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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING FILMS OF EBASTINE

TEJASVI TORGAL, SHWETA BORKAR, PRASHANT BHIDE, ASMITA ARONDEKAR

Goa College of Pharmacy, 18th June Road, Panaji, Goa 403001, India
Email: swe_bha26@rediffmail.com

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ABSTRACT

Objective: To overcome the limitations of fast dissolving tablets, a novel fast dissolving film of ebastine was formulated for attaining quick onset of action, aiding in the enhancement of bioavailability favorable in severe conditions of allergies.

Methods: Films of ebastine were prepared by the solvent casting method using hydroxypropyl methylcellulose E-15, hydroxypropyl methylcellulose K-4 as a film base with different concentrations of crospovidone as superdisintegrant and polyethylene glycol-400 as a plasticizer. Further physical characteristics such as uniformity of weight, thickness, and drug content uniformity, tensile strength, folding endurance, percentage elongation, surface pH, disintegration and *in vitro* drug release were evaluated.

Results: The optimized formulations with film base hydroxypropyl methylcellulose E-15 and hydroxypropyl methylcellulose K-4 containing 8% crospovidone showed 99.34 % and 97.42 % of maximum cumulative percentage release respectively exhibiting first order kinetics. However, no significant change was observed in stability studies.

Conclusion: The concept of formulating fast dissolving films of ebastine offers a suitable approach in exhibiting rapid onset of action with improved delivery.

Keywords: Ebastine, Fast dissolving films, Hydroxypropyl methylcellulose, Crospovidone, *In vitro* dissolution studies

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INTRODUCTION

Recently, fast dissolving films (FDF), a more advanced drug delivery system have started gaining popularity and acceptance as new drug delivery systems, which aim to enhance the rapid onset of action to provide the drug molecule in a more convenient dosage form of administration and patient compliance formulation [1].

Allergic manifestation is quite uneasy and requires immediate medical treatment, thus the delivery system has to show the rapid onset of action which except for fast dissolving tablets (FDT), no other drug delivery system shows. FDT though shows advantages over other conventional forms in terms of rapid onset of action and better patient compliance, it has limitations like fear of swallowing and choking, expensive manufacturing processes storage, handling and stability issues. Additionally, due to taste masking of a bitter drug in FDF, colors and flavors available in FDF's, this formulation gives a better consumer and aesthetic appeal than any other dosage form [2, 3].

Histamine is a key mediator in the development of allergy symptoms and oral H1 antihistamines are among the most widely used treatment for symptomatic relief in conditions such as allergic rhinitis and chronic idiopathic urticaria [4]. Ebastine is a second-generation long-lasting and selective H1 histamine receptor antagonist which is an effective treatment for both seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. Ebastine provides efficacy throughout the 24 h dosing interval with once-daily administration and clinical benefit are seen from the first day of treatment. It is rapidly absorbed after oral administration and undergoes extensive hepatic and intestinal first-pass metabolism [5, 6].

Their conventional tablet available in the market has a major drawback of less onset of action, which is required in the patients with allergic conditions. Hence, for an antihistaminic drug-like ebastine, we aimed to develop a quick disintegrating dosage form, thus exhibiting rapid relief from allergic conditions.

MATERIALS AND METHODS

Materials

Ebastine was a gift sample from Microlabs Ltd., Verna-Goa. Hydroxypropyl methylcellulose (HPMC) E-15 and hydroxypropyl methylcellulose (HPMC) K-4 (Colorcon Asia Ltd, Goa), Crospovidone (Signet chem, Mumbai), aspartame (Dr. Reddy's, Hyderabad), carmoisine (Magnildye chem, Mumbai) and strawberry flavor (S-world flavours and fragrances, Bengaluru) were received as gift sample. All the other chemicals used in analytical grade were procured from Lobacheme Pvt. Ltd, Mumbai.

Methods

Preformulation studies

The identification of the drug was carried out by Fourier Transform Infrared spectroscopy (FTIR) (Shimadzu, UV 2700). The purity of the drug was found out by the melting point determination by the open capillary method. Standardization of the drug was carried out using a UV spectrophotometer (Labindia UV 3092). Drug-excipient compatibility was assessed by Differential Scanning Calorimetry (DSC) (Shimadzu, DSC 60+) and FTIR spectral analysis.

