Review Article

Role of Superdisintegrants in Rapid Dissolving Oral Films

Shruthi BK*, Dr V. Chandrakala, S. Srinivasan
Department of Pharmaceutics, East Point College of Pharmacy, Rajiv Gandhi University of Health Science, Bidarahalli, Bengaluru, Karnataka, India.
***Corresponding author's E-mail:** shrubk081198@gmail.com

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ABSTRACT

Rapid dissolving oral film is the most advanced solid oral drug delivery system, that dissolve or disintegrate with in few seconds once placed in mouth without taking water or chewing. Drug directly reaches into systemic circulation therefore avoids first pass metabolism so bioavailability of medication may be improved. Now a days most of the pediatric, geriatric and dysphagia patients who find difficulty in swallowing, the rapid dissolving oral films often helps to overcome such type of complications. In terms of stability, handling, administration, and distribution, rapid dissolving oral films have grater advantages than tablet, capsules, or syrups. These compositions pharmacological activity is demonstrated by disintegration followed by dissolving. Hence disintegration has a major role for facilitating drug activity and thus gain popularity among other dosage forms. In this review, more importance is given on utilization of various super disintegrants comparing with other disintegrants. The different biological sources of super disintegrants (natural and synthetic), their properties, concentrations and modification to improves disintegration time are also high- lighted in this article.

Keywords: Rapid dissolving oral films, disintegrants, super disintegrants, rapid disintegration, rapid dissolution, swelling.

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INTRODUCTION

Oral route is the most selective route of administration for the systematic effect. Almost, 60% of all the formulations are solid dosage form. Tablet is the most preferable dosage form due to ease of handing, transportation, manufacturing and improve patient compliance.[1] Oral drug delivery system has advantages like dose uniformity, self-use and stable delivery. RDOF (rapid dissolving oral film) was created in 1970 as an alternative to traditional dosage forms and was first used for systemic drug delivery in 2004.[2] These systems contain solid dosage forms that disintegrate and dissolve rapidly in the oral cavity without the need of water (within 1 min) as a result quickly reach into bloodstream hence maximum bioavailability is been attained.[2,3] In some circumstances, such as geriatric, pediatric, bedridden, diarrhea, sudden episode of allergic attack, coughing, emetics, exigency(cardiac), patient experience difficulties in swallowing the traditional oral dosage form. To overcome this problem a novel formulation, rapid dissolving oral films (RDOF) was developed. They can also be used for local anesthetics such as tooth discomfort, oral ulcers, cold sores or coughing. RDOF contains some water-soluble API, polymer, saliva stimulating agent, sweetener, plasticizer and depending upon the formulation even super disintegrants are used.[2] Oral fast dissolving improves the efficacy of APIs compared to fast dissolving tablets, by disintegrating in the buccal cavity once they come in contact with saliva and without chewing.[1]

There are various requirements for incorporating API into film, such as the following:

- Pleasant taste. In case of bitter taste, taste masking agent are used.
- The dose of up to 40mg dose can be loaded.
- Less and moderate molecular weights are preferable.
- Increased stability.
- Solubility in saliva and water.
- Ability to penetrate in the buccal mucosal tissue.

oral thin film generally having area around 2*2 cm^2.[1,2] Polymer plays an important role while formulating oral thin film some natural polymers commonly used are pullulan, guar gum, sodium alginate, xanthan gum chitosan and few synthetic polymers used are HPMC E-3, HPMC E-5, HPMC E-15, Poly vinyl alcohol (PVA). Sweeteners are used to mask the bitter taste of rapid dissolving oral films examples are mannitol, sodium saccharin, fructose, sucrose. Plasticizers are used to maintain flexibility, increase tensile strength and elastic nature of film examples are glycerin, glycerol, PEG-400, tween-80.[2] Super disintegrants are used to provide rapid disintegrations as result of the combined effect of both water absorption and swelling.[4] In the current days rapid dissolving oral films are well proven and accepted technology used for the systemic

delivery of active pharmaceutical ingredients. RDOF can be used for various category of drugs Such as antihistamine, antiulcer, anti-asthmatic, antiepileptic, hypertension, heart attack, motion sickness, antitussive, paralysis, mental disorders, and repeated emesis.[5,6,7,8,9,10]

Advantages of rapid dissolving oral films: [1,4,11]

- It is light weight and more flexible.
- It disintegrate/dissolve rapidly in mouth.
- Without water RDOF can be administrated.
- Action takes place quickly.
- There is no risk of chocking.
- Stability can be increased.
- Bypasses the gastrointestinal track and thus increases the bioavailability.
- Lowering the dosage reduces adverse effect.
- It is simple to distribute.
- Leaves good odor to mouth.
- Small in size so it improves patient compliance.
- Distribution is easy.
- Easy formulation and placed on the market around 12-16 months.

