REVIEW ARTICLE

A Review on Conventional and Modern Techniques to Develop Orodispersible Films

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ABSTRACT

Nowadays, solubility of active pharmaceutical ingredient (API) is one of the biggest challenges faced by the researchers during the development of pharmaceutical oral dosage form. Developing a new molecule is very expensive than formulating a dosage form of existing API. Orodispersible film (ODF) is one of the alternatives for the conventional dosage form as it dissolves and directly absorbed from the mouth. It is suitable for the delivery of poorly soluble drugs. It does not require water for the administration and gives quick absorption and high bioavailability. There are various techniques that can be used to improve the solubility of poorly soluble drugs in ODFs, namely, surfactants, superdisintegrants, and printing technology. Water-soluble polymers are used as the film former, but the different concentration and different combination of polymers and use of various additives like surfactant; superdisintegrants can show the significant effect on the solubility. It can be used for both local and systemic action. ODFs are gaining popularity and are widely accepted by the consumers, but it is still lacking in some areas due to the absence of pharmacopoeial specifications for disintegration, mechanical properties, etc.

Key words: Disintegration, orodispersible films, pharmacopoeial, printing technology, superdisintegrants, surfactants

INTRODUCTION

Developing a new chemical entity or drug requires a long period and investment of millions on research and development. However, the surety of success is still not there. That is why the pharmaceutical companies and researchers are working on the development of new novel dosage forms to increase safety, efficacy, and bioavailability of drug as well as patient compliance.[1]

Solubility is an important factor in the drug development process. About 35–40% of the new chemical entities developed are less aqueous soluble results in low bioavailability that is why it is major concern for the scientist to develop and design formulation. The drugs with high permeability and low solubility fall in the category of BCS class II and class IV. Some examples of poorly soluble drugs are aceclofenac, phenytoin, ezetimibe, etc. To get absorb by cell membrane, the drug should be solubilized. Poorly absorbed drugs have slow drug absorption and lead to inadequate bioavailability and gastrointestinal mucosal toxicity.[2] The researchers have developed oral dispersible dosage form which disintegrates in the oral cavity or buccal cavity. This formulation is stable in the solid state but dissolves rapidly when comes in contact with the saliva or buccal mucosa. The various orodispersible dosage forms are orodispersible tablets (ODT), orodispersible granules, oral lyophilisates, orodispersible films (ODF), etc.[2]

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Received: 31-05-2018
Revised: 15-06-2018
Accepted: 23-06-2018

ODF

The films that rapidly dissolves in the mouth or oral cavity is generally termed as ODF (European Medical Agency), Oro-dispersible film are termed as ODF (Food and Drug Administration). It was developed in 1970 as an alternative to conventional dosage forms such as tablet and capsule. It is a robust way for the delivery of poorly soluble drugs.[2]

ODF are fast-dissolving films. The thickness of ODFs is 50–150 um. ODFs are administered into the oral cavity. It dissolves within 1 min when come in contact with saliva. It does not require water for the administration and gives quick absorption and instant bioavailability.[3]

As there is no need of swallowing the ODFs, it is suitable for the pediatrics and geriatric patients or patients suffering from dysphagia. The problems such as chocking and degradation through first-pass metabolism are the major problem with tablets, and the friability is the major problem for ODT which can be overcome with the ODFs.

The special features of ODFs are:
- Different size should be available.
- Film should be thin and elegant.
- Film should not require water for the disintegration.
- There should be rapid release and absorption.
- It should stick to the oral cavity.

Advantages of ODFs are:
- Convenient and accurate dosing.
- More patient compliance.
- No first-pass effect.
- No water requires for administration.
- Enhance bioavailability with rapid onset of action.
- No risk of chocking.

Disadvantages of ODFs:
- Suitable for only potent drugs as higher dose cannot be incorporated.
- Dose uniformity is a technical challenge.
- For poorly soluble drugs, special techniques are required.

