doi.org/10.36721/PJPS.2020.33.1.REG.183-189.1

Development and pharmaceutical evaluation of oral fast dissolving thin film of escitalopram: A patient friendly dosage form

Madiha Mushtaque[1], Iyad Naeem Muhammad[1]*, Syed Muhammad Fareed Hassan[1], Aatka Ali[1,2] and Rida Masood[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy & Pharmaceutical Science, University of Karachi, Karachi, Pakistan
[2]Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan

Abstract: The current study focused on the development, optimization and pharmaceutical evaluation of a mouth dissolving film of Escitalopram 5mg. The designing and optimization of the formulations have been carried out through Design-Expert ® Ver. 9, using central composite response surface methodology. The software generated six optimized formulations have been fabricated via solvent casting method incorporated with HPMC and PEG 400 as Plasticizer. The developed formulations were assessed for various quality attributes including weight variation, drug-excipients interaction, dryness/ tack test, thickness, percent elongation, swelling index, disintegration, folding endurance, surface pH, content uniformity, assay, moisture uptake, stability, and organoleptic properties. A validated spectrophotometric method has been used to ascertain drug content. The formulations were subjected for stability studies for six months in accordance with ICH accelerated stability studies guidelines. No stability issue has been observed. All the test formulations have shown satisfactory in vitro release of escitalopram whereas most promising results have been exhibited by F5 and F6 formulations. The study concluded that a unique, novel, safe and stable formulation of oral fast dissolving thin films of escitalopram can be formulated with ease. The preparation method was simple and reproducible with scale-up tendency so that it can fulfill the need of the commercial manufacturing process.

Keywords: Escitalopram, oral, fast dissolving, thin films, evaluation, formulation.

INTRODUCTION

The major objective of this research is to prepare the alternative dosage form for Escitalopram delivery especially for non-cooperative patients as it doesn't need chewing or water for swallowing. Fast dissolving oral thin films now become a point of convergence amongst all other dosage forms (Patil and Shrivastava, 2012). Generally, fast-dissolving drug delivery systems are formulated as a tablet that can disintegrate quickly. Fast dissolving oral thin films are considered as novel drug delivery system in which film disintegrated rapidly when placed over the tongue or at the buccal cavity without water or by munching (Arya *et al*., 2010). The thin film of escitalopram can be beneficial for patients suffering from anxiety and panic disorders because of its ease in handling and ideal in traveling as well as for elderly patients who faced difficulty due to dysphagia. Escitalopram is metabolized via cytochrome P450 iso-enzyme CYP2C19 so the developed dosage form can by-pass the first pass effect and avoids the drug-drug interaction (Lee *et al*., 2017). Moreover, it can also be an alternative choice for the hepatic impaired patient. Although escitalopram is commercially available as a tablet, the developed film formulation encompasses the ease of manufacturing as well as patient compliance.

**Corresponding author:* e-mail: iyanaeem@uok.edu.pk

MATERIALS AND METHODS

Materials

The sample of escitalopram oxalate was gifted by Nabi Qasim Pharma Karachi, Pakistan. Hydroxypropyl methylcellulose, polyethylene glycol 400, hydrochloric acid and sodium dodecyl sulfate were obtained from Sigma Aldrich, Steinheim, Germany. Cross carmellose and vanillin were purchased from Anvochem, Cheshire, United Kingdom, and Xinhua Perfume Co Ltd. China respectively. Citric acid was procured from Riedel de Haen chemicals. Methanol was obtained from BDH Laboratories, Poole, England. Distilled water was obtained from in-house distillation assembly Hamitton Laboratories, Kent, England.

