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Investigation Of Different Polymers, Plasticizers And Superdisintegrating Agents Alone And In Combination For Use In The Formulation Of Fast Dissolving Oral Films

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Abstract: Natural gums may not essentially form a film with acceptable properties like disintegration time etc. This is due to high molecular weight and high viscosity of natural gums. Therefore their use is limited in oral fast dissolving film. To make them useful, it was one of the attempts to combine them with semi-synthetic or synthetic polymers and to check resultant properties of film for their acceptability. Films were prepared from aqueous dispersions of polymers. Some natural, semi-synthetic and synthetic polymers were used. Polymers and their combinations which have proven acceptability were tried to observe the effect of superdisintegrating agents. Sodium starch glycolate and croscaremellose sodium were used as superdisintegrating agents. Among them which have shown disintegration satisfactory, were further selected to observe the effect of plasticizer that is propylene glycol (PG) and polyethylene glycol 400 (PEG 400) on film forming ability, disintegration, weight variation, thickness and folding endurance etc. Pullulan alone, and HPMC E15 + pectin have shown best film acceptability. Combination of pullulan, guar gum, xanthan gum and carrageenan has shown excellent of film formation. Addition of pectin in HPMC E5 has shown increase disintegration time than HPMC E5 alone indicating that natural polymer pectin increases disintegration time. Films prepared by using PEG 400 were sticky in nature. Good acceptability was observed in films prepared by using PG. However, both of these plasticizers have not shown considerable effect on disintegration time of film. Formulation prepared using propylene glycol as the plasticizer had good appearance, high folding endurance and acceptable disintegration time.

Keywords: Fast dissolving oral film, Plasticizer, Film-forming polymers and Superdisintegrating agents.

Introduction

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance[1]. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients[2]. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for

pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water[3]. Fast dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed[4]. They impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs[5]. Oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, plasticizers, superdisintegrating agents, sweeteners, flavors, colors, saliva stimulating agents, preservatives, surfactants etc but the most essential ingredients of oral films are polymers, plasticizers and superdisintegrating agents[2]. A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of polymer, is one of the most important and critical parameter for successful development of the film formulation[6]. The polymers can be used alone or in combination to obtain the desired film properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type and amount of polymer in the formulation[7]. As the strip forming polymer (which forms the platform for the oral film) is the most essential and major component of the film, at least 45%w/w of polymer should generally be present based on the total weight of dry film but typically 60 to 65%w/w of polymer is preferred to obtain desired properties[8]. Plasticizer is a vital ingredient of the fast dissolving films. Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. Typically the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight[5]. The disintegration of the strip in the oral cavity depends on the type of superdisintegrating agent and the amount of disintegrating agent in the formulation. A variety of superdisintegrating agents are available for preparation of fast dissolving films. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit[9].

Materials And Methods

Materials

All the chemicals used were of analytical grade and were used without further purification. Distilled water was used as a solvent throughout the study.

Method

Preparation Of Oral Fast Dissolving Films

Oral fast-dissolving film was prepared by the solvent-casting method. Water soluble film polymers (35% w/w) were dissolved in sufficient volume of distilled water and then superdisintegrating agents (4% w/w), citric acid (6% w/w) (Saliva stimulating agent) were added slowly so as to form uniform viscous solution by using magnetic stirrer at speed of 300 rpm for 3 hr. After that plasticizers (20% w/w) and saccharin sodium (sweetener) (5% w/w) Peppermint oil (flavour), Tartrazine (colour) added in polymeric solution to form a clear viscous solution. The excipients were added in such a quantity that they form smooth, transparent and flexible film. Then both the solutions were mixed by using magnetic stirrer at speed of 300 rpm for 1hour,degassed under vacuum, resulting solution was cast as a film into the petri-dishes (area of 63.585 cm^2) and kept at room temp. for a period of 24 hours. After that film was dried in drying oven, collected and cut into 2cm×2cm size.

Evaluation Of Fast Dissolving Films

Appearance Of Films

Films were evaluated visually for appearance such as smooth surface, transparency, colour etc.