Formulation of fast dissolving films

In the present study, the fast-dissolving films of ebastine were prepared by a solvent casting method. The polymer solution was prepared using weighed quantities of polymers (table 1) and kept for swelling overnight in 4 ml of distilled water. To this aqueous solution of polymer, plasticizer was added and stirred for 60 min on a magnetic stirrer covered with aluminum foil to prevent the loss of solvent. The drug solution was prepared using the appropriate quantity of drug and excipients in the remaining quantity of distilled water and ethanol. This drug solution was subjected to sonication for 20 min to ensure uniform dispersion of insoluble ingredients. After sonication, the polymer solution was added with continuous stirring for 7 to 8 h with aid of magnetic stirrer. One hour before casting the film, color and flavor were added to the final drug-polymer solution. Finally, after thorough mixing and dispersion, the drug-polymer solution was cast in a glass petri dish, 4 cm in diameter. Casted films were then subjected to drying in a vacuum oven at 40 °C for 24 h. After drying, the casted film was slowly removed from petri dish and cut into films of 2 x 2 cm in size and packed in laboratory prepared aluminium foil packages [7].

Evaluation of fast dissolving films

General appearance

The films were tested for size, shape, color, presence or absence of odor, surface texture, physical flaws, consistency and legibility of any recognizable markings.

Drug content uniformity

The drug content of the films was determined by dissolving the film of 2x2 cm in 5 ml of methanol and 20 ml of 0.1 N HCl in a 100 ml volumetric flask. The mixture was sonicated for 10 min till the entire film dissolved and the final volume was made up by adding 0.1 N HCl. 10 ml of the resulting solution was diluted to 100 ml with 0.1 N HCl. Absorbance was measured at 257 nm. Drug content was calculated according to the formula below

$$\text{Drug content} = x \times \frac{100}{10} \times \frac{10}{100}$$

"x" value was determined by substituting the obtained absorbance value in the equation of calibration curve concentration of dilution. Drug content was determined in triplicate for each formulation; mean and standard deviation was calculated [8].

Table 1: Composition of fast dissolving films

Ingredients												
Formulation	**Ebastine**	**HPMC E-15**	**HPMC K-4**	**PEG-400**	**Crospovidone**	**Tween-80**	**Citric acid**	**Aspartame**	**Carmoisine**	**Strawberry**	**Purified water**	**Ethanol**
	(mg)	**(mg)**	**(mg)**	**(ml)**	**(mg)**	**(ml)**	**(mg)**	**(mg)**	**(ml)**	**(ml)**	**(ml)**	**(ml)**
F1	125.7	500	-	0.2	-	0.3	20	40	q. s	0.8	6	6
F2	125.7	450	50	0.2	-	0.3	20	40	q. s	0.8	6	6
F3	125.7	500	-	0.2	30	0.3	20	40	q. s	0.8	6	6
F4	125.7	500	-	0.2	40	0.3	20	40	q. s	0.8	6	6
F5	125.7	500	-	0.2	50	0.3	20	40	q. s	0.8	6	6
F6	125.7	450	50	0.2	30	0.3	20	40	q. s	0.8	6	6
F7	125.7	450	50	0.2	40	0.3	20	40	q. s	0.8	6	6
F8	125.7	450	50	0.2	50	0.3	20	40	q. s	0.8	6	6

Weight variation

A 2 cm x 2 cm piece was cut from three different places of the cast film. Each film was weighed and weight variation was calculated. The mean with standard deviation was calculated.

Thickness [9]

The thickness of the film was measured by digital vernier caliper at three different strategic locations. It is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of the dose in the film. The mean with standard deviation was calculated.

Tensile strength [10, 11]

The tensile strength was determined using tensile strength tester (laboratory designed) as shown in fig. 1. A 3 cm x 1 cm film free from air bubbles or physical imperfections was held longitudinally in the tensile grip on the tester. The test was performed at 6 mm of initial grip separation. Weights were added to the pan till the film specimen broke. All measurements were performed in triplicate. The mean with standard deviation was calculated. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Load of failure}}{\text{Strip thickness X strip width}}$$

Folding endurance [8, 12]

Folding endurance is determined by repeated folding of the film at the same place until the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value. The mean with standard deviation was calculated.