Disadvantages of rapid dissolving oral film: [1,4]

- Larger doses of drug cannot be incorporated in the oral films.
- Bringing uniformity in the dosage form is difficult.
- It has the ability to absorb water.
- For packing special equipment's are required.
- Is not suitable for the drugs that cause irritation in the oral mucosa cannot be incorporated.
- Formulation process is costly compared with oral dissolving tablets.

Table 1: Comparison between rapid dissolving oral film and oral tablets. [12]

Sl.no	Rapid dissolving oral films	Mouth dissolving oral tablets
1.	Greater dissolution due to large surface area	Less dissolution due to less surface area
2.	There is no risk of chocking	There can be fear of choking
3.	They are flexible and durable	They are brittle and less durable than OTF
4.	Only less dose can be incorporated in formulation	High dose can be incorporated in formulation
5.	Patient compliance is more	Patient compliance is less than OTF

Table 2: Types of film and their properties:[5]

Properties	Flash release water	Mucoadhesive melt away water	Mucoadhesive sustained release water
Area(cm^2)	2-8	2-7	2-4
Thickness(µm)	20-70	50-500	50-250
Structure	Single layer	Single or multiple layer	Multi-layer
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	Low/Non soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension or solid solution
Application	It is applied to the upper plate of the tongue	It is applied to the gingival or buccal region	It is applied to the gingival or oral cavity
Dissolution	60sec	1-3 min	8-10 hr.

Classification of Mouth Dissolving Films[5]

1. Flash release water
2. Mucoadhesive melt away water
3. Mucoadhesive sustained release water

Table 3: Composition of Fast Dissolving Film [13]

Sl. No	Ingredients	Quantity (%w/w)
1.	Active pharmaceutical ingredient	1-30%
2.	Polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva stimulating agent	2-6%
5.	Super disintegrants	1-8%
6.	Sweetening agent	3-6%
7.	Flavors, colors, fillers	q. s

Methods to Formulate Rapid Dissolving Oral Thin Film[14,15,16,17]

Solvent casting method

In this method additives are dissolved in water, then water soluble polymer and drug is added to it and stir to form homogeneous mixture ultimately the formed mixture/solution is casted on petri plate and dried.

It is the most preferrable method to formulate rapid dissolving oral thin films because it gives better uniformity, more flexible, thickness and clarity than other method/techniques.

Hot melt extrusion

In this method, all the materials required to make films are taken together into its solid powder form. Then, this mixture is extruded under high temperature to form a homogeneous mass and then casted to form smooth films. The obtained films than cooled, trimmed and packaged. The major disadvantage of this process due to the use of high temperature during extrusion.

Rolling method

A carrier is rolled with a suspension containing medication. Vehicles mainly used here is water and ratio of water and alcohol. The films are dried on the rollers and it provides required shape and size.

Solid dispersion extrusion

In this method solid dispersion is formulated by extruding immiscible components with drug and then shaped in to films with the help of dies.

Super disintegrants

Super disintegrants, are a class of compounds which primary aid is to provide rapid disintegration and dissolution due to combination effect of swelling and water absorption by the formulation. Due to swelling mechanism of super disintegrants, the wetted surface of the carrier increases, which promotes the permeability and dispersibility of the system, hence it decreases the disintegration and dissolution time.

At low concentration that is 1-8% super disintegrants are more effective than disintegrants with considerable mechanical strength and disintegrating efficiency. 1 gram of super disintegrants will absorbs 10-40 gms of aqueous medium. After absorption it creates stress and entire oral film structure to break apart. [18,19]

Super disintegrants are selected on the basis of the following criteria [20,21]

- It should have rapid disintegration rate.
- It should produce good mouthfeel to patient.
- It should show good flow property.
- It should be non-toxic and non-irritants.
- It should be more flexible with API.