Film Forming Capacity

It is ability of film formers to form film with desired properties. Relative film forming ability was determined on the basis of rating given to each film. Rating was given out of +++++ such as poor (+), average (++), good (+++), best (++++) and excellent (+++++) [10].

Thickness Of The Film

The thickness of films was measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each film. Mean SD is calculated. The standard range for film thickness should not be less than 5 %. This is essential to assure uniformity in the thickness of the film.

Weight Variation Of The Film

Weight variation was studied by individually weighing 6 randomly selected film strips. Average weight of films calculated. The weight of each film should not deviate significantly from average weight[11].

Folding Endurance

It is measured manually for the prepared oral film. A film was repeatedly folded at 180^0 at the same place till it breaks. This test was performed on three films of each formulation and mean ±SD was calculated.

in vitro Disintegration Time

In vitro disintegration time was determined visually in a beaker of 25 ml phosphate buffer pH 6.8 with swirling every 10 seconds. The disintegration is the time when film breaks or disintegrates. All studies were performed in triplicate.

Results And Discussion

Polymers: The different batches of oral films of natural and semi-synthetic polymers were prepared and evaluated for their different parameters, which are shown in table 1 and effect of polymers on film forming capacity shown in fig. 1. Some of natural polymers which were used alone or combination showed good film forming capacity and have smooth and transparent appearance such as pullulan, pullulan + guar gum +xanthan gum + carageenan, and pectin. However, semi-synthetic polymers which were alone or combination showed good film forming capacity and have smooth and transparent appearance such as HPMC E5, HPMC E15, HPMC E50, HPMC E5 +xanthan gum, HPMC E15 + guar gum, and HPMC E15 +xanthan gum. The combination of natural as well as semi-synthetic polymers also provide best oral film such as HPMC E15+pectin, which showed good film forming capacity and have smooth and transparent appearance. Depending on the appearance and film forming capacity of different polymers used alone or combination, the selected polymers which showed good appearance and film forming capacity were further prepared with superdisintegrating agents and evaluated for disintegration time.

Superdisintegrating Agents: The batches of oral films of natural and semi-synthetic polymers with superdisintegrating agents were prepared and evaluated for appearance and disintegration time, which are shown in table 2 and effect of superdisintegrating agents on disintegration time shown in fig. 2. Oral films were suitably prepared using different superdisintegrating agents such as sodium starch glycolate (SSG) and croscaremellose sodium (CCS). Film gives better result prepared with HPMC E15 +pectin+ SSG, which showed smooth, transparent appearance and disintegration time of 45 sec; and HPMC E15 +pectin+ CCS showed smooth, transparent appearance and disintegration time of 50 sec. The selected polymers (alone or combination) used with superdisintegrating agents which showed good appearance, film forming capacity and accepted disintegration time were further prepared with different plasticizers and evaluated for folding endurance and disintegration time.

Table 1: Evaluation of films of explored polymers

Sr. no.	Polymers Used	*Film forming capacity	Appearance
1)	HPMC E5(500mg)	+++	Transparent,smooth,good appearance
2)	HPMC E15(500mg)	+++	Transparent,slightly rough
3)	HPMC E50(500mg)	+++	Transparent,rough appearance
4)	Carboxy methyl cellulose(500mg)	++	NotTransparent,rough,turbid
5)	Pullulan(500mg)	++++	Very Transparent,smooth
6)	Pullulan(250mg) + Guar gum (100mg)+xanthan gum(100mg) + carageenan(50mg)	+++++	Smooth,transparent
7)	PVA(500mg)	+++	Transparent
8)	Sodium alginate(500mg)	-	Does not form film
9)	PVP K30(500mg)	+	Semitransparent
10)	Chitosan(500mg)	++	Transparent
11)	Guar gum(500mg)	+	Not Transparent, rough, turbid
12)	Carageenan(500mg)	------	Does not form film
13)	HPMC E5(400mg)+ Carageenan(100mg)	++	Semi Transparent,rough, turbid
14)	HPMC E5(400mg) + Guar gum(100mg)	+++	Transparent,smooth
15)	Xanthan Gum(500mg)	++	Sticky, transparent
16)	HPMC E5(400mg) +Xanthan Gum(100mg)	+++	Smooth,transparent
17)	HPMC E15(400mg) + Guar gum(100mg)	+++	Transparent,smooth
18)	HPMC E15(400mg) +Xanthan Gum(100mg)	+++	Smooth,transparent
19)	Pectin(500mg)	++	Smooth, transparent
20)	HPMC E15(300mg)+Pectin(200mg)	++++	Smooth, transparent

