Original Article

SOLID DISPERSION OF NEBIVOLOL HYDROCHLORIDE IMPREGNATED BUCCAL PATCH: FORMULATION AND CHARACTERIZATION

CLINTON JOSE[1], SNEH PRIYA[1*], DIVYA JYOTHI[2], HIMANSHU JOSHI[3], CYNTHIA LIZZIE LOBO[1], KRITHI S. P.[1]

[1]Nitte (Deemed to be University), NGSM Institute of Pharmaceutical Sciences (NGSMIPS), Department of Pharmaceutics, Derelakatte, Mangaluru, India, [2]Nitte (Deemed to be university), NGSM Institute of Pharmaceutical Sciences (NGSMIPS), Department of Pharmacognosy, Derelakatte, Mangaluru, India [3]College of Pharmacy, Graphic Era Hill University, Bhimtal Campus, Utterakhand
Email: snehpriya123@nitte.edu.in

ABSTRACT

Objective: The objective of the present investigation was to design and characterize a mucoadhesive buccal patch of Nebivolol hydrochloride in order to administer a small dose of a drug to treat hypertension effectively and thereby avoiding disadvantages such as patient noncompliance and low bioavailability.

Methods: The buccal patches were prepared by solvent casting method. The polymers used to formulate patches were HPMC K 15 M, PVP K 30, and propylene glycol was used as plasticizer and ethanol as the solvent. The drug-polymer compatibility studied was conducted by FTIR.

Results: All the developed Patches had good transparency and stability. All formulated patches showed pH in the range of 6.49 to 7.22, and drug content was more than 90%. The folding endurance value showed that the patches are flexible and non-brittle. The *in vitro* residence time was found to more than 30 min. Thickness, % moisture absorption, and % moisture loss values were in a normal range. The drug release study was conducted for 8 h, and it was found drug release was decreased with the increase in polymer concentration. The *in vitro* release profiles of the drug from all the formulations appeared to follow Korsmeyer Peppa's exponential model, and release exponent (n) was found to be more than 0.45 so that the release can be characterized by Non–Fickian (anomalous) diffusion.

Conclusion: From the results, it was concluded that drug released from formulated buccal patches follows sustained release pattern, Hence can be used for the treatment of the hypertensive patient.

Keywords: Nebivolol hydrochloride (NBH), Mucoadhesive buccal patch, HPMC K 15 M

INTRODUCTION

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the arteries' blood pressure is elevated. High blood pressure is present if it is often at or above 140/90 mm Hg. Hypertension is classified as either primary (essential) hypertension or secondary hypertension [1, 2]. The oral route is the most popular and convenient drug administration route. However, oral administration cannot achieve the maximum bioavailability of many drugs because of rapid or extrahepatic first-pass metabolism [3]. Among the different approaches to avoiding the first-pass metabolism, the buccal route seems convenient [4].

Buccal administration refers to a route of administration or topical route of administration. Drugs held or applied in the buccal area (in the cheek) diffuse through the oral mucosa (tissues that line the mouth) and enter directly into the bloodstream. Buccal administration may provide better bioavailability of some drugs and more rapid onset of action than oral administration. The medication does not pass through the digestive system and thereby avoids the first-pass metabolism. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments, and gels, have recently been developed. However, buccal patches offer greater flexibility and comfort than other devices. Besides, a patch can circumvent the relatively short residence time of oral gels on mucosa since the gels are easily washed away by saliva. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. There are mainly 3 methods to prepare mucoadhesive buccal patch; they are solvent casting technique, hot-melt extrusion technique, and solvent evaporation method [5].

Polymers frequently used in the buccal delivery system are CMC, HEC, HPC, HPMC, MC, Chitosan, etc.