Rationale for film formulations design

The escitalopram formulations had been designed statistically with Response surface central composite method with two factors includes a) the Concentration of Polymer and b) The concentration of Plasticizer that is by means of a computer application Design expert® version 7.0, 2005, Stat-Ease, Inc. USA (table 1)

Preparation method of film

Weighed all excipients and active pharmaceutical ingredients (±0.01) utilizing weighing balance (Shimadzu libror EB-430, Kyoto, Japan) and then dissolved all water-soluble ingredients in water including vanillin, PEG, SLS, cross carmellose to make clear viscous

solution via homogenizer (Nissei AM-3 OSK 9260-3 Ogawa Seiki Co. Ltd, Tokyo, Japan) at speed of 1200-1500 rpm and 50-60°C for 15 min. After that mixed HPMC in water and again homogenized at the same speed and time. Escitalopram oxalate was dissolved in methanol and then added in the above mixture by using homogenizer at the same speed and time. Finally, the viscous solution was transferred on the glass plate and spread it with the help of local made roller and dried in an oven (Ehret H.Jurgens & Co. D 2800, Bremen, German) at 50-60°C for 12 hr, and then cut into 3*2cm pieces (see fig. 1). For formulation composition has been calculated via Design Expert Ver. 7.0 and for statistical Analysis carried out by using MS- Excel 2010

Physicochemical evaluation

Physical appearance

Homogeneity, surface smoothness, color, transparency, Odor and overall acceptance are the parameters observed for the assessment of physical appurtenance (Nalluri *et al*., 2013).

Weight variation

Take the 20 films and individually weighed each film. The mean and standard deviation were computed.

Thickness

The film thickness of six samples was measured from five different locations using screw gauge (micrometer screw gauge, China) then average thickness and standard deviation were calculated (Senthilkumar and Vijaya, 2015, Raghavendra and Kumar, 2017).

Folding endurance

Folding endurance of 6 films was studied by folding the film repetitively, folding one side of the film at the same place till it cracked. The folding endurance expresses the number of times the film folded at the same place, in order to develop visible cracks or to break the specimen (Patel Jitendra *et al*., 2013).

Percent elongation

The percent elongation of the strip was determined by stretching the films and was calculated by the following formula:

Elongation at break (%) = increase in length at breaking point (mm) ×100%

Original length (mm)

Surface ph

The pH of the films was assessed by moistening them with 0.5 ml distilled water for 1hr. The electrodes of the pH meter (Jenway 370, Chelmsford, England) were brought in contact with film surface and note down the readings when equilibrium attained. The same procedure was performed in triplicate for six film samples (Raghavendra and Kumar, 2017, Yasmeen *et al*., 2012)

Uniformity of drug content

The film was taken in a 100ml flask and make up the volume with 0.1N HCl and continuously shake for two hours by means of mechanical shaker IKA® 260 Basic, Staufen Germany). Then subsequent solution having concentration approx. 50µg/ml was filtered using Whatman grade I filter paper. Then test solution was prepared by using 1 ml solution from the previous one and detect the absorbance by using double beam UV-Visible spectrophotometer (1800, Shimadzu, Kyoto, Japan) at the wavelength of 238nm. Absorbance was taken in triplicate (Metkari *et al*., 2014).

Disintegration test

The disintegration time was determined by placing a film in the petri dish. The distilled water was poured over the film and the time was measured until it disintegrates (Vaidya *et al*., 2013).

Assay

The drug content was quantified by using UV-visible spectrophotometric method (Kakde and Satone, 2009). A total of ten films were dissolved in methanol by sonication for 5 min (Digital ultrasonic cleaner Supersonic X-3, China). The stock solution was further diluted with 0.1 N HCl to make 50µg/ml concentration and analyzed at 238nm.

Dryness test/tack

Tack or dryness test is the obstinacy with which film adhere to the accessory (Radhakisan *et al*., 2012). Randomly, six films were taken from each formulation and the different quality parameters were checked with the help of paper such as; set to touch, tack-free, dust free, dry to recoat, dry hard, dray to touch, dry through and dry paint free (Khatoon *et al*., 2013, Vaidya *et al*., 2013).

Dissolution test

The *in vitro* dissolution studies test was performed on Basket method (Erweka dt 590) in 900ml of 0.1 N HCl at 50 rpm and 37±0.5°C as per USP guidelines (USP, 2013). The sampling was carried out at an interval of 30 sec for 30 min. Each time the 5ml sample was drawn and replaced by the equal quantity of fresh medium. The samples were filtered through 0.45µm filter paper prior to analysis via the validated spectrophotometric method.

