sample S10, which had the highest thickness, exhibited slightly prolonged CAF release probably due to the multidimensional structure and longer drug diffusion distance. Drug release profiles were in rank-order with the determined film disintegration times. Although somewhat slower CAF dissolution was observed from the subset II, (Figure 4b), more than 80% CAF was released from all the investigated samples within 30 min. Standard deviation within triplicate samples was in the range from 0.35 to 6.07%. This implies rather low variability of data.

3.9. Printability Evaluation

The comprehensive results of the investigated substrate printability evaluation are presented in Figure 5 as radar charts of the selected performance indicators. Experimentally determined parameters mathematically transformed, in order to standardize the values and facilitate printability comparison. The higher radar chart factor values are considered favorable (0%—not acceptable, 100%—acceptable) and the higher radar chart surface area indicates better printability. Boundaries suggested by Visser et al. for mechanical properties correspond to 100% [8]. The highest porosity, thickness and complex modulus values as well as the highest printed pattern score correspond to 100%. Scores from 0 to 100% were drawn on radar charts.

Sample S3 was eliminated from printability assessment, due to observed CAF crystallization and excessive brittleness, which was also reflected in the very high Young's modulus value. Radar chart for the subset I samples (Figure 5a) revealed that sample S2 has higher relative surface area (20.4%) compared to sample S1 (6.9%). Mechanical properties were the main factor that contributed to sample S2 better printability, as these films were mechanically stronger but, at the same time, flexible enough to endure printing. The opposite, lower brittleness in conjunction with poor mechanical resistance observed in the sample S1 negatively affected its printability. The appearance of the printed patterns was also favorable in the case of S2 sample contributing to its overall performance as the drug printing substrate.

Within the subset II, sample S5 had notably higher relative surface area (59.2%) in comparison to samples S6 (26.1%) and S7 (42.1%). As the elongation at break was higher than 10%, its contribution was equal for all three samples. Tensile strength and Young's

modulus values were not critical for printability the of subset II samples, as they exhibited high flexibility, with appropriate tensile strength and Young's modulus values. High drug load and porosity were main discriminative factors. Sample S5 had the highest values of those two parameters, as well as the favorable printed pattern appearance. It can be assumed that similarity in structure of samples S5 and S7 contributed to similarity in factors that affected their printability, while S6 was structurally different and complex modulus was the main parameter that positively affected its printability.