***Rating was given out of +++++**

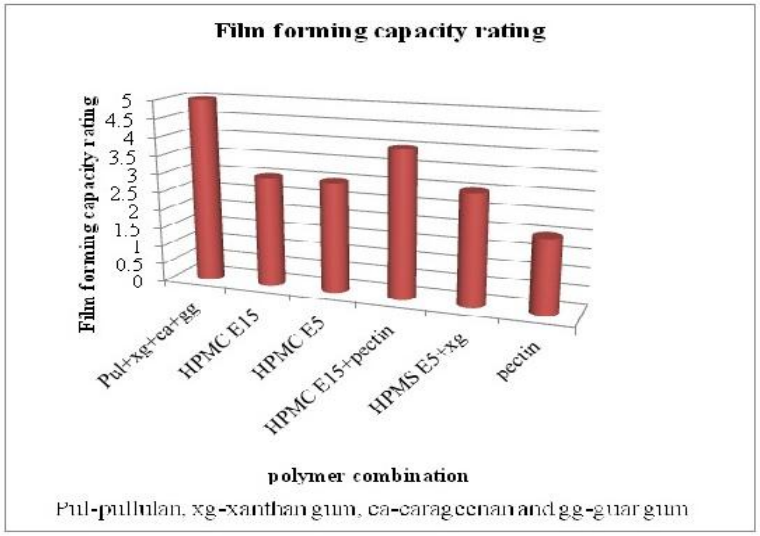

Figure 1: Effect of polymers on film forming capacity

Table 2: Evaluation of films using superdisintegrating agents

Sr. no.	Polymer+ superdisintegrating agent	Appearance	Disintegration time (in phosphate buffer pH 6.8)
1)	Xanthan Gum(500mg) + SSG(30mg)	Sticky, Transparent	6 minute
2)	Xanthan Gum(500mg) + CCS(30mg)	Sticky, Transparent	4 minute
3)	HPMC E15(500mg) + SSG(30mg)	Smooth, transparent	35 sec
4)	HPMC E15(500mg) + CCS(30mg)	Smooth, transparent	25 sec
5)	HPMC E15(300mg) +Pectin(200mg)+ SSG(30mg)	Smooth, transparent	45 sec
6)	HPMC E15(300mg)+Pectin(200mg) + CCS(30mg)	Smooth, transparent	50 sec
7)	HPMC E15(400mg) + guar gum(100mg) + SSG(30mg)	Smooth, transparent, turbid	5 minute
8)	HPMC E15(400mg) +guar gum(100mg) + CCS(30mg)	Smooth, transparent,turbid	4 minute
9)	HPMC E50(500mg)+ SSG(30mg)	Smooth, transparent	2 minute
8)	HPMC E50(500mg)+ CCS(30mg)	Smooth, transparent	1 minute 40 sec
9)	HPMC E5(500mg) + CCS(30mg)	Smooth, transparent	1 minute 6 sec
10)	HPMC E5(500mg) + SSG(30mg)	Smooth, transparent	35 sec
11)	HPMC E5(300mg) + Pectin(200mg)+ CCS(30mg)	Smooth, transparent	55 sec
12)	HPMC E5(300mg) + Pectin(200mg)+ SSG(30mg)	Smooth, transparent	50 sec
15)	Pectin(500mg) + CCS(30mg)	Smooth, transparent	1 minute 15 sec
16)	Pectin(500mg) + SSG(30mg)	Smooth, transparent	1 minute 19 sec