The major components of ODFs are:
- Active Pharmaceutical Agent - 5–30%.
- Water-soluble film forming polymer - 40–50%.
- Plasticizers - 0–20%.
- Fillers, color, flavor, sweetener, etc. - 0–6%.
- Surfactants - quantity sufficient.[3]

The various polymers used in ODFs are sodium carboxymethyl cellulose, hydroxyethyl cellulose, polyacrylic acid, hydroxypropyl cellulose, hypromellose (semisynthetic), etc., and the natural polymers are Chitosan, alginate, starch, maltodextrin, etc.[4]

The various plasticizers used in ODFs are: Glycerol, propylene, glycol, polyethylene glycol, sorbitol, etc.[5]

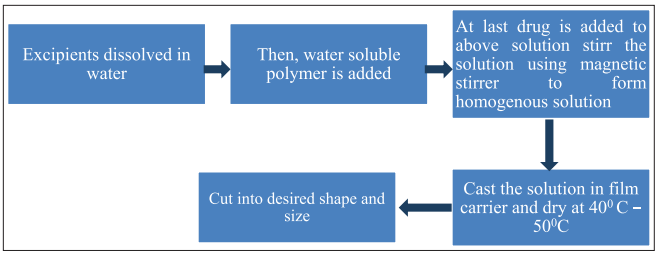

Fig ure 1: Flowchart for the process of solvent casting method

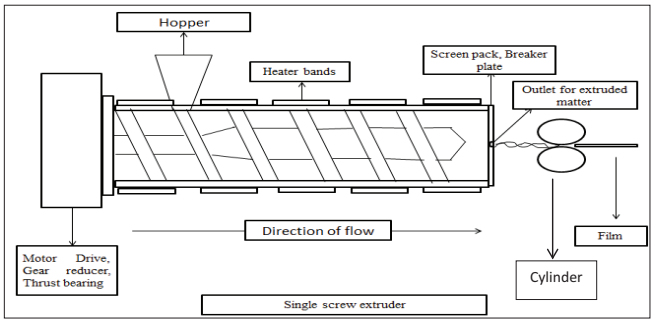

Figure 2: Hot-melt extrusion method

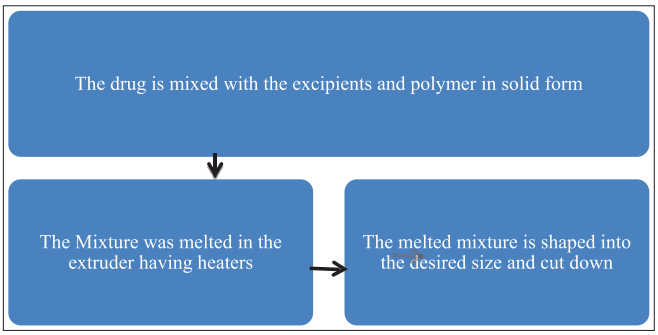

Figure 3: Process for hot-melt extrusion technique

Different techniques are used to prepare ODFs to ensure the production of even and uniform film with good elegance.

THE DIFFERENT TECHNIQUES FOR THE PREPARATION OF ODFS

Solvent-casting method

It is the most common method used for the preparation of the films because it is feasible due to straightforward method and low cost. Most commonly used solvents are water and ethanol. Film-forming water-soluble polymers and dissolved or dispersed in the solvent and then the active pharmaceutical ingredient (API), plasticizer, and other excipients are added to the polymer solution and allowed to mix fitly for overnight using magnetic stirrer. Then, the solution is cast on a casting apparatus or glass mold using coating knife which properly distributes the solution. Let it to dry overnight in an oven at 40°C–50°C. Then, peeled and cut into desired size and shape [Figure 1].[6]

Hot-melt extrusion

It is substitute for solvent-casting method. It is used when there is no use of organic solvent. Hot-melting extrusion is a process of shaping the mixture of polymer, API, excipients into the film b melting all components. Then, the film is cut down into desired shape and size. This method is not suitable for thermolabile APIs because APIs are subjected at high temperature in this method [Figures 2 and 3].[7,8]

Spray technique

In this technique, the polymer is dissolved in the solvent and the API and other excipients are mixed in it to form a clear solution. Then, the solution is sprayed on a suitable material such as glass, polythene film of non-siliconized kraft paper or sheet that acts as carrier support. Let it to dry and then the film layer is peeled off and cut into the required size and shape [Figure 4].