Fig. 1: Laboratory designed tensile strength tester

Percent elongation [10]

When stress is applied, a film sample stretches and this is referred to as a strain. A strain is the deformation of strip divided by the original dimension of the sample.

$$\text{Percent elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

***In vitro* disintegration time [9]**

In vitro disintegration time was determined visually in a petri dish containing 10 ml of pH 6.8 phosphate buffer which mimicked the properties of simulated saliva. The disintegration time is noted as a time at which film disintegrates. Three readings were taken. The mean with standard deviation was calculated.

Surface pH [13, 14]

The pH was measured using electrode pH meter, by making surface contact of the electrode with an oral film which was prior made slightly wet with water. The procedure was performed in triplicate and mean with standard deviation was reported.

***In vitro* dissolution studies [15]**

In vitro dissolution studies were carried out using USP Type II (modified paddle type) dissolution apparatus. The dissolution was carried out in 900 ml of 0.1 N HCl maintained at 37.5±0.5 °C at 50 rpm. A 2 x 2 cm film (a size which contains unit dose) was cut from

cast film and placed on a glass slide and covered with mesh to hold film sample in place. This was then placed at the bottom of the dissolution bowl. 5 ml samples were taken at 2 min intervals till 10 min, after that 5 ml samples were taken every 5 min till 30 min. The replenishing of the dissolution medium was done after each sample was withdrawn. The drug content was then determined spectrophotometrically at λ_{max} of 257 nm and drug release was calculated.

Accelerated Stability studies [10, 16]

Stability studies of optimized formulations were carried out as per ICH guidelines by storing the sample at 40 °±2 °C/75%±5% RH for 30 d. Samples were analyzed for drug content, weight variation, thickness, tensile strength, surface pH, disintegration time and *in vitro* dissolution studies.

RESULTS

General appearance

All the films were square, translucent to opaque, pink in color, with flat surfaces, and has a smooth texture. The size of the film was 20 mm in length and breadth, and there was an absence of any odor and physical flaws.

Drug content uniformity

Drug content uniformity results of all eight formulations are tabulated in table 2. The percent drug content was observed to be in the range of 94.83±0.076-101.17±0.029 % which are in the acceptable limits.

Weight variation

Weight variation results are shown in table 2. Weights were observed in range of 0.057±0.001 mg to 0.111±0.003 mg. Variation among different formulations was obtained which may be related to type and amount of polymer used.

Thickness

Thickness results are tabulated in table 2. Thickness is in range 0.095±0.004 mm to 0.177±0.003 mm. Results indicate satisfactory thickness for oral administration.

Tensile strength

The results are shown in table 2. Tensile strengths range in 0.541±0.011 kg/mm to 0.807±0.010 kg/mm. The values can be correlated to varied type and amount of polymer used in all formulations.

Folding endurance

The results are shown in table 2. Folding endurance is in range 265.67±2.08 to 322.33±2.52. Results can be correlated to the type of polymers used.

Percent elongation

Percent elongation values are listed in table 2. Values range from 10.56±0.96% to 19.44±0.96%. It can be correlated to the type and amount of polymers used.

***In vitro* disintegration time**

The results are tabulated in table 3. *In vitro* disintegration time values are in the range of 29.67±1.53 s to 121.33±0.58 s. Results varied with type and amount of polymers and superdisintegrant. Formulation F_1 and F_2 showed the highest disintegration time i.e. 112.33 s and 121.33 s respectively as crospovidone was not added to these formulations. Disintegration time of optimized formulation i.e. F_4 was 29.67 s in which only single polymer i.e. HPMC E-15 was used and 8% (40 mg) crospovidone were used as a superdisintegrant (fig. 2). Disintegration time of second optimized formulation i.e. F_7 was 34.67 s in which combination of polymers HPMC E-15, HPMC K-4 and 8% (40 mg) Crospovidone was used. It is observed that disintegration time of the film with a base as HPMC E-15 alone and films with a base as HPMC E-15 and HPMC K-4 in combination showed a decrease from 45 to 29.67 s and 50.66 to 34.67 s with an increase in the concentration of crospovidone from 6 to 8% respectively, further increase in the concentration of crospovidone increased the disintegration time possibly due to blockade of capillary pores which prevents the entry of fluid into the film.