Stability studies

The films were wrapped with both butter paper and aluminum foil. The films were subjected to accelerated stability studies by keeping in a stability chamber (Nuaire 23) for a period of six months at 40°C±2°C/75% RH±5%. The samples were evaluated at 0, 1, 3 and 6 months for different quality attributes as per ICH guidelines Q1A R(2) (ICH, 2003). Dangre *et al*. in 2019 carried out similar studies for the preparation of fast dissolving buccal film of clonidine hydrochloride (Dangre *et al*., 2019).

Table 1: Composition of Formulation by Design Expert ® Ver. 7.0

Composition gm (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
HPMC	3.8(10%)	1.9 (5%)	2.85 (7.5%)	3.8 (10%)	1.9 (5%)	1.9 (5%)	2.85 (7.5%)	3.8 (10%)	3.8 (10%)	1.9 (5%)
PEG	0.76 (2%)	0.76 (2%)	0.475 (1.25%)	0.76 (2%)	0.19 (0.5%)	0.19 (0.5%)	0.475 (1.25%)	0.19 (0.5%)	0.19 (0.5%)	0.76 (2%)
Cross Carmellose	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)	0.38 (1%)
SLS	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)
Vanillin	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)	0.18 (0.47%)
Citric acid	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)	0.76(2%)
Water	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)	20 (52.63%)
Methanol	11.11 (29.24%)	13.01 (34.24%)	12.34 (32.48%)	11.11 (29.24%)	13.58 (35.74%)	13.58 (35.74%)	12.34 (32.48%)	11.68 (30.74%)	11.68 (30.74%)	13.01 (34.24%)
Escitalopram	0.83 (2.18%)	0.83 2.18%)	0.83 (2.18%)	0.83 (2.18%)	0.83 (2.18%)	0.83 (2.18%)	0.83 (2.18%)	0.83 (2.18%)	0.83 (2.18%)	0.83 (2.18%)
Total	38 (100%)	38 (100%)	38 (100%)	38 (100%)	38 (100%)	38 (100%)	38 (100%)	38 (100%)	38 (100%)	38 (100%)

Table 2: Formulation results (statistical Analysis)

Formulation Code	Weight Mean (mg) ±S.D	Thickness (µm) Mean ±S.D	Folding Endurance Mean ±S.D	Percent Elongation Mean ±S.D	Surface PH Mean ±S.D	% Drug content	Disintegration Time (Sec.) Average± S.D	% Assay
F1	35.6±7.24	100±10.11	-	-	5.33±0.29	-	-	-
F2	32.75±2.44	53.33 ±4.17	127.3±1.6	106.33±2.92	5.90±0.15	98.76%	34.67±3.08	98.41%±0.002
F3	31.75±2.29	72.333±4.45	137.8±1.3	108.33±3.24	5.33±0.17	97.04%	33.00±1.67	97.93%±0.004
F4	31.75±7.57	103.5±15.20	-	-	5.50±0.28	-	-	-
F5	33.7±3.06	53.5±2.88	128.0±2.5	105.33±2.33	6.43±0.30	99.77%	30.67±1.21	99.56%±0.003
F6	33.5±3.12	52.5±1.87	128.7±1.0	105.00±2.36	6.28±0.05	99.95%	30.50±1.38	99.94%±0.002
F7	31.8±2.54	73.33±4.13	138.5±1.4	108.67±1.72	5.33±0.17	96.39%	33.17±0.98	97.74%±0.002
F8	43.8±7.72	106±15.03	-	-	5.78±0.10	-	-	-
F9	46.8±7.65	106.16±18.76	-	-	5.80±0.08	-	-	-
F10	34.25±3.16	51.83± 1.940	127.0±1.1	106.33±2.92	5.87±0.17	98.82%	35.33±2.73	98.79%±0.002

[a]SD= Standard Deviation

Palatability test

The palatability parameters such as taste, mouthfeel, handling, and acceptability were assessed and scored on a scale set as value one (1) worst to value five (5) best (Liew *et al*., 2012).

RESULTS

The results of weight variation, thickness, folding endurance, percent elongation, pH- surface, % Drug Content, Disintegration time and assay are represented in Table 2 of formulations F1- F10. Stability studies of Formulations F2, F3, F5, F6, and F7 & F10 are displayed in Table 3. Palatability Scores of F5 & F6 are illustrated in Table 4. Comparative Dissolution profile of different formulations represented in fig. 2

DISCUSSION

Pharmaceutical evaluation

Physical Appearance

All the formulations were shown acceptable appearance except F1, F4, F8, and F9.

