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Applications of Alginates in the Design and Preparation of Orodispersible Dosage Forms

Garba M. Khalid and Francesca Selmin

Abstract

Orodispersible dosage forms are attractive and innovative drug delivery systems that can fulfill individual patient needs, especially in children, elderly and among dysphagic patients. Indeed, they rapidly disperse in the mouth upon contact with the saliva without the need for water or munching. Examples of such dosage forms include orodispersible tablets (ODT), and orodispersible films (ODF). The ability to obtain ODF with different dimensions (sizes and thicknesses) makes them a suitable for personalized dosing of single or a fixed-dose combination of drugs in special patient populations. Several biopolymers are currently being exploited in the development of orodispersible dosage forms including alginates due to their versatility, availability, naturally occurring, and biosafety profile. This chapter provides an appraisal on the various applications of alginates in the preparations and their role on the properties of orodispersible dosage forms and highlights future perspectives of this very versatile biopolymer for these innovative drug delivery systems.

Keywords: alginates, orodispersible films, orodispersible tablets, solid dosage forms, personalized therapy

1. Introduction

Orodispersible dosage forms can ameliorate the lack of compliance associated with the administration of conventional oral solid-dosage forms (i.e., capsules and tablets), or even oral liquid-dosage forms in some patients with swallowing difficulties and hence, have the potential to improve medication adherence [1]. Indeed, since their appearance into the pharmaceutical market, their development has grown gradually, moving from orodispersible tablets (ODT) to orodispersible films (ODF) which presents several advantages to completely eliminate the fear of choking in some patients [2, 3]. Moreover, pharmaceutical companies have amplified research in these dosage forms because they can easily extend their product portfolio [4].

ODF have the size of a postage stamp and are individually packed so that transportation and patient handling are friendly (**Figure 1a**). ODF consist of a single or multilayer sheet of suitable materials intended to be placed in the mouth where they rapidly dispersed upon contact with the saliva without need of water or munching (**Figure 1b**). They provide the opportunity to meet the needs of specific

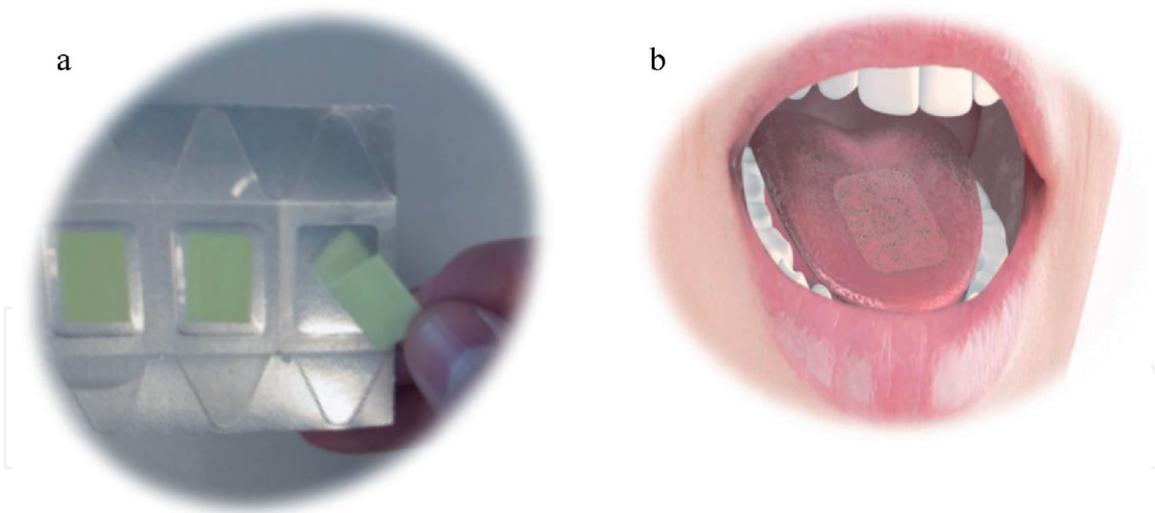


Figure 1. Typical ODF handling from packaging material (a); ideal ODF administration without water (b).