Table 2: Evaluation of fast dissolving films

Formulation code	Percentage drug content (%) mean±SD*	Weight variation (mg) mean±SD*	Thickness (mm) mean±SD*	Tensile strength (kg/mm) mean±SD*	Folding endurance (No. of folds) mean±SD*	Percent elongation (%) mean±SD*
F1	100.43±0.101	0.057±0.001	0.095±0.004	0.571±0.011	316.00±1.00	18.33±1.67
F2	94.83±0.076	0.074±0.001	0.159±0.004	0.805±0.002	278.33±3.06	10.56±0.96
F3	95.92±0.101	0.061±0.001	0.104±0.005	0.552±0.021	319.33±1.53	18.89±0.96
F4	101.08±0.014	0.063±0.000	0.112±0.004	0.566±0.013	322.33±2.52	19.44±0.96
F5	101.17±0.029	0.066±0.000	0.127±0.003	0.541±0.011	304.00±2.00	16.67±0.00
F6	99.00±0.125	0.078±0.000	0.154±0.003	0.799±0.006	290.67±2.89	11.67±0.00
F7	100.42±0.104	0.095±0.001	0.162±0.003	0.807±0.010	284.33±2.08	12.78±0.96
F8	98.67±0.113	0.111±0.003	0.177±0.003	0.795±0.012	265.67±2.08	11.11±0.96

*SD standard deviation

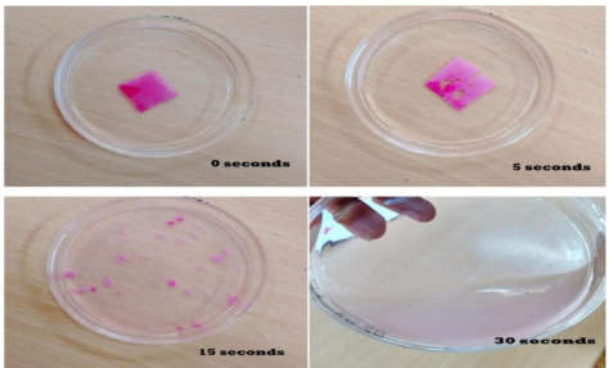

Fig. 2: *In vitro* disintegration study of formulation F4

Surface pH

The results are tabulated in table 3. Surface pH values are in range 6.43±0.20 to 6.87±0.03. It is seen that surface pH values are close to neutral pH hence the risk of irritation to oral mucosa is reduced.

***In vitro* dissolution studies**

All formulations were subjected to *in vitro* dissolution studies in 0.1 N HCl using modified USP dissolution test apparatus type II. The amount of plasticizer used is the same for all formulations while type and amount of polymer are varied. Also the amount of superdisintegrant is varied or absent in some formulations. Thus release may be influenced by type and amount of polymer and amount of crospovidone. Results are tabulated in table 3. At the end of 30 min, drug release is approximately 89.55–99.34 % for all the formulations containing crospovidone as superdisintegrant (F_3 to F_8). Formulations F_1 and F_2 which do not contain crospovidone showed 68.62% and 58.18% cumulative drug release respectively at the end of 30 min. Hence it is seen that the formulations in which crospovidone (superdisintegrant) was not added showed poor release than the ones in which crospovidone was added, this proves that crospovidone aided in better and faster release of the drug from the formulations in which it was added. Also, the amount of release was affected by the type and amount of polymer used, Formulation F_1, F_3, F_4 and F_5 with single HPMC E-15 base showed greater release than F_2, F_6, F_7 and F_8 which had the base of HPMC E-15 and HPMC K-4. This proves that the type and amount of polymer also affected the release from all the formulations. The formulations prepared with HPMC E-15 alone as a film base with crospovidone as a superdisintegrant in the concentration of 6, 8 and 10% showed 92.60, 99.34, and 95.01 % respectively at the end of 30 min. The formulations prepared with HPMC E-15 and HPMC K-4 in combination as a film base with crospovidone in the concentration of 6, 8 and 10 % showed 89.56, 97.42 and 92.46 % respectively at the end of 30 min. It is observed that drug release from the film increased from 92.6 to 99.34 % and 89.56 to 97.42 % with an increase in the concentration of crospovidone from 6 to 8 % respectively, further increase in the concentration of crospovidone i.e. from 8 to 10 % decreased the drug release due to the increase in disintegration time. Data were subjected to kinetic treatment to determine the release pattern. All the formulations can be best fitted in the first-order kinetics (fig. 3).