Nebivolol Hydrochloride (NBH) is a drug with low water solubility and high membrane permeability, as in class 2 in the Biopharmaceutical Drug Classification System. NBH is a beta-blocker that exerts its actions by exhibiting a high selectivity for B-adrenergic receptors and reducing peripheral vascular resistance by modulating nitric oxide release [6]. Nebivolol is indicated as medicine for Essential Hypertension but, it has some drawbacks like extensive first-pass metabolism, gastric irritancy, and low bioavailability. Further, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affect its absorption rate, resulting in a low and variable oral bioavailability. Formulation of poorly water-soluble drugs as solid dispersions leads to increased solubility and decreased gastrointestinal side effects. The resulted of that marked improvement in their dissolution rates and decreased gastrointestinal side effects. An increase often helps it in their relative bioavailability [7, 8]. So, to improve the solubility, bioavailability and avoid hepatic metabolism, in the present study, an attempt was made to develop solid dispersion loaded buccal patches of Nebivolol [9, 10]. NBH also has a low molecular weight and high partition coefficient, making it a suitable candidate for the buccal delivery system.

MATERIALS AND METHODS

Materials

Nebivolol Hydrocholride was a gift sample Cipla Pharma Ltd. (Banglore, India). Hydroxy propylmethyl cellulose (K15 M) was obtained from Yarrow chem products. (Mumbai, India) and Polyvinyl pyrolidone K 30 (PVP K30) was obtained from Central drug house (P) Ltd. (Delhi, India). Ethanol was obtained from Merck specialities Private Limited, (Mumbai, India). Propylene glycol 800 was obtained from Sisco laboratories (Mumbai, India). All other chemicals used were of analytical grade and procured from Hi media laboratories (Mumbai, India).

Fabrication of nebivolol solid dispersion infused buccal patch

The buccal patches containing Nebivolol solid dispersions were prepared by incorporating solid dispersions of Nebivolol in a different composition of Hydroxypropyl methylcellulose (HPMC) K15 M polymer. Solid dispersions of Nebivolol were prepared as by Shah I *et al.*, in that 1:7 ratio of drug and PVP K 30 was taken. Different percentages of HPMC K 15 M were taken and dissolved in 20 ml of ethanol. The beakers containing polymer solution were kept aside for 24 h for swelling of the polymer. Further, 5 ml of ethanol was added to it, and the dispersion was stirred. Then propylene glycol was added to the polymer solution and mixed well.

Accurately weighed amounts of Nebivolol loaded solid dispersion were taken, added slowly in the polymeric solution, and stirred on

the magnetic stirrer to obtain a uniform solution. This solution was then made up into 30 ml using ethanol, and then the solution was poured on the Petri dish of diameter 9 cm and kept for drying. These were left undisturbed at room temperature for one day. After drying, medicated patches of 2×2 cm2 areas were cut using a sterile stainless steel borer, each film containing 10.0 mg of the drug. The cut patches were used for further studies [6, 11]. The composition of different formulation showed in table 1.

Drug excipient compatibility studies

To determine whether there are any interactions between the drug and excipients, FTIR spectroscopic analysis was performed using the instrument BRUKER Alpha II in the region of 2000 to 400 cm-1. All individual components of drug, drug-polymer mixture and patch were analysed.

Table 1: Composition of of each mucoadhesive buccal patch (area 2×2 cm²)

Formulation coed	Solid dispersion equivalents to 10 mg of nebivolol	HPMC K 15 M (mg)	Propylene glycol (%)	Aspartame (mg)	Peppermint oil (ml)	Ethanol
F1	80	20	30	0.25	0.02	Q. S.
F2	80	25	30	0.25	0.02	Q. S.
F3	80	30	30	0.25	0.02	Q. S.
F4	80	35	30	0.25	0.02	Q. S.
F5	80	25	20	0.25	0.02	Q. S.
F6	80	25	40	0.25	0.02	Q. S.

Characterization of buccal mucoadhesive patches

Weight variation

A weight variation test was carried out using digital balance (Mettler Toledo), by weighing three films containing a specific amount of drug from each formulation. The standard deviations (SD) were calculated from the individual weight of the film [11-13].

Film thickness

The thickness of the films was determined using a micrometer screw gauge. Thickness of 10 films of each formulation was determined and the average was calculated.