subpopulation of patients suffering from a variety of disorders such as dysphagia due to pathological or psychological issues. In addition, children and elderly, and patients with limited access to water and/or restricted water intake can also benefit from their merits [1, 5]. Indeed, the possibility to change size, shape and color of the ODF have open new scenarios to prepare small batches for personalization of dose in special patient population [6]. Furthermore, ODF can be advantageously used as a carrier for other technologies, such as microparticles, nanocrystals and self-emulsifying systems [5, 7–9], which regulate the drug release patterns and, hence, its bioavailability. However, the main ODF pitfalls are related to the limited formulation space [10] which implies a limited drug loading capacity. Secondly, palatability drives the compliance for ODF loaded formulations, but the formulation space often limits the addition of taste masking agents; even if both bitter and/or astringent taste of a drug can be opportunely reduced and/or eliminated [11, 12]. Thirdly, the manufacturing process at the industrial scale is mainly based on solvent-casting technologies, which require production chains with specialized equipment common only to transdermal patches, and therefore, the number of manufacturers worldwide are limited. Nevertheless, similar to transdermal patches, the dose loaded in an ODF is defined by their size and, therefore, the same production chain could be used to prepare batches of different drug strengths. Because of this peculiarity, researchers are striving to optimize and/or to develop technologies to exploit this peculiarity in the extemporaneous compounding of small batches of ODF in a pharmacy setting [5]. Since the term “customized dosage form” should be related not only to a tailored dose but also to doses on-demand, shape and color of a dosage form [13], this innovation would also allow end-users to easily identify their own medicine, improving medication safety and adherence [5].

ODF are generally made up of plasticized hydrocolloids or blends made thereof that can be laminated by several techniques and sealed in a moisture-protective packages [1]. The active pharmaceutical ingredient (API) can be dissolved or dispersed as such or as nanocrystals [7] or loaded into microparticles [8] depending on the physicochemical properties of the drug and the desired release pattern. Other ODF formulation components are; surfactants, viscosity modifiers, taste-masking agents and coloring agents, when required [5, 14, 15].

Among the critical quality attributes of ODF, satisfactory tensile properties to guarantee packaging and handling during administration without breakage, the disintegration and dissolution in the oral cavity, acceptable taste [5], esthetic

appearance, and stability of the dosage form itself and the loaded drug(s) need to be carefully studied. For instance, the choice of taste-masking agents depends not only on the improvement of palatability, but also on their compatibility with other formulation components, the possible impact on the drug's solubility and dissolution rate, and mechanical properties of the final ODF formulation [5, 12]. This chapter provides an appraisal of the various applications of alginates in the design and preparation of orodispersible dosage forms as new emerging drug delivery systems to overcome some limitations with the conventional solid dosage forms. The literature was generated from the Scopus, and PubMed data bases by searching single or the combination of the following keywords; alginate, alginates, orodispersible film, orodispersible tablet, and orodispersible dosage forms.

2. Preparation methods orodispersible dosage forms

Orodispersible dosage forms can be broadly divided into two based on their current commercial availability, i.e., orodispersible tablet (ODT) and orodispersible films (ODF). Each of them requires a specialized type of equipment, polymers and other formulation additives or excipients since they both have some similarity and distinctive peculiarities. The market penetration and commercial success of either ODT or ODF depends on the taste of the finished product since the palatability of the drug product in orodispersible dosage forms determines patient acceptability and subsequently therapeutic success of drug loaded. Therefore, different taste masking strategies are employed to mask unpleasant tastes or odors of drugs in orodispersible dosage forms such as the use of microencapsulation, complexation technique, using taste masking agents such as sweeteners and flavoring agents [3, 14].

Orodispersible tablets (ODT) have the same appearance with the conventional tablets. However, unlike the conventional tablets, they are expected to rapidly disintegrate within 3 min as a result of their high porous network with the rapid penetration of water and/or other fluids. They can be prepared by direct compression, heat molding technique, or freeze-drying using specific excipients such as alginates (**Table 1**) or their particle engineering products [3].

Orodispersible films (ODF) are mainly prepared by solvent casting technology, electrospinning, hot-melt extrusion and more recently by various printing techniques for dose personalization [3, 5]. In some cases, a combination of these methods is used to obtain an ODF with desired properties or to achieve the desired technological and therapeutic objectives. For instance, various printing technologies have been coupled with other ODF preparation techniques such as solvent casting and fused deposition modeling (FDM) 3D printing to prepared ODF on-demand. Moreover, hot-melt extrusion (HME) is a solvent-free, continuous process. It has a short processing time, suitable for small-scale on-demand preparation of medicines, and is easy to scale-up. Several thermoplastic polymer-carriers and other additives used during extrusion processing are generally regarded to be safe for human consumption [28]. Over the last two decades, HME has been employed as a novel cost-effective pharmaceutical manufacturing technique of different oral solid-dosage forms. It has been suitably used in the preparation of immediate-release, novel taste-masked and abuse deterrence tablets formulations [28, 29], chrono-modulated drug delivery systems [30], for immediate release formulation of ODF [2, 3], and ODF containing poorly water soluble and highly polymorphic drugs [31–33]. Thus, the combination of HME and additive printing technology has been shown to offer several advantages [6, 33]; first, the ability to fabricate immediate-release, modified-release, and other novel drug delivery dosage forms, second, the ease to prepare personalized oral drug delivery products,