Super disintegrants are widely used in the tablet preparation to improve the productiveness of solid dosages forms. They reduce the drug disintegration and dissolution time by breaking entire pill into a little fragment in the saliva without need of water and provide quick on set of action. Super disintegrants are used in the rapid mouth dissolving films only when it is required according to solubility of the drug. When a drugs solubility, gel formation and complexation are poor, it's important to boost its hydration capacity and complexation.[22,23,24]

Mechanism of Action of Super Disintegrants

1. Swelling.
2. Porosity and capillary action (Wicking).
3. Combination effect.

Swelling

Swelling is the most widely accepted mechanism of action that requires water penetration for disintegration in formulation. Formulation has more porosity show slow disintegration due to appropriate swelling force. Particles of disintegrants swells /expands when it come in contact with suitable media, this causes the formulation to swell and break.[18, 25]

Capillary action / Wricked

Here the first step is disintegration by porosity/capillary action. Porosity produces route for the fluid penetration. When it comes in contact with a suitable aqueous medium, the medium penetrants into the formulation displacing air absorbed on the particles. This weakens the intermolecular bonds and break the formulation into small particles. Water uptake by the formulation depends upon hydrophilicity of the drug/excipients. Liquid is drawn up or wicked into these pathways through capillary action and breaks the boning of inter particles which causes the formulation to break apart.[18]

Combination effect

The combination effect of both swelling and porosity/capillary action by the formulation occur due to swelling mechanism of super disintegrants, the moistened surface of the carrier increases, which promotes the wettability and dispersibility of the system, hence it decreases the disintegration and dissolution time.[18]

Types of Super disintegrants

Natural super disintegrants

The natural super disintegrants involves various natural substances like gums, mucilage, and other substances of natural origins that are more effective at low concentrations and have greater disintegration efficiency and mechanical strength. They are comparatively cheaper, abundantly available, non-toxic and non-irritating in nature.[26] Some examples of natural super disintegrants are locust bean gum, guar gum, gum karaya, cassia fistula gum.

Synthetic super disintegrants

These are group super disintegrants, they are more effective in low concentration and reduces the disintegration and dissolution time.[26]

Table 4: Different Natural Super disintegrants and Their Effect.[26-33]

S. No	Plant mucilage	Drug	Result
1.	*Plantago ovata* mucilage	Prochlorperazine maleate	Dispersion time within 8 seconds. At Concentration of 8% w/w.
2.	Fenugreek seed mucilage	Metformin hydrochloride	It shows 15.6 sec disintegration time and 100% drug release within 18 minutes at concentration of 4% w/w.
3.	*Lepidium sativum*	Nimesulide	Disintegration time of 17 sec and mean dissolution time 5.27 sec. at 10% w/w concentration, found better than other synthetic disintegration like Ac-di-sol and SSG.
4.	*Hibiscus rosa* - sinensis Linn. Mucilage powder.	Aceclofenac	At concentration of 6% w/w showed disintegration time of 20 sec.
5.	*Ocimum gratissimum* mucilage powder and seed powder	Metformin hydrochloride	At 5%w/w concentration, mucilage powder and seed powder both at disintegrated in 43 sec. and 45 sec. respectively
6.	Chitosan	Cinnarizine	Good mouth feels and disintegration time of 60 sec. at the level of 3% w/w.

Table 5: Various Synthetic Super disintegrants and Their Properties.[3,26,22,34,35,36,37,38]

SL No	Synthetic Super disintegrants	Properties	Concentration and mechanism of disintegration	Drug used
1.	Croscarmellose Sodium	It is insoluble in water, although it rapidly swells to 4 – 8 times its original volume on contact with water. 0.81 – 0.83 m^2/g is the specific area and swelling index is 65±1.7% v/v.	It may be used in the range of 2%w/w. Fast absorption of water followed by rapid swelling. *The drug levocetirizine with 2% croscarmellose sodium show disintegration time of 15 sec and drug release was 96.80%.*	• Fenofibrate • Donepezil hydrochloride • Lovastatin • Levocetirizine
2.	Sodium starch glycolate	Rapid absorption causes swelling of up to 6%. Rise in concentration causes gelling and loss of disintegration and Swelling index 52±1.2% v/v.	It is used in the limit of 2-8%w/w. Fast water uptake followed by speed swelling. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects. The drug Loperamide having 6% SSG as super disintegrants with 0.2ml PG and HPMC-E50 as polymer show disintegration time of 3.48sec, drug content uniformity was 99.04% and dissolution study was found to be 99.4%.	• Fenofibrate • Donepezil hydrochloride • Loperamide
3.	Crospovidone	It is absolutely insoluble in water. Rapidly disperses and swell in water. Increase in the rate of swelling compared to other disintegrants. Large surface level to volume ratio than other disintegrants. Swelling index 58±1.5% v/v.	It is used in the range of 2-5% w/w. combination of swelling and wicking. Least disintegration time of 10.33 sec, and more than 90% drug release with in 5min was seen for the film containing drug as donepezil hydro-chloride polymer sodium alginate and cross povidone as super disintegrants compared to (CCS, SSG). The drug lovastatin with 4% Crospovidone as super disintegrants show disintegration time of 7sec, drug content uniformity was 98.86% and dissolution study was found to be 99.27%.	• Donepezil hydrochloride • Lovastatin
4.	Polacrilin potassium	No lumps formation after disintegration. Eye compatibility with excipients and common therapeutics.	It is used in range of 0.5-5%w/w. Quick water uptake followed by rapid swelling and as a taste masking agent for various drugs.	