Weight variation

Formulation F1, F4, F8, and F9 was not found to be within range as deviation were too high and other formulations were found to be within range (table 2). It was stated in the literature Average weight of the film must not deviate more than ±7.5% and no film should deviate more than 15% (Sabar, 2013). Variation in weight might be due to the use of variable quantities of ingredients (Dwivedy *et al*., 2014).

Thickness

The thickness of the formulations F2, F5, F6 and F10 containing 5% polymer was found to be better than formulations containing 7.5% and 10% polymer content. The average thickness of the formulations having 5% polymer concentration was in the range of 51-53 µm. The standard deviation was also less. Whereas formulations F3 and F7 containing 7.5% polymer exhibited more uniform thickness compared to formulations containing 10% polymer content (see table 2). Although, the results of thickness variation are in agreement with the reported values i.e. 130±3 µm (Vaidya *et al*., 2013) the voids or spaces were observed in the formulations F1, F4, F8 and

Table 3: Stability studies (Statistical Analysis)

Time (Months)	Formulation	Drug Content (%)	Disintegration (Sec.)
0	F2	98.37%±0.001	34.7±3.08
	F3	97.89%±0.002	33.0±1.67
	F5	99.52%±0.003	30.7±1.21
	F6	99.90%±0.001	30.5±1.38
	F7	97.80%±0.002	33.2±0.98
	F10	98.85%±0.002	35±2.73
1	F2	98.37%±0.003	34.3±3.01
	F3	97.99%±0.003	33.5±1.38
	F5	99.33%±0.002	30.5±1.22
	F6	99.71%±0.001	30.5±1.38
	F7	97.99%±0.002	32.8±1.60
	F10	99.23%±0.003	35.2±2.56
3	F2	98.56%±0.002	34.7±2.73
	F3	97.80%±0.003	33.0±1.41
	F5	99.04%±0.003	31.2±1.60
	F6	99.81%±0.001	30.8±0.98
	F7	97.70%±0.003	32.8±1.33
	F10	98.75%±0.002	39.5±2.59
6	F2	98.75%±0.002	34.5±2.95
	F3	97.70%±0.004	33.5 ±1.38
	F5	99.33%±0.002	30.8±1.47
	F6	99.90%±0.002	30.5±2.07
	F7	97.89%±0.002	33.3±1.03
	F10	98.95%±0.002	35±2.61

a) n = 6 in each case b) The values are expressed as Mean ± SD

Table 4: Results of platibility scores

Parameters	F5	F6
Taste	3	3
After Taste	3	3
Mouth Feel	4	4
Ease of handling	4	4
Acceptance	3	3
Total Score	17	17

*(1) worst to value five (5) best

F9 having 10% polymer quantity. The viscosity of the solutions having higher polymer concentration was too high and the presence of lumps in the solution created a great challenge to spread evenly during film casting. Ideally, film thickness should be within the range between 50-1000µg (Jain and Mundada, 2015). It has been observed from the results that the thickness of the formulation is correlated with the concentration of polymer. Similar observations have been found in Lorazepam formulation (Bais *et al*., 2016). The thickness of the film is associated with the accuracy of dose in the film formulation (Dnyaneshwar *et al*., 2014, Irfan *et al*., 2015).

Folding endurance

A normal value of folding endurance is in between 100-150 (Choudhary *et al*., 2011, Vaidya *et al*., 2013) and less than 25 with respect to a number of folds (Dwivedy *et al*., 2014). The folding endurance of the developed films was found to be within limits as reported by different researchers (See table 2).

It has been observed that the folding endurance of alendronate films was found to be in between 18-40 in terms of a number of folds (Karunakar *et al*., 2016). Folding endurance of the film has directly linked with mechanical properties and it has clearly obvious that the folding endurance is affected by the concentration of plasticizer (Irfan *et al*., 2015).