Type of orodispersible dosage form	Type of alginate used	Role of the alginate in the formulation	Special notes	Reference
ODF	Sodium alginate and alginate oligosaccharides	Drug carriers	<ul style="list-style-type: none"> Both placebo and posaconazole mucoadhesive films formulations containing the sodium alginate and alginate oligosaccharides exhibited antifungal properties on <i>Candida</i> species. 	[16]
ODF	Alginate hexyl amide derivative	Film-forming polymer	<ul style="list-style-type: none"> New film-forming alginate hexyl amide derivative was prepared. Repaglinide bioavailability was enhanced by the new film-forming alginate derivative. 	[17]
ODF	Sodium alginate	Film-forming polymer	<ul style="list-style-type: none"> Nebivolol hydrochloride was loaded in the ODF using solvent casting technique. Croscarmellose sodium was used as super-disintegrant in the formulation 	[18]
ODF	Sodium alginate	Film-forming polymer	<ul style="list-style-type: none"> Fluconazole mucoadhesive films were prepared to provide prolonged release of the drug for topical treatment of candidiasis. Sodium alginate was used alone or in combination with sodium carboxymethyl cellulose, Carbopol, and polycarbophil. 	[19]
ODF	Sodium alginate	Film-forming polymer	<ul style="list-style-type: none"> Terbutaline sulphate sublingual films were prepared by solvent casting with the sodium alginate singly or in combination with xanthan gum, Carbopol, or HPMC E5 and maltodextrin. The films disintegrate rapidly with faster absorption rate compared to conventional tablet from the pharmacokinetic study on healthy human volunteers. The formulated films can be use in the management of acute episodes of asthma attacks. 	[20]
ODF	Sodium alginate	Film-forming polymer	<ul style="list-style-type: none"> Levocetirizine HCl film was prepared with the addition of sodium starch glycolate as disintegrating agent. A full 3² factorial design was applied to optimize the concentration of the sodium alginate and disintegrant 	[21]
ODF	Sodium alginate	Film-forming polymer	<ul style="list-style-type: none"> Piroxicam ODF were prepared by solvent casting. 	[22]
ODF	Sodium alginate	Disintegrant	<ul style="list-style-type: none"> Sildenafil citrate was loaded in the ODF resulted in decreased disintegration time with increasing concentration of the sodium alginate in the formulation. 	[23]

Type of orodispersible dosage form	Type of alginate used	Role of the alginate in the formulation	Special notes	Reference
ODT	Calcium alginate	Superdisintegrant	<ul style="list-style-type: none"> • Mini ODT were prepared by direct compression using mannitol and MCC as filler/ binder excipients. • Addition of the calcium alginate have shown to improve the disintegration time of the mini ODT. 	[24]
ODT	Alginic acid and calcium alginate	Superdisintegrant	<ul style="list-style-type: none"> • Xerogels containing alginic acid, or calcium alginate and a mixture of both were isolated using oven and rotary evaporation methods. • Mini ODT were prepared with the xerogels developed from the alginates with improved wettability and ultimately rapid disintegration. 	[25]
ODT	Sodium alginate	Taste masking agent	<ul style="list-style-type: none"> • Solid dispersion was used to deter the taste of fexofenadine HCl by controlling the rate of drug release in the saliva pH 	[26]
ODT	Sodium alginate	Superdisintegrant	<ul style="list-style-type: none"> • Meclizine HCl ODT was formulated by direct compression using sodium alginate as such or in combination with xanthan gum to reenforce the superdisintegrant properties of the former and to improve the mechanical quality of the tablets. 	[27]

HPMC: hydroxypropyl methyl cellulose; MCC: microcrystalline cellulose; HCl: hydrochloride.

Table 1.
Applications of alginates in orodispersible dosage forms.

thirdly, the ability to load drugs that are prone to polymorphic transformation in the presence of water or solvent system [33], and finally, the ability to reduce several unit-operations related to traditional manufacturing processes such as granulation, milling, sieving, compressing, and coating. Hence, they are very efficient and economical, in particular for small-scale on-demand personalized formulations [34, 35]. Moreover, additive printing technology combines digital design, manufacturing, and controls together, which is an accurate, timesaving, continuous process to meet individual patient needs [28, 36]. Therefore, the combination of HME and additive printing can be applied as a fabrication tool in the field of digital health for the remote manufacture and dispensing of personalized orodispersible dosage forms having shapes, sizes, and doses that are optimized for a particular patient or group of patients based on their needs [28]. Consequently, the therapeutic efficacy and medication adherence can be enhanced owing to the flexibility and autonomy of the treatment process provided by the combination of these technologies.