Table 7: Marketed Films: [3,38,40]

S. No	Brand name	Manufacture/Distributer	API	Uses
1	Listerine	Pfizer	Cool mint	Mouth fresheners
2	Gas-X	Novartis	Simethicone	Antacid
3	Triaminic	Novartis	Dextromethorphan HBr	Anti-allergic
4	Theraflu	Novartis	Dextromethorphan HBr	Anti-allergic
5	Suppress®	InnoZen®Inc	Menthol	Cough suppressant
6	Chloraseptic	Prestige	Benzocaine Menthol	Sore throat
7	Benadryl	Pfizer	Diphenhydramine HCL	Anti-allergic
8	Klonopin Wafers	Solvay Pharmaceuticals	Clonazepam	Treatment of anxiety
9	Orajel	Del	Menthol/Pectin	Mouth ulcer
10	Ondansetron ODF	Setofilm	Bioalliance Pharma	Anti-emetic
11	Sudafed PE	Wolters Kluwer Health Inc.	Phenylephrine	Relieving Congestion
12	Ondansetron	Zuplenz (R)	Monosol Rx	Anti-emetic
13	Donepezil	Donepezil Rapid film	Labtec	Alzheimer's disease

Table 8: Current Patents on Fast Dissolving Films/Strips [41,42,43,44,45,46,47,48]

S. No	Title	Inventor	Patent Number
1	Bioerodable films for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al.	6159498
2	Fast dissolving film for oral administration of drug	Friend et al.	2004/0208931
3	Oral thin film vaccine preparation	Brian Pulliam	2012/103464A2
4	Water soluble film for oral administration with instant wettability	Zerbe et al.	5,948,430
5	Fast dissolving consumable films containing sweeteners	Lori et al.	2003/0211136
6	Bitter taste masked oral thin film formulation of Sildenafil citrate	Dae-Kun Song et al.	2013/085224A1
7	Fast dissolving consumable films containing a modified starch for improved heat and moisture resistance	David et al.	2004/0247648
8	pH-sensitive compounds in taste masking within oral thin film strips	A Mark Schobel et al.	2509631A4
9	Dissolving thin films xanthone supplement	Kupper et al.	7182964B2
10	Fast dissolving orally consumable films	Sau-Hung Spence Leung et al.	6596298B2
11	Disintegrable films for diagnostic devices	Meathrel et al.	7,470,397
12	Rapidly disintegrating film for delivery of pharmaceutical and cosmetic agents	Scott D Bamhart et al.	1680079A2
13	Dissolvable tobacco film strips and method of making the same	Wern et al.	7946296B2
14	Quick dissolving oral thin film for targeted delivery of therapeutic agents	Hai – Quan Mao et al.	2011/0305768A1
15	Thin film strip	Berry et al.	7,241,411
16	Pharmaceutical carrier devices suitable for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al.	7579019B2
17	Film comprising nitro-glycerine	Maibach and Todd	20100215774

CONCLUSION

Many pharmaceutical industries are changing their products from tablets to fast dissolving oral thin films. Since films have more advantages than tablets, capsules and syrups in terms of stability handling, transportation and administration. This technology gives excellent platform for patent non-infringing product. Super disintegrants swells when come in contact with water or any suitable medium and shows faster disintegration time when compared to disintegrants, they provide good mechanical strength to films and facilitates easy transportation. From the above review it is concluded that natural and synthetic super disintegrants both have better effects on rapid dissolving oral thin films, usually they are

used when the drug is poorly water soluble, poor gel formation, to increase the good hydration capacity, and complexation. Therefore, rapid dissolving oral films have been successfully commercialized by using various kinds of super disintegrants.

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