Percent elongation

All the formulations were exhibited 5% - 8% percent elongation (See table 2). Among them, F3 and F7 formulations were shown slightly more elongation owing to their higher concentration of polymer and plasticizer. As it has been reported in the literature that plasticizer concentration directly affects percent elongation (Asija *et al*., 2013). In one of the study, percent elongation was found to be in between 5 - 20% and revealed that higher the percentage of polymer and plasticizer, the greater the percent elongation (Bhupinder and Sarita, 2012). Percent elongation has directly correlated with the concentration of plasticizer and polymer increases. (Irfan *et al*., 2015).

Surface pH

The pH of all the formulations was found to be close to neutral pH and within range of 5.33-6.43 (See table 2). The pH of formulations F5 and F6 was more close to salivary pH, therefore, may have less irritation potential to the buccal mucosa. As it has been mentioned that the basic or acidic surface pH cause irritation of buccal mucosa (Kunte and Tandale, 2010, Bala *et al*., 2013). (Sabar, 2013). It has been observed that optimized the formulation of montelukast sodium film pH was found to be in between 6.31-6.72 which is closed to salivary pH (Jain and Mundada, 2015).

Fig. 1: Formulation F6

Uniformity of drug content

It was detected that drug content within all six formulations was within range (See table 2). Active ingredient content uniformity ought to be within a range between 85-115% (Vaidya *et al*., 2013) Content uniformity range must be within a range of 85-110% (Bhyan *et al*., 2011, Dixit and Puthli, 2009).

Disintegration time

The disintegration time of all the formulations was found to be within a range of 30 -36 seconds (See table 2). It was observed that an increase in polymer concentration affects the disintegration time. The time of disintegration limit for the orally disintegrating tablet is 30 seconds or less (FDA, 2008, Chauhan *et al*., 2019). These guidelines can be functional on fast dissolving oral thin film for development of formulation as well as quality control. The results of disintegration were correlated with another study in which disintegration time was found to be within 25-50 seconds (Bhupinder and Sarita, 2012). Another study showed that the increasing percentage of HPMC lead to increase in disintegration time (Dwivedy *et al*., 2014).

Assay

The formulations F1, F4, F8, and F9 showed no promising results while the rest of the formulations were in the normal range as per USP criteria i.e. 90-110% (USP, 2013). The drug content of formulations F5 & F6 was found to be 100%. (See table 2).

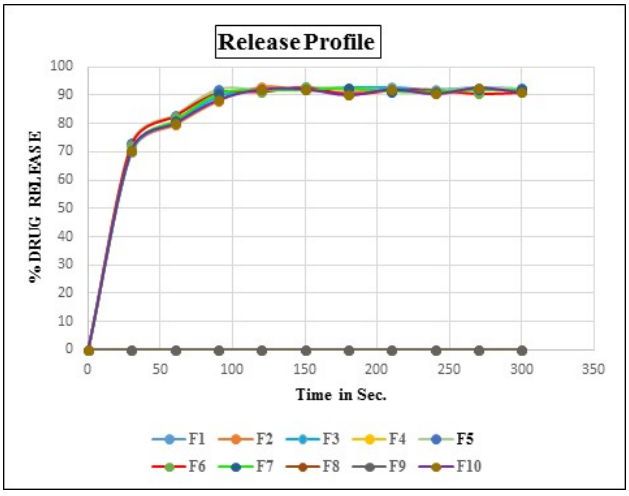

Fig. 2: Comparative dissolution profile

Dryness /tack test

It has been observed that the formulations F1, F4, F8 and F9 having 10% HPMC concentration, failed to meet quality attributes in terms of tackiness owing to their uneven surfaces. In contrast, the rest of the formulations having 5% and 7.5% polymer content passed the tack test.

Dissolution time

Dissolution time of the developed films was assessed by USP apparatus I (basket method) as it has been reported that film formulations have ability to float on the dissolution medium in paddle apparatus (Mandeep *et al*., 2013, Bhyan *et al*., 2011). About 90.91%- 92.42% drug released was observed in 1.5-2 minutes (see fig. 2). It was found that the increase in the concentration of Plasticizer i.e. PEG is slightly increased in the dissolution time.