3. Application of additive manufacturing in personalized orodispersible dosage forms

The concept of personalized therapy is gaining attention in recent years with the aim of providing appropriate drug(s), dosage regimens, and/or medical care based on the individual patient's peculiarities such as age, medical history, diagnostic results, or genetic information aiming to minimize medication errors such as drug interactions, side effects, and adverse drug reactions and to obtain maximum therapeutic benefits [37, 38]. Technologically speaking, personalized therapy is centered towards personalized dosing, or dose precision and providing age-appropriate dosage forms capable of addressing patients' specific requirements. As an example, in the case of children, it has been estimated that the availability of authorized and commercially available medicine for children varies between 48% and 54% of all approved medicines and that up to 50% of pediatric patients receive an unlicensed or off-label prescription [39]. Indeed, it has been recognized that children are unable to or have difficulties with swallowing tablets or capsules. Moreover, crushing tablets, opening capsules, or mixing powders to extemporaneously prepare the required dose with liquids may lead to dose variability, contamination, drug instability, taste and solubility problems, and other consequences for safety of the patient and the efficacy of the treatment. It is therefore of paramount importance to develop age-appropriate dosage forms, as pointed out by the World Health Organization's (WHO) initiative 'better medicines for children'. Therefore, personalized orodispersible dosage forms such as ODF or ODT prepared on-demand by additive printing technologies can potentially legitimize personalized and precise dosing in patients with special needs.

Additive printing presents a promising future for the point-of-care manufacturing of medicines. Technologies such as two-dimensional (2D) and three-dimensional (3D) printing appeared capable of producing individualized oral drug delivery systems, such as ODF with customizable drug dose strengths, and in some cases with pre-defined drug release patterns [40, 41]. The use of computer-aided design (CAD) software to design different dimensions of a 3D object prior to printing displays the potential of 3D printing for the concept of precision dosing of active pharmaceutical ingredients (APIs) [41]. Despite the significant technological advancements made so far during the 21st century on conventional pharmaceutical manufacturing processes, especially being cost-effective for large-scale industrial production, they can be inherently labour intensive, time-consuming, and dose inflexible. This poses significant challenges for certain groups of patients that require tailored dosing (particularly among pediatrics and geriatrics) or for certain medicines that require frequent dose adjustments (e.g., drugs

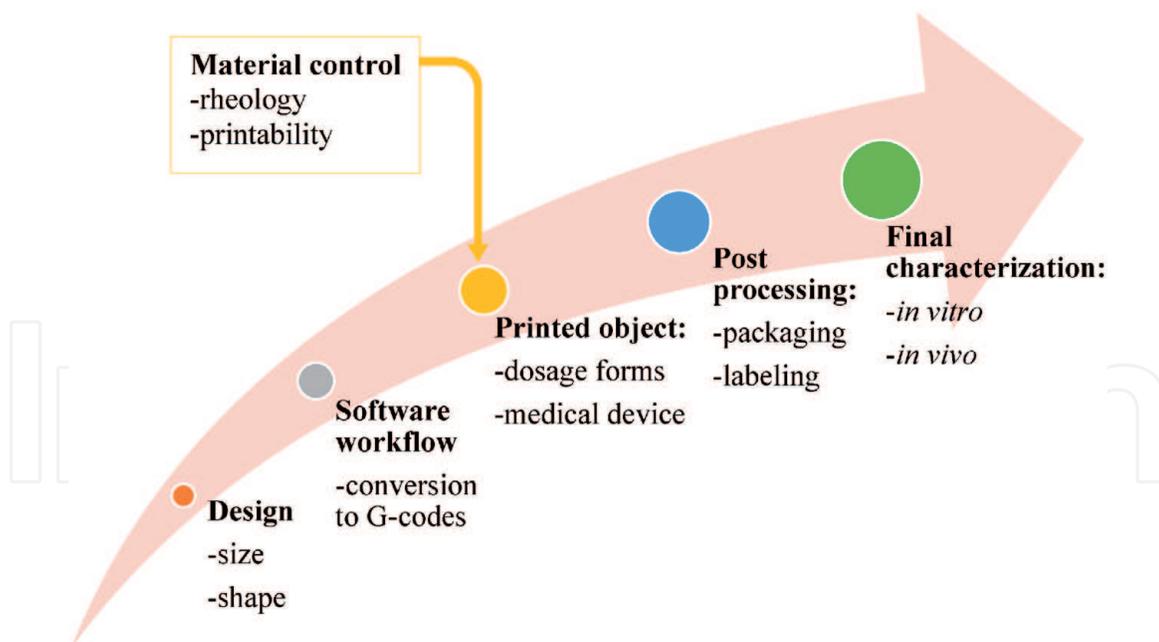


Figure 2.
Schematic flow chart of additive printing process from design and material selection to the finished product characterization.