***SSG-sodium starch glycolate, CCS- croscarmellose sodium**

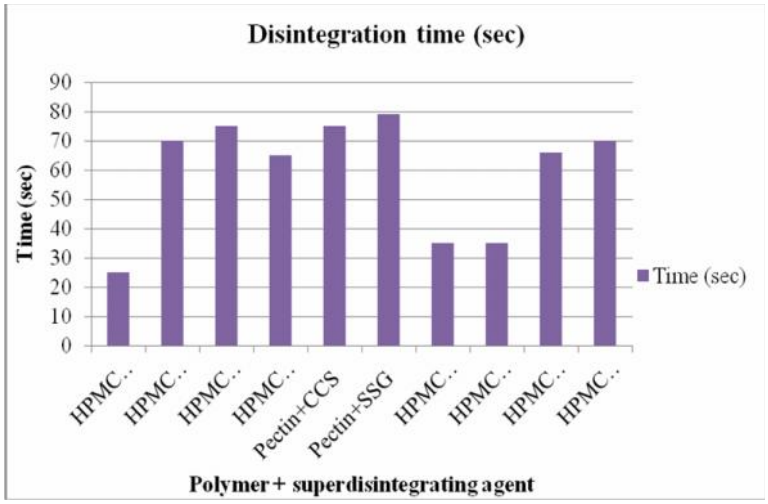

Figure 2: Effect of superdisintegrating agents on disintegration time

Plasticizers: The different batches of oral films with different plasticizers were prepared which are shown in fig. 3 and evaluated for various parameters, which are shown in table 3 and Effect of plasticizers on disintegration time and folding endurance are sown in fig. 4 and 5 respectively. Oral films were suitably prepared using different plasticizers such as propylene glycol (PG) and polyethylene glycol (PEG 400). Formulation prepared using PG as the plasticizer had good appearance. Film prepared using PEG 400 as the plasticizer did not possess good appearance and/or were somewhat sticky to touch. This may have been due to the formation of a moist layer on the surface of film, which could potentially affect its appearance and handling. Therefore, PG was found to be better plasticizer than PEG 400 for the preparation of films. Polyethylene glycol 400 (PEG 400) and propylene glycol (PG) were selected as the plasticizers to be used separately. In addition, concentration of PEG 400 and PG less than 10% was not enough to plasticize the films because the formed films were brittle and fragmented easily. On the other hand, concentration of PEG and PG higher than 30% posed problems in drying the films. Moreover, the formed films were sticky, difficult to handle and remove from the petri dish. From the data shown in Table 3, it can be seen that films prepared using PG resulted in higher folding endurance than those prepared using PEG 400. Formulation containing PEG 400 or PG as the plasticizer at the same respective polymer concentration exhibited almost similar disintegration times indicating that the concentration as well as the type of plasticizer used not much affect on the disintegration of the film.