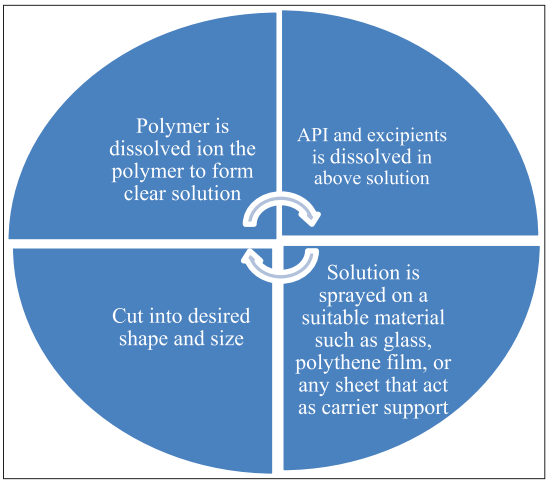

Figure 4: Spray technique

Solid dispersion extrusion

It is defined as the dispersion of one or more active ingredients in a matrix at solid state prepared by fusion, melting-solvent method. In the melting method, the drug is mixed with the melted carrier and stirred until the homogenous melt is obtained. It is prepared by dissolving a drug and carrier in a solvent, and then the solvent is evaporated. It improves the solubility and dissolution of the poorly soluble drugs.[9]

- Glyburide is a poorly soluble hypoglycemic drug. ODF of glyburide was prepared by solid dispersion method using polyethylene glycol 4000 and polyethylene glycol 6000 (1:1) shows better dissolution which means the solubility of drug is enhanced.[10]
- ODF of mefenamic acid prepared by the solid dispersion using eudragit shows the enhanced dissolution than the conventional dosage.[11]
- Solid dispersion of X drug was prepared using PEG6000, and polyvinyl pyrrolidine gives the better drug release and if it is followed by solvent evaporation method, then it gave even more release.[11]
- Solid dispersion of triclosan with hydroxylpropyl-β-cyclodextrin (HPBCD) with solubilizing agent poloxamer shows enhanced dissolution.[12]
- Solid microcrystalline dispersion of olanzapine with polyvinylpyrrolidone (PVP) shows the effective result by improving the solubility and enhancing the dissolution rate.[13]

In this method, the API is mixed with suitable solvent and the solution is added in melted polymer along with immiscible components then the mixture is extruded which gives formulation in the form of solid dispersion. Finally, the dispersion is shaped into film of desired size [Figure 5].

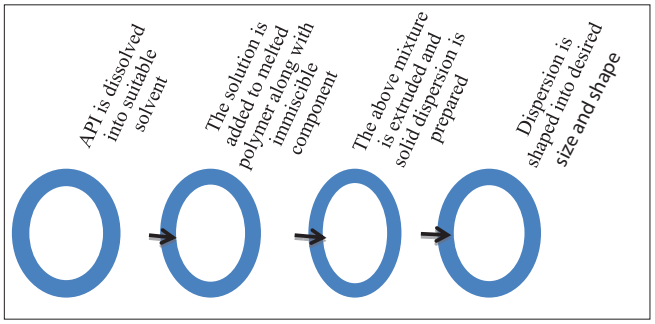

Figure 5: Process for solid dispersion method

Rolling method

In this method, the API, polymers, and other excipients are mixed with the suitable solvents, for example, water and alcohol. Then, the solution or suspension containing API is rolled on carrier. Then, the film is dried and cut into the desired shape and size [Figure 6].