with narrow therapeutic index). Therefore, to achieve pharmacotherapeutic goals with greater efficacy, quality and safety in patients with special needs, the use of innovative approach such as additive printing technologies are required within pharmaceutical field to facilitate the preparation of small-scale, on-demand and dose-flexible formulations such as ODF. Additive printing process which enables the design of a customized oral dosage forms is triggering a paradigm shift in the way medicines are manufactured and administered [42]. Furthermore, this process could make possible the printing of medicines in pandemic outbreak areas to mitigate drug shortages and supply chain disruptions, and potential for making available printing of medicines in war zones, in clinical trials in hospital settings [43, 44] and preparation of individualized fixed-dose combination products [44–46]. Perhaps, the current regulatory landscape on additive printing is flexible enough to accommodate this technology for mass production in addition to its benefits in extemporaneous compounding of medicines. Thus, according to United States Food and Drug Administration's (FDA) guidelines for additive printing, once the printing device/equipment is optimized, the first step is the design process, which can include a standard design with distinct pre-specified dimensions, in the case of ODF for instance; the design of an ODF area and desired thickness which ultimately defined the dose of loaded API according to individual patient needs. Once the device design is converted to a digital file, the software workflow phase begins, and that file is further processed to prepare it for printing (**Figure 2**), at this stage, the printing parameters are optimized. Concurrently with this step, material controls are established for materials used in the printing of the dosage form (i.e., rheological evaluation, and printability). After printing is complete, post-processing of the built dosage form (e.g., packing and labelling) takes place. After post-processing, the final finished dosage form is ready for characterization [47].

4. Applications of alginates in orodispersible dosage forms

Alginate is a natural polymer used widely in pharmaceutical, food, and biomedical applications because of its biodegradable and biocompatible properties. Alginate and its derivatives are considered low or nontoxic, and non-immunogenic

hence suitable for human consumption [48, 49]. Moreover, various alginate salts (ammonium, calcium, sodium, potassium) and propylene glycol alginate derivatives are generally regarded as safe (GRAS) ingredients, for oral administration by the FDA. Like many other pharmaceutical products, the selection of excipients for orodispersible dosage forms requires thoughtful consideration based on the peculiar properties of the dosage form itself such as rapid disintegration, drug-excipient compatibility, biocompatibility with body fluids such as saliva and GIT fluids. Therefore, alginate and its derivatives have found different applications in the design and preparation of orodispersible dosage forms. As an example, sodium alginate has been used as an orodispersible film-forming polymer to provide mucoadhesive properties of the films or to increased drug loading or both. These applications are mostly accomplished with the sodium alginate alone to load poorly soluble drugs in ODF [22], or in combination with other polymers such as polyvinyl alcohol, chitosan, Carbopol 974P, and sodium carboxymethyl cellulose [22, 23, 50]. Various ODF formulations applying the uniqueness of alginates to provide different functions in the dosage form are exemplified in (**Table 1**). Indeed, it is worthy to note that, alginate-based orodispersible films have shown high tensile strength and high hydrophilicity with disintegration time within few seconds [20, 51]. Hence, the use of alginate in ODF represent good systems to formulate orodispersible dosage forms, promoting hydrophilic properties and ultimately suitable disintegration time which is fundamental quality for ODF. Nevertheless, few studies have explored alginate as a film-forming agent in ODF preparations either singly or in combination with other polymers. Thus, highlighting missing gaps to explore in discovering other potentials of alginates in ODF formulations [51].

Similarly, various alginate derivatives have also found application in the formulation of ODT where they serve different functionality. For instance, alginic acid and its salts have been used as disintegrants, super-disintegrants, and/or fillers in ODT formulations [24, 25]. Soulairol and co-workers developed xerogels containing alginic acid, calcium alginate or the combination thereof in the design and formulation of orodispersible mini tablets where they have been shown to provide enhanced super-disintegrant properties [25]. Further, Yehia et al., employed the use of sodium alginate as a taste-masking agent in ODT through solid dispersion technique. The authors succeeded in masking the taste of fexofenadine hydrochloride by controlling the rate of drug release in the saliva pH as confirmed by healthy human volunteers [26]. A summary of the various applications of alginates in ODT is also provided in (**Table 1**).

5. Conclusion

Alginates have wide range of application in the design and preparation of orodispersible dosage forms. The choice of a particular alginate type depends on several factors, such as the type of the orodispersible dosage form to be prepared, i.e., ODT or ODF, the physicochemical properties of the alginate and that of the drug itself, and the nature of the release pattern of the loaded drug(s). Most of the alginate's applications in ODF and ODT are in the solvent casting and direct compression method for their preparations, respectively. Thus, exploring alginates applications in the preparation of these dosage forms by other techniques such as 3D printing, freeze drying, and particle engineering can open new scenarios in their application in the development of these innovative drug delivery systems.