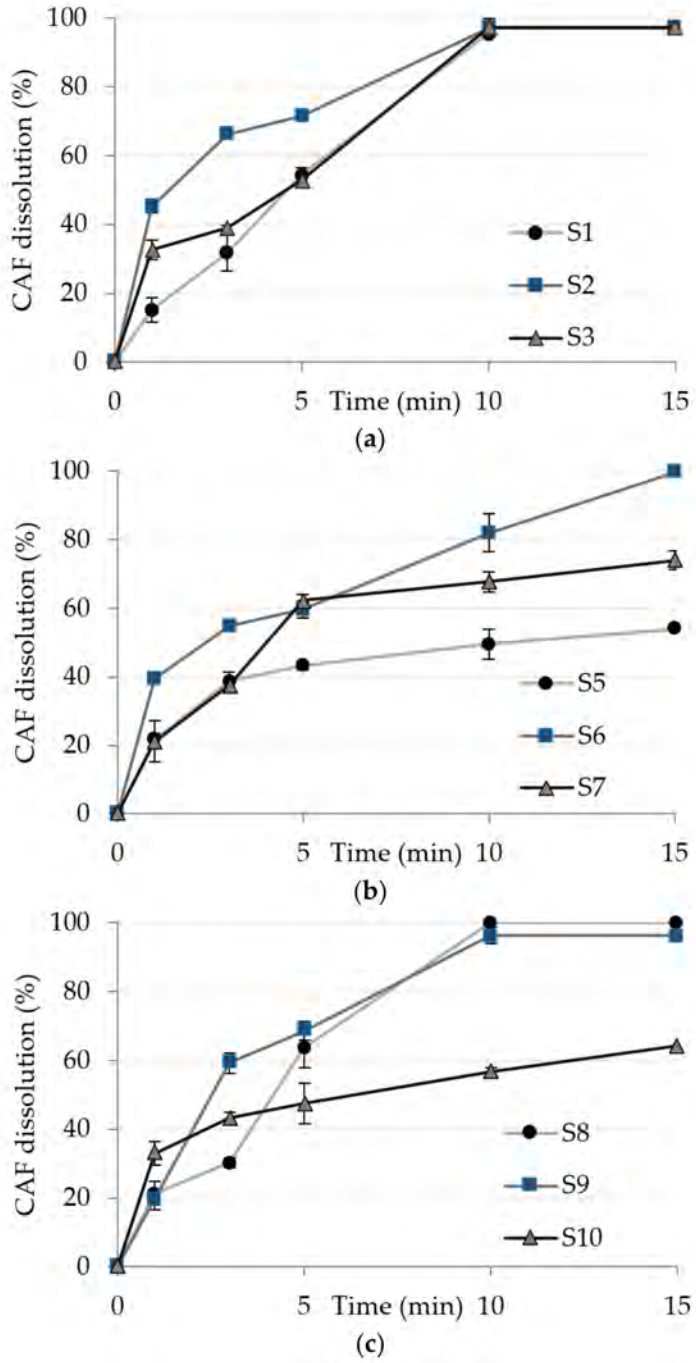

Figure 4. Dissolution profiles of caffeine (CAF) from the investigated samples: (**a**) subset I; (**b**) subset II and (**c**) subset III

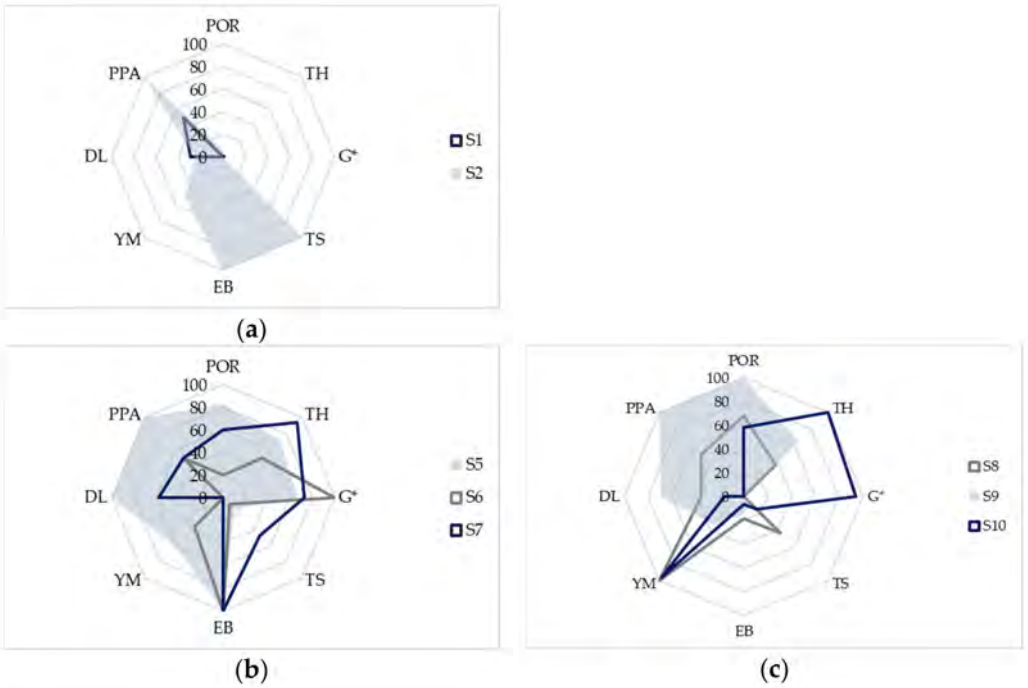

Figure 5. Radar charts for printability assessment of the investigated samples: Subset I (**a**); subset II (**b**) and subset III (**c**). POR—porosity, TH—thickness, DL—drug load and PPA—printed pattern appearance.

Within the subset III, samples S8 and S10 had similar relative surface areas (23.5% and 23.7%, respectively), although different parameters contributed to their printability. Sample S9 exhibited slightly higher relative surface area (29.9%) as higher porosity, and consequently higher drug load, with the good printed pattern appearance which positively affected its printability. Elongation at break values of the investigated wafer edible sheets were lower than 10%, so this parameter did not affect the subset III sample printability. The main difference between S8 and S10 samples printability was higher thickness and complex modulus for S10. As mentioned previously, high thickness values could indicate higher drug load, which was not the case with sample S10 as its drug load was not remarkable higher.

4. Conclusions

The results obtained indicate that different types of printing substrates may be used for drug inkjet printing. Although single polymer thin films with targeted mechanical properties could be used as printing substrates, their major disadvantage is low drug load, since drug deposition is limited to the film surface. Structured orodispersible film templates provided substantial advantages over the single polymer films with regards to the amount of drug incorporated. The appropriate combination of particulate matrix material and base polymer is important to ensure uniform porosity and good mechanical properties. Wafer edible sheets had comparable drug load to structured orodispersible film templates, but their mechanical properties were limiting for multiple printing cycles.