Semisolid casting

In this method, the solution of water-soluble polymer is prepared. Then, the solution of acid-insoluble polymer us prepared by sodium hydroxide or ammonium. After that, the plasticizers are added to it that results in the gel mass. It is finally casted into the ribbons or film using the heat-controlled drums. The average thickness of film using this method is 0.005–0.05 inch. 1:4 is the ratio for the water-insoluble polymer to the film-forming polymer [Figure 7].[14]

Printing technology

The printing technique in ODFs is the latest and flexible technique, in which the drug is printed onto the surface of the polymer film. It is useful only in case of highly potent drugs because very small amount of drug can be incorporated into

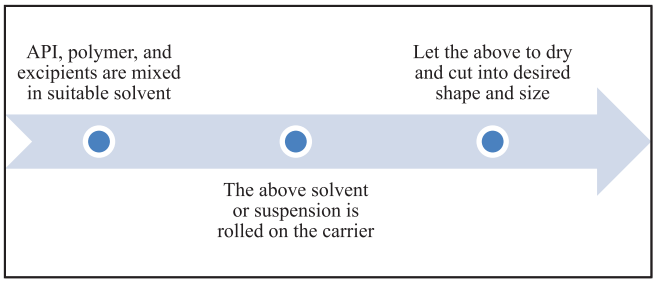

Figure 6: Process for rolling method

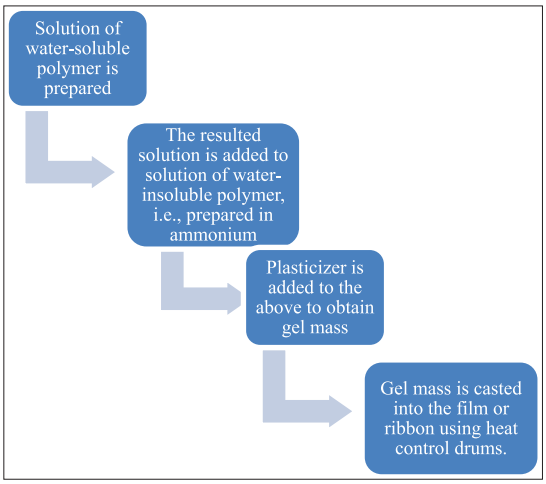

Figure 7: Process for semisolid casting method

the film using this technique, mainly used for the poorly water-soluble and potent drugs. The various type of printing technology is 3D printing, flexographic printing technology, etc.[15]

- Rasagiline mesylate and tadalafil are incorporated on the polymer films in four printing cycles, it shows comparable results with the solvent-casting method. It is flexible, cost-effective, and can be used for small scale.[16]
- Piroxicam which is a poorly soluble drug was printed on a film using flexographic printing technique and piezoelectric inkjet printing. Piroxicam solution was made using polyethylene glycol and ethanol. More than 90% of drug release was found in 5 min.[17]
- Aripiprazole is poorly soluble drug. Hence, Fused Deposition Printing technique was used to print the amorphous aripiprazole onto the film and was compared with the casted film. It was found that the film prepared using printing technique had better dissolution.[18]

Comparison of methods

There are different methods for the preparation of the ODFs such as solvent-casting method, hot-melt extrusion method, and rolling method. depending on the nature of the API and the excipients we choose different techniques. Like for thermolabile substances, we use solvent-casting method, for substances not compatible with solvents, we use hot-melt extrusion method. [13]

- Verapamil ODFs show better dissolution if prepared using the solvent-casting method than the hot-melt extrusion.[19]
- Hot-melt extrusion is a robust method to get better dissolution in many cases, especially when we cannot use solvents it is better than the other methods of preparation. Hot-melt extrusion enhances the bioavailability of the drug.[20]
- ODFs containing piroxicam as API and maltodextrin as polymer was prepared using hot-melt extrusion and solvent-casting method, but the dissolution of drug with solvent-casting method good compared to the hot-melt extrusion.[12]

Techniques used for solubility enhancement of API in ODFs

The ODFs are suitable for water-soluble drugs as it is dissolved with saliva and get absorbed, but for poorly water-soluble drugs, we need to use some techniques or add some aid to increase the solubility of that drug. The various techniques are:

Surfactants

Surfactants are the molecules with distinct polar and non-polar regions. The surfactants may be cationic, anionic, or neutral. The surfactants decrease the surface tension between two molecules and promote the solubility. Surfactant acts as dispersing, wetting, and solubilizing agent in ODFs. The various surfactants that we can use in ODFs are tween, sodium lauryl sulfate, etc.[1]

Tween 80 (polysorbate80) shows an effective result on the dissolution of the sildenafil citrate by enhancing solubility[21] and piroxicam[22] oral dispersive films that is a poorly soluble drug.

- Tween 20 and PVP combination decrease the solubility which results in the dissolution time for the piroxicam oral film which is a BCS II drug.[23]
- Cremphor EC shows a significant effect on the solubility and thus effect dissolution of the ritonavir ODF.[23]
- Eudragit used in levocetirizine ODFs as taste-masking agent but also shows a significant effect on the dissolution rate.[24]

Superdisintegrant

Super disintegrants primarily affect the rate of disintegration of the dosage. It promotes moisture penetration and dispersion of the dosage. Disintegration has a significant emphasis on the bioavailability of the drug. The mechanisms of action of disintegrants are swelling or wicking or chemical reaction or enzymatic action.

- Crospovidone in ODF of X drug shows the significant effect on the solubility.
- In dextromethorphan hydrobromide ODF, microcrystalline cellulose was used as superdisintegrant because of

which solubility was increased the dissolution time was reduced.[25]
- Polyplasdone was used in the ODF of sildenafil citrate which shows a significant change in the dissolution time.[21]
- Sodium starch glycolate was used as superdisintegrant in phenobarbitol ODF and shows an emphasis on the solubility thus the dissolution rate of the film.[26]

Cosolvent

A cosolvent is a substance that is added to a mixture of two or more separate substances that are typically immiscible, to make them miscible.

- Ethanol (90%) was used as the casting solution for the poorly water-soluble drug Diazepam as it influences the mechanical property, disintegration time of the film. It affects the viscosity of the casting media that's why we need more film-forming agent, but it evaporates and so residue remains which make it safe to use by the patient.[27]
- In development printing dosage form of piroxicam, the solubility study was performed in different solvents and cosolvents with ethanol, water, PEG, glycerol, etc. Ethanol-PEG shows better solubility and used as cosolvents and the printing technique used was flexographic printing. This results in the enhanced dissolution of the drug.[12]

Nanotechnology

It is the branch of science that deals with the dimension and tolerances of <100 nm. When the particle size of any particle is minimized to the nanoscale, then its particle properties could be change and that can be helpful in development of dosage. Nanotechnology can be implemented for the BCS II drugs to increase its solubility. There are different techniques to form a nanoparticle such as mechanical attrition, chemical precipitation, sol-gel technique, and electrodeposition. In ODFs, nanotechnology shows significant effect on the dissolution and bioavailability of the drug.

- ODF prepared using nanoparticle of X drug made by wet stirred media milling using HPMC and glycerine and followed by film casting and drying has an emphasis on dissolution compared to the conventional method.[28]
- The nanoparticle of Griseofulvin, that is, BCS class II drug loaded on the polymer film shows the 100% release of the drug. The nanoparticle was prepared in an aqueous suspension through wet stirred media milling.[29]
- Naproxen, fenofibrate, and griseofulvin are the few drugs that were used in ODFs as API and to increase the solubility the nanoparticles were prepared using wet stirred media milling method in HPMC solution containing glycerine. Some stabilizers were also used to prevent aggregation of the nanoparticles and dose uniformity.[30]

Complexation

Complexation is the process of making an atom or compound forms a complex with another. It is used for analysis, solubility enhancement, and many other purposes.