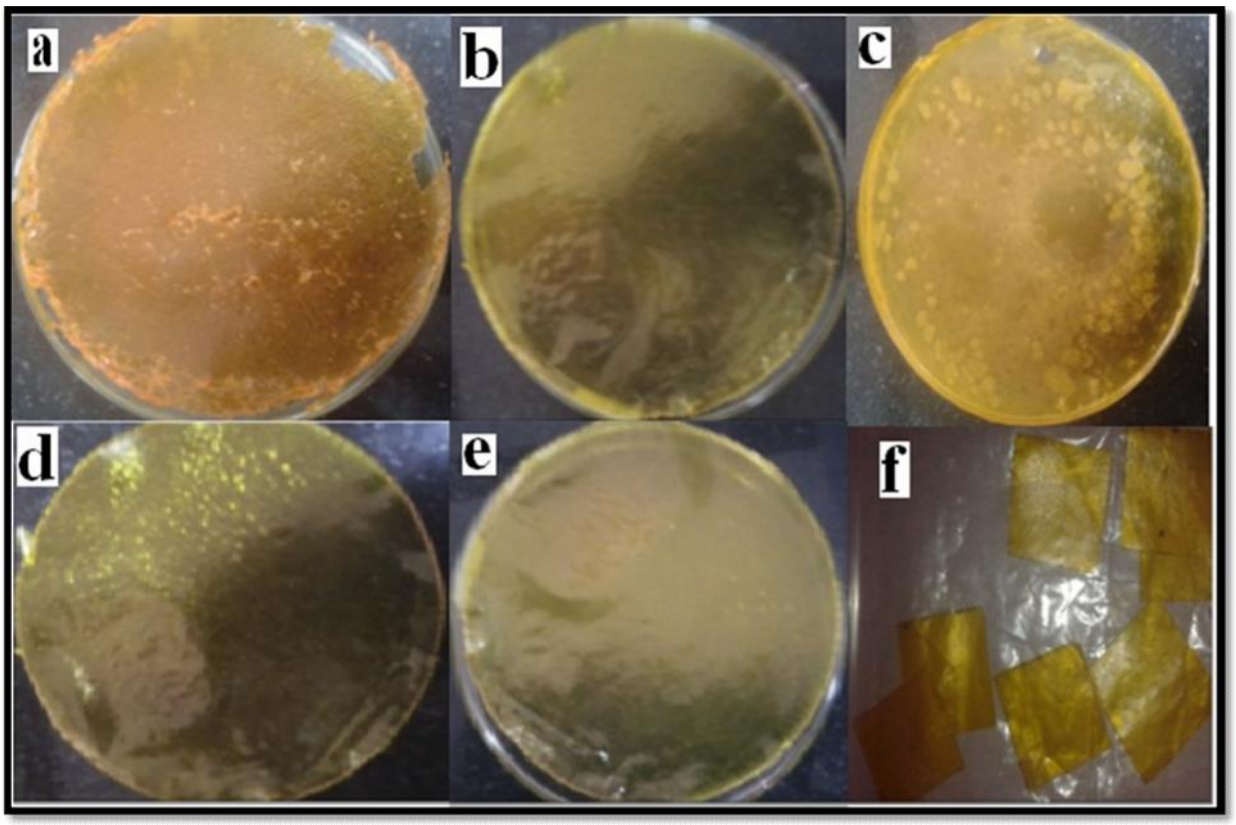

Figure 3: Images of different batches of fast dissolving oral films-

a) HPMC E15+pectin+glycerol, b) HPMC E15+pectin+propylene glycol, c) HPMC E15+pectin+sorbitol, d) HPMC E15+pectin+PEG 400, e) HPMC E15+PG and f) HPMC E15+pectin+propylene glycol (2 cm x 2 cm)

Table 3: Evaluation of films using plasticizers

Sr. no.	Polymer + superdisintegrating agent + plasticizer	Weight of film (mg)	Thickness (mm)	Folding endurance (no.)	Disintegration time (phosphate buffer pH 6.8) (sec)
1)	HPMC E15(500mg) +CCS(30mg) + PG(0.5ml)	85	0.13	50	80 sec
2)	HPMC E5(500mg) +CCS(30mg) + PG(0.5ml)	78	0.11	80	85 sec
3)	HPMCE15(300mg) +Pectin(200mg)+CCS(15mg) +SSG(15mg)+ Sorbitol(0.5ml)	108	0.14	285	95 sec
4)	HPMCE15(300mg) +Pectin(200mg)+CCS(15mg) +SSG(15mg)+ Glycerol(0.5ml)	100	0.11	275	40 sec
5)	HPMCE15(300mg) +Pectin(200mg)+CCS(15mg) +SSG(15mg)+ PEG 400(0.5ml)	81	0.08	135	60 sec
6)	HPMCE15(300mg) +Pectin(200mg)+CCS(15mg) +SSG(15mg)+PG(0.5ml)	74	0.07	185	66 sec