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References

- [1] Cilurzo F, Musazzi UM, Franzé S, et al. Orodispersible dosage forms: biopharmaceutical improvements and regulatory requirements. *Drug Discov. Today* [Internet]. 2018;23:251-259. Available from: <http://dx.doi.org/10.1016/j.drudis.2017.10.003>.
- [2] Manjeet B. Pimparade, Anh Vo, Abhijeet S. Maurya, Jungeun Bae, Joseph T. Morott, Xin Feng, Dong Wuk Kim, Vijay I. Kulkarni, Roshan Tiwari, K. Vanaja, Reena. Murthy, H. N. Shivakumar, D. Neupane, S. R. Mishra, S. N. Murthy and MAR. Development and Evaluation of an Oral Fast Disintegrating Anti-allergic Film Using Hot-melt Extrusion Technology. *Eur. J. Pharm. Biopharm.* [Internet]. 2017;119:81-90. Available from: <http://dx.doi.org/10.1016/j.ejpb.2017.06.004>.
- [3] Cilurzo F, Musazzi UM, Franzé S, et al. Orodispersible dosage forms: biopharmaceutical improvements and regulatory requirements. *Drug Discov. Today*. 2018;23.
- [4] Garba M. Khalid, Francesca Selmin, Umberto M. Musazzi, Chiara GM Gennari PM and FC. Trends in the Characterization Methods of Orodispersible Films. *Curr. Drug Deliv.* 2020;1-16.
- [5] Musazzi UM, Khalid GM, Selmin F, et al. Trends in the production methods of orodispersible films. *Int. J. Pharm.* 2020;576.
- [6] Khalid GM, Musazzi UM, Selmin F, et al. Extemporaneous printing of diclofenac orodispersible films for pediatrics Extemporaneous printing of diclofenac orodispersible films for pediatrics. *Drug Dev. Ind. Pharm.* [Internet]. 2021;0:1-9. Available from: <https://doi.org/10.1080/03639045.2021.1908335>.
- [7] Lai F, Franceschini I, Corrias F, et al. Maltodextrin fast dissolving films for quercetin nanocrystal delivery. A feasibility study. *Carbohydr. Polym.* [Internet]. 2015;121:217-223. Available from: <http://dx.doi.org/10.1016/j.carbpol.2014.11.070>.
- [8] Musazzi UM, Passerini N, Albertini B, et al. A new melatonin oral delivery platform based on orodispersible films containing solid lipid microparticles. *Int. J. Pharm.* [Internet]. 2019;559:280-288. Available from: <https://doi.org/10.1016/j.ijpharm.2019.01.046>.
- [9] Talekar SD, Haware R V., Dave RH. Evaluation of self-nanoemulsifying drug delivery systems using multivariate methods to optimize permeability of captopril oral films. *Eur. J. Pharm. Sci.* [Internet]. 2019;130:215-224. Available from: <https://doi.org/10.1016/j.ejps.2019.01.039>.
- [10] Borges AF, Silva C, Coelho JFJ, et al. Outlining critical quality attributes (CQAs) as guidance for the development of orodispersible films. *Pharm. Dev. Technol.* 2017;22:237-245.
- [11] Cilurzo F, Cupone IE, Minghetti P, et al. Nicotine Fast Dissolving Films Made of Maltodextrins: A Feasibility Study. *AAPS PharmSciTech* [Internet]. 2010;11:1511-1517. Available from: <http://www.springerlink.com/index/10.1208/s12249-010-9525-6>.
- [12] Cilurzo F, Cupone IE, Minghetti P, et al. Diclofenac fast-dissolving film: Suppression of bitterness by a taste-sensing system. *Drug Dev. Ind. Pharm.* 2011;37:252-259.
- [13] Vakili H, Nyman JO, Genina N, et al. Application of a colorimetric technique in quality control for printed pediatric orodispersible drug delivery systems containing propranolol hydrochloride. *Int. J. Pharm.* [Internet]. 2016;511:606-618. Available from: <http://dx.doi.org/10.1016/j.ijpharm.2016.07.032>.