- Triclosan (TC) ODF was formulated using various film-forming polymers, film modifiers, and solvent. The HPBCD and poloxamer 407 was used to improve the solubility of TC. The TC-HPBCD and TC-poloxamer complex was formed which improves the dissolution of the film.[31]
- Etoricoxib has low solubility and poor taste. To mask the taste and improve the solubility in the mouth-dissolving film, the complexation technique was used. β-Cyclodextrin (β-CD) was used as a complexing agent and the film was prepared by using solvent casting method.[32]
- Aripiprazole film was prepared using β-CD and HPBDC as complexing agent to increase the solubility and hence improve the dissolution of the API and effect of both was compared. It was found that HPBDC forms better complex and has more efficacy.[32]

CONCLUSION

ODF are good alternative to other conventional dosage form (tablets and capsules) in mean of ease of administration, efficacy, cost effectiveness, etc. It is suitable for the dose development of drugs belonging to BCS class II. Numerous techniques are used to increase the solubility of the drugs in the ODFs. The printing technology is advantageous over the existing technologies since we can administer the small dosage of highly potent drugs onto the films with accuracy and precision. It is a cost-effective and flexible technology that can also be used for the small-scale production. It also allows for the production of multidrug dosage form. However, the improvements are still required for the large-scale production and the pharmacopoeia specifications are absent which is the biggest drawback of ODFs.

REFERENCES

1. Irfan, M., Rabel, S., Bukhtar, Q., Qadir, M.I., Jabeen, F., Khan, A., 2016. Orally disintegrating films: A modern expansion in drug delivery system. Saudi Pharm. J. 24, 537–546.
2. Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V.K., Khosa, R.L., 2012. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J. Adv. Pharm. Educ. Res. 2, 32–67.
3. Karki, S., Kim, H., Na, S.-J., Shin, D., Jo, K., Lee, J., 2016. Thin films as an emerging platform for drug delivery. Asian J. Pharm. Sci. 11, 559–574.