Table 3: Evaluation of fast dissolving films

Formulation code	*In vitro* disintegration time (s) mean±SD*	Surface pH mean±SD*	Percent cumulative drug release at end of 30 min mean±SD*
F1	112.33±1.53	6.43±0.20	68.623
F2	121.33±0.58	6.74±0.04	58.183
F3	45.00±1.00	6.58±0.04	92.606
F4	29.67±1.53	6.78±0.03	99.341
F5	37.67±1.53	6.87±0.03	95.014
F6	50.67±1.53	6.86±0.05	89.559
F7	34.67±0.58	6.82±0.07	97.417
F8	44.00±2.00	6.86±0.04	92.463

*SD standard deviation

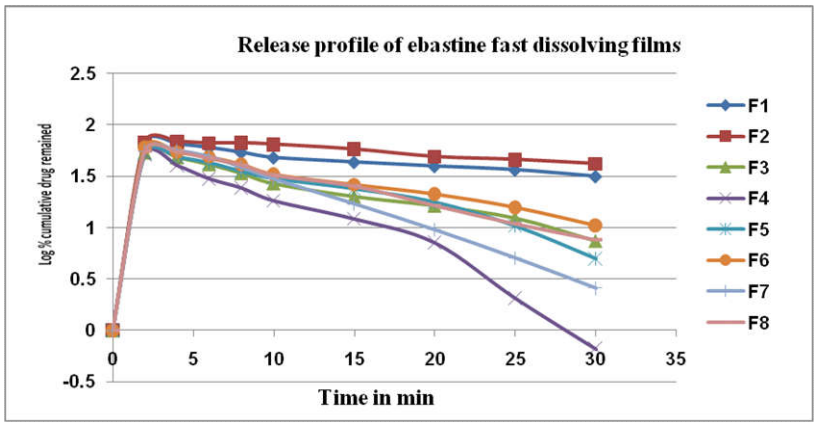

Fig. 3: *In vitro* release profile of ebastine fast dissolving films

Accelerated stability studies

The optimized formulations F_4 and F_7 were subjected to stability studies at 40 °C±2 °C/75±5% RH for one month. Samples were analyzed for drug content, weight variation, thickness, tensile strength, surface pH and dissolution. No significant variation was found in the results of stability samples.

DISCUSSION

FDFs of ebastine were prepared by the solvent casting method using HPMC E-15 and HPMC K-4 as a film base with different concentrations of crospovidone as superdisintegrant and polyethylene glycol-400 (PEG-400) as a plasticizer. HPMC E-15 alone was used in four formulations while in the other four formulations a combination of HPMC E-15 and HPMC K-4 was used in the ratio of 9:1 respectively. As most of the excipients are soluble in water, it was used as one of the solvents for casting the films. Ebastine being insoluble in water but sparingly soluble in ethanol it was uniformly dispersed using the combination of water and ethanol as solvents. Ethanol also aided in quick uniform drying of the films as compared to the slow drying with only purified water used as a solvent during trials. The amount of both the solvents was also optimized in this process. Plasticizer was used in the formulation to improve the film properties. PEG-400 was used as a plasticizer and was tried at varied concentrations to observe its effect on film formation and film properties. Tween 80 was added as a surfactant. Crospovidone gave better films with good disintegration properties. Thus crospovidone was used as a superdisintegrant which aided in a faster dissolution of films within seconds and quick release of an active agent. The effect of varied concentrations of crospovidone on the disintegration time of the film and drug release was also observed. The amount of drug to be added to the casting solution was determined by considering dose per unit film, the surface area of film and that of petri dish. The drug content of films was determined and the amount of drug to be added to casting the film was optimized. Acceptability of orally disintegrating or dissolving formulations largely depends on its aesthetic appeal and taste perceived in the mouth as the formulation disintegrates or dissolves before it is swallowed. Thus, strawberry flavor, carmoisine color and aspartame as sweetener were used in the formulation. On the interpretation of data obtained from physicochemical evaluation and *in vitro* dissolution studies, it was found that formulation F_4 and F_7 gave the best results among all others and hence were considered as optimized formulations in their respective polymer base to provide the drug in the more convenient and patient compliant formulation.