Similar observation was found in Amlodipine besylate films release rate is increased from 82%- 100% in 5 minutes after addition of the glycerin 14% to 20% as glycerin is water soluble (Sabar, 2013) In pantoprazole formulation it was observed that the increase in the concentration of HMPC and high concentration glycerin dissolution time is also enhanced (Dwivedy *et al*., 2014). It was mentioned in USP27 that, the major component of the formulation must be within limit i.e. 85%-115% and relative S.D. must be NMT equal to 6.0% (Nishigaki *et al*., 2012). Jain *et al*., in 2015 have developed formulations of Montelukast in which it has been observed that the concentration of the polymer has a direct relation with the disintegration time and the drug release decreases (Jain *et al*., 2015).

Stability profile

All the formulations showed satisfactory stability in terms of disintegration time and drug content (table 3).

Palatability

Different parameters of palatability of optimized formulation F5 and F6 were found to be acceptable (table 4).

CONCLUSION

It is concluded that the solvent casting method proved to be an easy and less time-consuming method for the development of escitalopram fast disintegrating film. The developed film formulations were overall shown promising results in terms of their thickness, weight variation, percent elongation, and dryness/tack test, content uniformity, folding endurance, assay, physical appurtenance, disintegration, palatability, dissolution time, surface pH and stability. The release of the drug found to have a direct relation with polymer concentration while pronounce effects were also observed with varying concentration of plasticizer. The designed formulations can by-passes the first pass effect thus it can be more efficient in terms of therapeutic effects. Furthermore, it enhances the life cycle of product hence more attractive dosage form for manufacturing as well as encompasses more compliance.

REFERENCE

Arya A, Chandra A, Sharma V and Pathak K (2010). Fast dissolving oral films: an innovative drug delivery system and dosage form. *Int J ChemTech Res*, **2**(1): 576-583.

Asija R, Sharma M and Gupta A (2013). Orodispersible Film: A novel approach for patient compliance. *Int. J. Med. & Pharm. Res.*, **1**(4): 386-390.

Bais PV, Upadhye KP and Dixit G (2016). Formulation and evaluation of fast dissolving oral melt-in-mouth of lorazepam for sublingual use. *World J. Pharm. Pharm. Sci.*, **5**(3): 763-75.

Bala R, Pawar P, Khanna S and Arora S (2013). Orally dissolving strips: A new approach to oral drug delivery system. *Int. J. Pharm. Investig.*, **3**(2): 67.

Bhupinder B and Sarita J (2012). Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate. *Int. J. Drug Dev. Res.*, **4**(1): 133-143.

Bhyan B, Jangra S, Kaur M and Singh H (2011). Orally fast dissolving films: Innovations in formulation and technology. *Int. J. Pharm. Sci. Rev. Res.*, **9**(2): 9-15.

Chauhan I, Yasir M and Verma M (2019). Oral delivery of zolmitriptan loaded fast distintegrating film: Formulation development, statistical optimization, *in-vitro* and *in-vivo* evaluation. *Journal of Applied Pharmaceutical Sciences and Research*, pp.13-22.

Choudhary DR, Patel V, Patel H and Kundawala AJ (2011). Formulation and evaluation of quick dissolving film of ondansetron hydrochloride. *Int J. Pharm. Res.*, **3**(4): 31-35.

Dangre PV, Phad RD, Surana SJ and Chalikwar SS (2019). Quality by Design (QbD) assisted fabrication of fast dissolving buccal film for clonidine hydrochloride: Exploring the quality attributes. *Advances in Polymer Technology*, 2019. Article ID 3682402, 13 pages

Dixit RP and Puthli SP (2009). Oral strip technology: Overview and future potential. *J Control Release,* **139**(2): 94-107.

Dnyaneshwar HR, Wale KK, Sayyed SF and Chaudhari SR (2014). Oro-dispersible film dosage form: A review. *World J. Pharm. Res.*, **3**(5): 1093-1111.

Dwivedy BN, Dabral P and Kumar R (2014). Preparation and evaluation of mouth dissolving film of pantoprazole sodium. *World J. Pharm. Pharmceut. Sci,* **3**(8): 1564-1576.

FDA US (2008). Guidance for industry orally disintegrating tablets. Center for Drug Evaluation and Research, US Department of Health and Human Services.