- [14] Dixit RP, Puthli SP. Oral strip technology: Overview and future potential. *J. Control. Release.* 2009;139:94-107.
- [15] Musazzi UM, Selmin F, Ortenzi MA, et al. Personalized orodispersible films by hot melt ram extrusion 3D printing. *Int. J. Pharm.* 2018;551:52-59.
- [16] Szekalska M, Wróblewska M, Trofimiuk M, et al. Alginate oligosaccharides affect mechanical properties and antifungal activity of alginate buccal films with posaconazole. *Mar. Drugs.* 2019;17.
- [17] Khames A. Hexyl alginate derivative, an amphiphilic innovative buccal film-forming material of promising mechanical and release characteristics for the improvement of repaglinide bioavailability. *Drug Des. Devel. Ther.* 2019;13:925-940.
- [18] Vijayanand P, Patil JS, Reddy MV. Formulation and comparative pharmacokinetic evaluation of orodispersible tablets and films of nebivolol hydrochloride. *J. Pharm. Investig.* 2015;45:237-247.
- [19] Yehia SA, El-Gazayerly ON, Basalious EB. Fluconazole mucoadhesive buccal films: in vitro/in vivo performance. *Curr. Drug Deliv.* [Internet]. 2009;6:17-27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19418952>.
- [20] Sayed S, Ibrahim HK, Mohamed MI, et al. Fast-dissolving sublingual films of terbutaline sulfate: Formulation and in vitro/in vivo evaluation. *Mol. Pharm.* 2013;10:2942-2947.
- [21] Singh S, Satyam G, Garima G, et al. Formulation and Evaluation of Rapidly Disintegrating Film of Levocetirizine Hydrochloride. *Der Pharm. Lett.* 2010;2:434-439.
- [22] El-Bary AA, Al Sharabi I, Haza'a BS. Effect of casting solvent, film-forming agent and solubilizer on orodispersible films of a polymorphic poorly soluble drug: an in vitro/in silico study. *Drug Dev. Ind. Pharm.* [Internet]. 2019;45:1751-1769. Available from: <https://doi.org/10.1080/03639045.2019.1656733>.
- [23] Shi LL, Xu WJ, Cao QR, et al. Preparation, characterization and in vitro evaluation of a polyvinyl alcohol/sodium alginate based orodispersible film containing sildenafil citrate. *Pharmazie.* 2014;69:327-334.
- [24] Soulairol I, Chaheen M, Tarlier N, et al. Evaluation of disintegrants functionality for orodispersible mini tablets. *Drug Dev. Ind. Pharm.* 2017;43:1770-1779.
- [25] Soulairol I, Sanchez-Ballester NM, Aubert A, et al. Evaluation of the super disintegrant functionalities of alginic acid and calcium alginate for the design of orodispersible mini tablets. *Carbohydr. Polym.* [Internet]. 2018;197:576-585. Available from: <https://doi.org/10.1016/j.carbpol.2018.06.002>.
- [26] Yehia SA, El-Ridi MS, Tadros MI, et al. Phenylalanine-free taste-masked orodispersible tablets of fexofenadine hydrochloride: Development, in vitro evaluation and in vivo estimation of the drug pharmacokinetics in healthy human volunteers. *Pharm. Dev. Technol.* 2015;20:528-539.
- [27] Kumar MV. Formulation and Evaluation of Meclizine Hcl Orally Dispersible Tablets by using Natural Super Disintegrants. *Int. J. Pharma Sci. Sci. Res.* 2016;2:53-80.
- [28] Wang H, Dumpa N, Bandari S, et al. Fabrication of Taste-Masked Donut-Shaped Tablets Via Fused Filament Fabrication 3D Printing Paired with Hot-Melt Extrusion Techniques. *AAPS PharmSciTech.* 2020;21:1-11.