Construction of radar charts enabled visualization of relative contribution of each of the parameters evaluated on the investigated substrates printability and facilitated their comparative analysis. Differences in substrate structure governed which parameters predominantly affected their printability. Printability of single-polymer thin films was mainly dependent on the elongation at break and tensile strength values. Major challenge is to obtain good balance between flexibility and brittleness in order to avoid excessive stretching or tearing of thin films. In the case of structured orodispersible film templates it was evident that porosity was the key contributor to high drug load and more porous films had overall better printability characteristics. Furthermore, Young's modulus and complex modulus must be taken into consideration as porous films can be overly rigid

which negatively affects their printability due to possible rupture during the printing. Additionally, the printed pattern appearance could be useful indicator of substrate printability and included in printability evaluation. The obtained results provide new insight into the printing substrate characteristics and can possibly contribute to development of printability scoring system that could facilitate substate selection and production.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/pharmaceutics13040468/s1, Figure S1: Viscosity flow curve, Table S1: Characteristics of ethanol, liquid vehicle and ink.

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ОЦЕНА ИЗВЕШТАЈА О ПРОВЕРИ ОРИГИНАЛНОСТИ ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду и налаза у извештају из програма iThenticate којим је извршена провера оригиналности докторске дисертације „Испитивање утицаја поступка израде и фактора формулације на критична својства квалитета орално-дисперзибилних филмова - могућност примене напредне анализе података у фармацеутско-технолошкој карактеризацији лекова", аутора Ерне Турковић, констатујем да утврђено подударање текста износи 3%. Овај степен подударности последица је цитата библиографских података о коришћеној литератури што је у складу са чланом 9. Правилника.

На основу свега изнетог, а у складу са чланом 8. став 2. Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду, изјављујем да извештај указује на оригиналност докторске дисертације, те се прописани поступак припреме за њену одбрану може наставити.

23.8.2024.

Ментор

Ј. Паројчић

проф. др Јелена Паројчић

UNIVERZITET U BEOGRADU
FARMACEUTSKI FAKULTET
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18.09.2023. godine

Na osnovu Statuta Univerziteta u Beogradu, prodekan Fakulteta je dana 18.09.2023. godine, donela

ODLUKU

ODOBRAVA se Tuzkovic Erni, studentu Farmaceutskog fakulteta, indeks br. 3/17, produžetak roka za završetak studija za školsku 2023/24.

Obrazloženje

Tuzkovic Erna, student na studijskom programu DAS: Farm. tehnologija, podneo je zahtev 03 br. 3/91 od 18.09.2023. godine prodekanu Fakulteta da mu se odobri produžetak roka za završetak studija.

Prodekan Fakulteta je razmatrala zahtev 18.09.2023. godine i ocenila da je zahtev osnovan, te je doneto rešenje kao u dispozitivu.

PRAVNA POUKA: Protiv ove odluke imenovani ima pravo prigovora dekanu Fakulteta u roku od 8 (osam) dana od dana prijema istog.

Odluku dostaviti: Imenovanoj-om, dekanu i Odseku za nastavu i studentska pitanja.

PRODEKAN ZA POSLEDIPLOMSKU NASTAVU
I KONTINUIRANU EDUKACIJU

Prof. dr Sandra Vezmar Kovačević

УНИВЕРЗИТЕТ У БЕОГРАДУ
ФАРМАЦЕУТСКИ ФАКУЛТЕТ
Посл.број: 5/170
Дана 27.09.2024.године

На основу члана 107. Закона о високом образовању Републике Србије, продекан Факултета је дана 27.09.2024. године, донела

Р Е Ш Е Њ Е

ОДОБРАВА се ЕРНИ ТУРКОВИЋ, студенту Фармацеутског факултета, индекс бр. **3/2017**, **продужетак рока за завршетак студија у школској 2024/2025.**

О б р а з л о ж е њ е

ЕРНА ТУРКОВИЋ, студент на студијском програму **ДАС – Фармацеутска технологија**, поднела је захтев бр. 5/170 од 27.09.2024. године продекану за последипломске студије Факултета да јој се одобри **продужетак рока за завршетак студија у школској 2024/2025.**

Продекан Факултета је разматрала захтев 27.09.2024. године и оценила да је захтев основан, те је донето решење као у диспозитиву.

ПРАВНА ПОУКА: Против овог решења именовани има право приговора декану Факултета у року од 8 (осам) дана од дана пријема истог.

Решење доставити: Именованом, декану, продекану за наставу, секретару, Одсеку за наставу и студентска питања и архиви.

ПРОДЕКАН ЗА ПОСЛЕДИПЛОМСКУ НАСТАВУ
И КОНТИНУИРАНУ ЕДУКАЦИЈУ

Република Србија Универзитет у Београду Фармацеутски факултет VI Београд

Проф. др Сандра Везмар Ковачевић

30. 09. 2024

Е. Турковић