Content uniformity of patches

To make sure uniform distribution of NBH in film, a content uniformity test was performed. The film was added to 100 ml of sorensons phosphate buffer (SPB) pH 6.4 contained in a 250 ml beaker was placed on a temperature controlled magnetic stirrer maintained at 37 °C. The medium was stirred at 300 rpm with a Teflon coated magnetic bead for 3 h. Then the solution was filtered through 0.45 μm membrane filter and the filtrate was examined for the drug content at 281 nm using UV-Spectrophotometer [13].

Surface pH study

The surface pH of the patch was determined in order to investigate the possibility of any side effects (*in vivo*). The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5±0.2) for 15 min at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute [11, 13].

Percentage moisture absorption

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films. Buccal films were weighed and placed in a desiccator containing 100 ml of a saturated solution of aluminum chloride and 75±5% RH was maintained. After three days the buccal films were taken out and reweighed. The percentage moisture absorption was calculated using this formula [14].

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

To evaluate the integrity of the patches in dry conditions percentage moisture loss test was carried out. The patches were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the patches were taken out and reweighed. The formula used to find out the percentage moisture loss is;

$$\% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Tensile strength

Tensile strength was measured using tensile analogy tester (model TKG, FSA, India). Films free from air bubbles or physical imperfections were selected for tensile testing. The two clamps of the tensile tester were adjusted such that the distance between them is 3 cm by moving the upper clamp. During measurement, the strips were pulled by top clamp at a rate of 100 mm/min; the force applied was measured until the film was broken. The film samples, which broke at the point of clamping and not between the clamps, were not included in the calculation. Triplicate results for each film were considered. Tensile strength can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film using the following equation [15].

$$\text{Tensile strength} = \frac{\text{Maximum force}}{\text{Area}}$$

Folding endurance

A small strip of film was cut evenly and separately folded at the same place until it broke. The number of times the film could be folded at the same place without breaking gives the folding endurance [16].

***In vitro* residence time**

The *in vitro* residence time was determined using a locally modified USP disintegration apparatus (Disintegration tester, Electrolab, Mumbai, India). The disintegration medium was composed of 900 ml of phosphate buffer pH 6.4 maintained at temperature 37±2 °C. A segment of pig buccal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive film with backing membrane was hydrated from film surface using 15 μl phosphate buffer pH 6.4 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and

down so that the film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the film from the mucosal surface was recorded (mean of triplicate determinations) [11].

Drug release study of the buccal patch

In vitro release study

The drug release studies were performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus was thermo stated at the temperature of $37\pm1°$ C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessel containing 500 ml of PB pH 6.8 phosphate buffer solution. At predetermined time intervals 3 ml of samples was withdrawn and replaced with fresh medium. After appropriate dilutions with simulated saliva was assayed spectrophotometrically at 281 nm. For drug release three films of each formulation were subjected and the average cumulative percentage drug release was determined [15].

Drug release kinetics

To study drug release kinetics of buccal patches formulation, data obtained from *in vitro* release studies were plotted in various kinetic models: zero order (see Equation: 1) as cumulative percentage of drug released versus time, first order (see Equation: 2) as log cumulative percentage of drug remaining versus time [17].

$$\text{Zero-order equation } Q_t = K_o t \text{.......1}$$

$$\text{First order equation } \ln Q_t = \ln Q_0 + K_1 t \text{.......2}$$

Where Q_t is the percentage of drug release at time t, K_0 and K_t are the coefficients of the equation.

Mechanism of drug release

Mechanism of drug release from vocal patches was evaluated by subjecting the data obtained from in vitro drug diffusion studies in Higuchi's model (see Equation: 3) as cumulative percentage of drug released versus the square root of time and Korsmeyer–Peppa's model (see equation: 4) as log cumulative percentage drug released versus log time [17].

$$\text{Higuchi equation } Q_t = K t^{1/2} \text{.......3}$$

$$\text{Korsmeyer and peppas equation } Q_t = K_p t^n \text{.......4}$$

K_p is constantly incorporating structural and geometrical characteristics of the release device and n is the release exponent indicate the release mechanism.