ICH (2003). ICH Harmonised Tripartite Guideline: Stability Testing Of New Drug Substances And Products Q1A(R2) 4ed. USA: International Conference on Harmonisation, Technical Requirements for Registration of Pharmaceuticals for Human Use, pp.1-20

Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F and Khan A (2016). Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharm. J*, **24**(5): 537-546.

Jain RA and Mundada AS (2015). Formulation, development, and optimization of fast dissolving oral film of montelukast sodium. *Int. J. Drug Dev. & Res.,* **7**(1): 40-46.

Kakde RB and Satone DD (2009). Spectrophotometric method for simultaneous estimation of escitalopram

oxalate and clonazepam in tablet dosage form. *Indian J. Pharm. Sci.,* **71**(6): 702.

Karunakar K, Kumar GV and Rao KS (2016). Design, evaluation and comparitive studies of oral thin films of alendronate. *Int. J. of Pharmacy and Analytical Research*, **5**(1): 95-107.

Khatoon N, Rao NR and Reddy BM (2013). Overview on fast dissolving oral films. *Int. J. Chem. Pharm. Sci.,* **1**(1): 63-75.

Kunte S and Tandale P (2010). Fast dissolving strips: A novel approach for the delivery of verapamil. *J. Pharm. Bioallied. Sci.,* **2**(4): 325.

Lee Y, Kim K, Kim M, Choi DH and Jeong SH (2017). Orally disintegrating films focusing on formulation, manufacturing process, and characterization. *J. Pharm. Investig.,* **47**(3): 183-201.

Liew KB, Tan YTF and Peh KK (2012). Characterization of oral disintegrating film containing donepezil for Alzheimer disease. *AAPS PharmSciTech*, **13**(1): 134-142.

Mandeep K, Rana AC and Nimrata S (2013). Fast dissolving films: An innovative drug delivery system. *Int. J. Pharm. Res. & Allied. Sci.*, **2**(1): 14-24.

Metkari VB, Kulkarni LV, Patil PS Jadhav PA, Jadhav PH and Yadav PS (2014). Fast dissolving film: Novel drug delivery system. *Current Pharma. Research*, **4**(3): 1225.

Nalluri BN, Sravani B, Maheshwari KM, Srianusha SV and Bramhini SR (2013). Development and evaluation of mouth dissolving films of salbutamol sulfate. *J. Chem. Pharm. Res.,* **5**(3): 53-60.

Nishigaki M, Kawahara K, Nawa M, Futamura M, Nishimura M, Matsuura K, Kitaichi K, Kawaguchi Y, Tsukioka T, Yoshida K and Itoh Y (2012). Development of fast dissolving oral film containing dexamethasone as an antiemetic medication: clinical usefulness. *Int. J. Pharm.*, **424**(1-2): 12-17.

Patel Jitendra C, Patel K and Patel N (2013). Advanced Pharmaceutics. *Int. J. Advance Pharm.,* **3**: 44-50.

Patil P and Shrivastava S (2012). Fast dissolving oral films: An innovative drug delivery system. *Int. J. Sci. & Res.,* **20**(70): 50-500.

Radhakisan UR, Chavan V and Tribhuvan N (2012). Mouth dissolving film and their patent: An overview. *Int. Res. J. Pharmacy*, **3**(9): 39-42.

Raghavendra HL and Kumar GP (2017). Development and evaluation of polymer-bound glibenclamide oral thin film. *J. Bioequiv. Availab*, **9**(1): 324-330.

Sabar MH (2013). Formulation and *in vitro* evaluation of fast dissolving film containing amlodipine besylate solid dispersion. *Int. J. Pharmacy & Pharm. Sci.*, **5**(4): 419-428.

Senthilkumar K and Vijaya C (2015). Formulation development of mouth dissolving film of etoricoxib for pain management. *Adv in Pham.,* pp.1-11

USP (2013). Escitalopram Tablets, United States Pharmacopeial Convention.

Vaidya MM, Khutle NM and Gide PS (2013). Oral fast dissolving drug delivery system: A modern approach for patient compliance. *World J Pharm Res.*, **2**(3): 558-577.

Yasmeen BR, Firoz S, Mouli YC, Vikram A, Mahitha B and Aruna U (2012). Preparation and evaluation of oral fast dissolving films of citalopram hydrobromide. *Int. J. Biopharm.*, **3**(2): 103-106.