***PG- Propylene glycol, PEG- Polyethylene glycol**

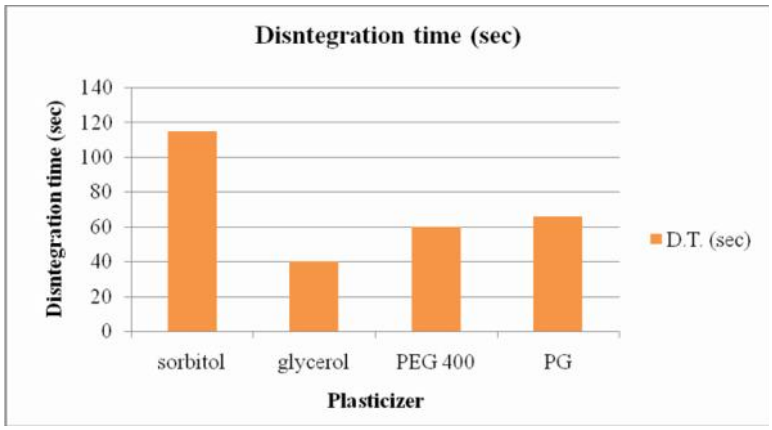

Figure 4: Effect of plasticizers on disintegration time

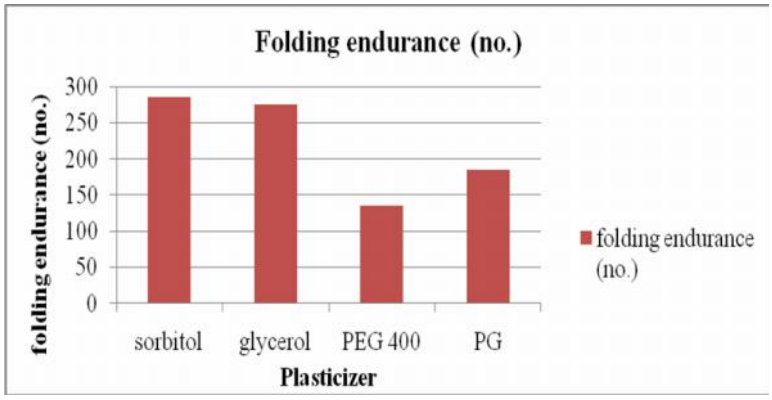

Figure 5: Effect of plasticizers on folding endurance

Conclusion

According to literature a film should be flexible and tough without being brittle. From the screening of components used in formulation of fast dissolving oral films, the film prepared by using combination of polymers such as HPMC E15, pectin, plasticizer such as propylene glycol and superdisintegrants such as SSG and CCS improve hydrophilicity, mouth feel, disintegration time, flexibility of the strip and reduces the brittleness of fast dissolving films.

References

1. Patel A, Prajapati D. Fast dissolving films (FDFs) as a newer venture in fast dissolving dosage forms. International Journal of Drug Development & Research. 2010; 2: 231-246.
2. Kaur R, Bala R. A Novel approach in oral fast dissolving drug delivery system –A review. American Journal of PharmTech Research. 2012; 2(1): 88-104.
3. Parmar D, Patel U. Orally fast dissolving films as dominant dosage form for quick release. IJPRBS. 2012; 1(3): 27- 41.
4. Saini S, Nanda A. Fast dissolving films (FDF): Innovative drug delivery system. Pharmacologyonline. 2011; 2: 919-928.
5. Kaur R, Bala R. Exploration of different polymers and optimization of concentration of plasticizer in the formulation of oral fast dissolving strip. International journal of pharmaceutical research and bio-science. 2012; 1 (2): 94-101.
6. Corniello CM, Quick-Dissolve Strips: From Concept to Commercialization. Drug Delivery. Tech., 2006, 6(2),68-71.
7. Kulkarni N, Kumar LD, Sorg A, Fast dissolving Orally Consumable Films containing An Antitussive and A mucosa coating agent, U.S. Patent 206942, Nov 6, 2003.
8. Nagar P, Chauhan I. Insights into Polymers: Film Formers in Mouth Dissolving Films. Drug Invention Today. 2011; 3(12): 280-289.
9. Puttalingaiah L, Kunchu K. Fast disintegrating tablets: An overview of formulation, technology and evaluation. RJPBCS. 2011; 3(3): 589-601.
10. Dixit R, Puthli S. Oral strip technology: Overview and future potential. Journal of Controlled Release. 2009: 94–107.
11. Patel R, Shardul N, Patel J, and Baria A: Formulation Development and Evaluation of Mouth Melting Film of Ondansetron. Arch Pharm Sci & Res 2009; 1: 212-217.

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