4. Preis, M., Knop, K., Breitkreutz, J., 2014. Mechanical strength test for orodispersible and buccal films. Int. J. Pharm. 461, 22–29.
5. Liew, K. Bin, Tan, Y.T.F., Peh, K.-K., 2014. Effect of polymer, plasticizer and filler on orally disintegrating film. Drug Dev. Ind. Pharm. 40, 110–119.
6. Ravi Kumar K and Mercy Sulochana, 2014. Fast Dissolving Films : A Unique Strategy for Drug Delivery. Asian J. Pharm. Res 4, 47–55.
7. Jani, R., Patel, D., 2015. Hot melt extrusion: An industrially feasible approach for casting orodispersible film. Asian J. Pharm. Sci. 10, 292–305.
8. Dixit, R.P., Puthli, S.P., 2009. Oral strip technology: Overview and future potential. J. Control. Release 139, 94–107.
9. Saharan, V.A., Kukkar, V., Kataria, M., Gera, M., Choudhury, P.K., 2009. Dissolution enhancement of drugs. Part I: Technologies and effect of carriers. Int. J. Heal. Res. 2, 107–124.
10. Betageri, G., 1995. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int. J. Pharm. 126, 155–160.
11. Shah, S., Maddineni, S., Lu, J., Repka, M.A., 2013a. Melt extrusion with poorly soluble drugs. Int. J. Pharm. 453, 233–252.
12. Strickley, R.G., Iwata, Q., Wu, S., Dahl, T.C., 2008. Pediatric Drugs-A Review of Commercially Available Oral Formulations. J. Pharm. Sci. 97, 1731–1774.
13. Modica de Mohac, L., de Fátima Pina, M., Raimi-Abraham, B.T., 2016. 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. 508, 42–50.
14. Amin, R.M.A., n.d. Manufacturing Techniques of Orally Dissolving Films.
15. Heer, D., Aggarwal, G., Kumar, S.L.H., 2013. Recent trends of fast dissolving drug delivery system - An overview of formulation technology. Pharmacophore 4, 1–9.
16. Janben, E.M., Schliephacke, R., Breitenbach, A., Breitkreutz, J., 2013. Drug-printing by flexographic printing technology - A new manufacturing process for orodispersible films. Int. J. Pharm. 441, 818–825.
17. Raijada, D., Genina, N., Fors, D., Wisaeus, E., Peltonen, J., Rantanen, J., Sandler, N., 2013b. A Step Toward Development of Printable Dosage Forms for Poorly Soluble Drugs. J. Pharm. Sci. 102, 3694–3704.
18. Jamróz, W., Kurek, M., Łyszczarz, E., Szafraniec, J., Knapik-Kowalczuk, J., Syrek, K., Paluch, M., Jachowicz, R., 2017. 3D printed orodispersible films with Aripiprazole. Int. J. Pharm.
19. Kunte, S., Tandale, P., 2010. Fast dissolving strips: A novel approach for the delivery of verapamil. J. Pharm. Bioallied Sci. 2, 325.
20. Shah, S., Maddineni, S., Lu, J., Repka, M.A., 2013b. Melt extrusion with poorly soluble drugs. Int. J. Pharm. 453, 233–252.
21. Hassanien Sagban, T., Yehia Ismail, K., 2014. Formulation and evaluation of orodispersible film of sildenafilcitrate. Int. J. Pharm. Pharm. Sci. 6, 81–86.
22. Cilurzo, F., Cupone, I.E., Minghetti, P., Selmin, F., Montanari, L., 2008. Fast dissolving films made of maltodextrins. Eur. J. Pharm. Biopharm. 70, 895–900.
23. Raijada, D., Genina, N., Fors, D., Wisaeus, E., Peltonen, J., Rantanen, J., Sandler, N., 2013a. A Step Toward Development of Printable Dosage Forms for Poorly Soluble Drugs. J. Pharm. Sci. 102, 3694–3704.
24. Sreekanth, J., Lakshmi, P.K., 2011. Formulation development of fast releasing oral thin films of levocetrizine dihydrochloride with eudragit EPO and optimisation through taguchi orthogonal experimental design. Int. J. Pharm. Sci. Rev. Res. 11, 115–123.
25. Auda, S.H., El-Badry, M., Ibrahim, M.A., 2014. Design, formulation and characterization of fast dissolving films containing dextromethorphan. Dig. J. Nanomater. Biostructures 9, 133–141
26. Yellanki, S.K., Jagtap, S., Masareddy, R., 2011. Dissofilm: A Novel Approach for Delivery of Phenobarbital; Design and Characterization. J. Young Pharm. 3, 181–188.
27. Visser, J.C., Woerdenbag, H.J., Crediet, S., Gerrits, E., Lesschen, M.A., Hinrichs, W.L.J., Breitkreutz, J., Frijlink, H.W., 2015. Orodispersible films in individualized pharmacotherapy: The development of a formulation for pharmacy preparations. Int. J. Pharm. 478, 155–163.
28. Sievens-Figueroa, L., Bhakay, A., Jerez-Rozo, J.I., Pandya, N., Romañach, R.J., Michniak-Kohn, B., Iqbal, Z., Bilgili, E., Davé, R.N., 2012. Preparation and characterization of hydroxypropyl methyl cellulose films containing stable BCS Class II drug nanoparticles for pharmaceutical applications. Int. J. Pharm. 423, 496–508.
29. Krull, S.M., Moreno, J., Li, M., Bilgili, E., Davé, R.N., 2017. Critical material attributes (CMAs) of strip films loaded with poorly water-soluble drug nanoparticles: III. Impact of drug nanoparticle loading. Int. J. Pharm. 523, 33–41
30. Vippagunta, S.R., Wang, Z., Hornung, S., Krill, S.L., 2007. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. J. Pharm. Sci. 96, 294–304.
31. Dinge, A., Nagarsenker, M., 2008. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS PharmSciTech 9, 349–56.
32. Senthilkumar, K., Vijaya, C., 2015. Formulation Development of Mouth Dissolving Film of Etoricoxib for Pain Management. Adv. Pharm. 2015, 1–11.

Source of Support: Nil. **Conflict of Interest:** None declared.