CONCLUSION

Collectively from the results obtained, it is revealed that the fast-dissolving films of ebastine can be considered suitable for clinical use in the treatment of allergic rhinitis and other conditions of allergies, where a quicker onset of action for a dosage form is desirable along with the convenience of administration [11]. The data demonstrated that 8% crospovidone with HPMC E-15 alone or in combination with HPMC K-4 as a film base was suitable for developing fast dissolving films of ebastine. Conclusively, the current study attained in successfully designing and evaluating the drug delivery system. Being a consumer-friendly alternative, switching the product franchise from oral disintegrating tablet to fast dissolving film provides a good platform for product non-infringing product development. Drug formulation technology is a good tool for product life cycle management for increasing the patent life of existing molecules or products.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. Revathi V. Fast dissolving drug delivery system. Pharma Times 2007;39:22-3.
2. Kaur M, Rana AC, Seth N. Fast dissolving films: an innovative drug delivery system. Int J Pharm Res Allie Sci 2013;2:14-24.
3. Gupta P, Bisht A, Rao NGR. Fast dissolving oral films: a comprehensive review. World J Pharm Res 2019;5:116–27.
4. Mishra R, Amin A. Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as a film-forming agent. Ind J Pharm Edu Res 2011;45:71-7.
5. Ebast. Available from: http://www.unitedpharmacies.com/Ebast-ebastine.html [Last accessed on 05 Sep 2014
6. Ebastine Pharmacology. https://www.medicineindia.org/pharmacology-for-generic/1145/ebastine [Last accessed on 04 Sep 2014]

7. Saini P, Kumar A, Sharma P, Visht S. Fast disintegrating oral films: a recent trend of drug delivery. Int J Drug Dev Res 2012;4:80-94.
8. Nafee NA, Boraie MA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm 2003;53:199-212.
9. Reddy U, Reddy S, Katta M, Thyagaraju K. A detailed review of fast dissolving oral films. Indo Am J Pharm Res 2018;8:1351–26.
10. Cilurzo F, Minghetti P, Como A, Montanari L. Maltodextrin fast dissolving film: a feasibility study. Eur J Pharm Biopharm 2008;70:895-900.
11. Roshan B, Ravindranath S. Osteoarthritis: pathophysiology and current treatment modalities. J Drug Delivery Ther 2019;9:661–8.
12. Lakshmi PK, Malavika P, Vidya K. Formulation and evaluation of oral films of atomoxetine hydrochloride. Int Res J Pharm 2018;9:105–9.
13. Kumar GV, Krishna RV, William GJ, Konde A. Formulation and evaluation of buccal films of salbutamol sulphate. Ind J Pharm Sci 2005;67:160-4.
14. Mashru RC, Sutariya VB, Sankalia MG, Parikh PP. Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Dev Ind Pharm 2005;31:25-34.
15. Bagul Uddhav, Gujar Kishore, Patel Nancy, Sanjeevani Aphale, Shalaka Dhat. Formulation and evaluation of sublimed fast melt tablets of levocetirizine dihydrochloride. Int J Pharm Sci 2010;2:76-80.
16. Zankhana Patel, Rahil Bhura, Samir Shah. Formulation optimization and evaluation of mouth dissolving film of ramosetron hydrochloride. Int J Curr Pharm Sci 2020;12:99-105.