- [29] Nukala PK, Palekar S, Patki M, et al. Abuse Deterrent Immediate Release Egg-Shaped Tablet (Egglets) Using 3D Printing Technology: Quality by Design to Optimize Drug Release and Extraction. *AAPS PharmSciTech*. 2019;20.
- [30] Dumpa NR, Sarabu S, Bandari S, et al. Chronotherapeutic Drug Delivery of Ketoprofen and Ibuprofen for Improved Treatment of Early Morning Stiffness in Arthritis Using Hot-Melt Extrusion Technology. *AAPS PharmSciTech*. 2018;19:2700-2709.
- [31] Cho HW, Baek SH, Lee BJ, et al. Orodispersible polymer films with the poorly water-soluble drug, olanzapine: Hot-melt pneumatic extrusion for single-process 3D printing. *Pharmaceutics*. 2020;12:1-16.
- [32] Modica de Mohac L, de Fátima Pina M, Raimi-Abraham BT. Solid microcrystalline dispersion films as a new strategy to improve the dissolution rate of poorly water soluble drugs: A case study using olanzapine. *Int. J. Pharm.* [Internet]. 2016;508:42-50. Available from: <http://dx.doi.org/10.1016/j.ijpharm.2016.05.012>.
- [33] Selmin F, Khalid GM, Musazzi UM, et al. Relevance of production method on the physical stability and in vitro biopharmaceutical performances of olanzapine orodispersible film. *Int. J. Pharm.* [Internet]. 2021;120697. Available from: <https://doi.org/10.1016/j.ijpharm.2021.120697>.
- [34] Zhang J, Xu P, Vo AQ, et al. Development and evaluation of pharmaceutical 3D printability for hot melt extruded cellulose-based filaments. *J. Drug Deliv. Sci. Technol.* [Internet]. 2019;52:292-302. Available from: <https://doi.org/10.1016/j.jddst.2019.04.043>.
- [35] Zhang J, Feng X, Patil H, et al. Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. *Int. J. Pharm.* [Internet]. 2017;519:186-197. Available from: <http://dx.doi.org/10.1016/j.ijpharm.2016.12.049>.
- [36] Jonathan G, Karim A. 3D printing in pharmaceuticals: A new tool for designing customized drug delivery systems. *Int. J. Pharm.* [Internet]. 2016;499:376-394. Available from: <http://www.sciencedirect.com/science/article/pii/S0378517315304622>.
- [37] Vogenberg FR, Isaacson Barash C, Pursel M. Personalized medicine: part 1: evolution and development into theranostics. *P T*. 2010;35:560-576.
- [38] Abubakar AR, Chedi BAZ, Mohammed KG, et al. Drug interaction and its implication in clinical practice and personalized medicine. *Natl. J. Physiol. Pharm. Pharmacol.* 2015. p. 343-349.
- [39] Selmin F, Musazzi UM, Cilurzo F, et al. Alternatives when an authorized medicinal product is not available. *Med. Access @ Point Care*. 2017;1:16-21.
- [40] Eleftheriadis GK, Katsiotis CS, Andreadis DA, et al. Inkjet printing of a thermolabile model drug onto FDM-printed substrates: formulation and evaluation. *Drug Dev. Ind. Pharm.* [Internet]. 2020;46:1253-1264. Available from: <https://doi.org/10.1080/03639045.2020.1788062>.
- [41] El Aita I, Ponsar H, Quodbach J. A Critical Review on 3D-printed Dosage Forms. *Curr. Pharm. Des.* 2018;24: 4957-4978.
- [42] Trenfield S, Basit A, Goyanes A. INNOVATIONS IN 3D: Printed pharmaceuticals. *drug Deliv.* 2020;2020:45-49.
- [43] Goyanes A, Madla CM, Umerji A, et al. Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD:

First single-centre, prospective, crossover study in patients. *Int. J. Pharm.* [Internet]. 2019;567:118497. Available from: <https://doi.org/10.1016/j.ijpharm.2019.118497>.

[44] Fernández-García R, Prada M, Bolás-Fernández F, et al. Oral Fixed-Dose Combination Pharmaceutical Products: Industrial Manufacturing Versus Personalized 3D Printing. *Pharm. Res.* 2020;37.

[45] Alomari M, Vuddanda PR, Trenfield SJ, et al. Printing T3 and T4 oral drug combinations as a novel strategy for hypothyroidism. *Int. J. Pharm.* 2018;549:363-369.

[46] Alhnan MA, Okwuosa TC, Sadia M, et al. Emergence of 3D Printed Dosage Forms: Opportunities and Challenges. *Pharm. Res.* [Internet]. 2016;33:1817-1832. Available from: <http://dx.doi.org/10.1007/s11095-016-1933-1>.

[47] FDA Technical Considerations for Additive Manufactured Medical Devices: available at: www.fda.gov/files/medical%20devices/published/Technical-Considerations-for-Additive-Manufactured-Medical-Devices---Guidance-for-Industry-and-Food-and-Drug-Administration-Staff.pdf. Accessed June 28, 2021.

[48] Patel MA, AbouGhaly MHH, Schryer-Praga J V., et al. The effect of ionotropic gelation residence time on alginate cross-linking and properties. *Carbohydr. Polym.* [Internet]. 2017;155:362-371. Available from: <http://dx.doi.org/10.1016/j.carbpol.2016.08.095>.

[49] Dalheim M, Vanacker J, Najmi MA, et al. Efficient functionalization of alginate biomaterials. *Biomaterials.* 2016;80:146-156.

[50] Boateng JS, Stevens HNE, Eccleston GM, et al. Development and

mechanical characterization of solvent-cast polymeric films as potential drug delivery systems to mucosal surfaces. *Drug Dev. Ind. Pharm.* 2009;35:986-996.

[51] Pacheco MS, Barbieri D, da Silva CF, et al. A review on orally disintegrating films (ODFs) made from natural polymers such as pullulan, maltodextrin, starch, and others. *Int. J. Biol. Macromol.* [Internet]. 2021;178:504-513. Available from: <https://doi.org/10.1016/j.ijbiomac.2021.02.180>.