RESULTS AND DISCUSSION

Buccal patches loaded with Nebovolol solid dispersion were prepared by solvent casting method. The prepared buccal patches were transparent, smooth, uniform and flexible as shown in fig. 1, except F6, which was tackier and non-uniform.

Fig. 1: Buccal patch of nebivolol solid dispersion

IR spectroscopy

The major IR peaks (wave number, cm^{-1}) of pure drug and optimized formulation F3 are given below; Pure NBH: 3397.75, 3187.33, 2903.02, 2845.37, 1749.30,1491.9, 1213.14, 1074.73; Optimized Formulation F3: 3312.97, 3188.78, 2923.41, 2735.69, 1740.33, 1488.83, 1209.09, 1069.62. The result showed that the principle IR peak of pure drug and an optimized formulation F3 were almost similar, signifying no interaction between drug and polymer during formation of patch [18].

Table 2: Weight variation, thickness, surface pH and % drug content of developed buccal mucoadhesive patch

Formulation	Weight variation(mg)±SD	Thickness (μm)±SD	Surface pH±SD	Drug content (%)±SD
F1	86.63±0.28	67±0.94	7.13±0.09	95.17±0.96
F2	104.51±0.19	89±0.81	6.87±0.09	92.20±0.76
F3	109.05±0.36	97±0.95	6.64±0.06	94.09±1.21
F4	114.71±0.32	107±1.63	6.51±0.11	90.88±1.09
F5	101.63±0.21	84±1.24	6.49±0.08	91.02±0.99
F6	103.21±0.24	88±0.47	7.22±0.06	88.45±1.22

mean±SD (n=3)

Weight variation, film thickness, surface pH, and content uniformity of patches

The results of weight variation, film thickness, surface pH and content uniformity are represented in table 2. The weights and thickness of different formulations were ranged between 8.63±0.28 mg to 114.71±0.32 mg and 67±0.94 μm to 107±1.3 μm, because of different concentration of polymer and plasticizer. As an acidic or alkaline pH may cause irritation to the buccal mucosa, an attempt was made to keep the surface pH as close to neutral as possible. The surface pH of formulations was found to be in the range of 6.49±0.08 to 7.22±0.06, which was well within range of neutral pH and has not cause irritation and ultimately achieves patient compliance. All the formulations exhibited fairly uniform drug content ranging from 88.45±1.22 % to 95.17±0.96 %, Formulation procedures involving fewer processing steps, no major drug loss was observed during the preparation of the films.

Percentage moisture loss and moisture absorption

The percentage moisture loss was found to be between 3.48±0.23 to 6.63±0.33 and percentage moisture absorption was found to be 3.9±0.10 to 5.71±0.33, as shown in table 3. The result revealed that the moisture absorption and loss was found to increase with increasing concentration of hydrophilic polymers as well as increase the concentration of hydrophilic plasticizer. The optimum moisture content in the formulations helps the film to remain stable, non-brittle and free from completely drying. Optimum values of moisture absorption in F3 formulation indicate less chance of microbial contamination and maintain integrity through the films shelf life [19, 20].

Tensile strength, folding endurance and *in vitro* residence time

Tensile strength is defined as the maximum stress applied at a point at which the film specimen breaks. The tensile strength measures the ability of a patch to withstand rupture. As the concentration of

hydrophilic polymer HPMC K 15 M was increased, there is increase in tensile strength, as shown in table 3.4. Polymers contain large number of chain of molecules and between these chains, homopolar bond and other types of bonds are possible. These bonds are either strong or feeble, depending on the nature of the polymer. According to the bonds formed force required to break the bonds and rupture the patch will differ. The mean value of tensile strength of patch containing different concentrations of HPMC K 15 M was found to vary between 4.11±1.51to 8.55±0.98 kg/mm2 (F1 to F4). As the concentration of plasticizer propylene glycol was increased (20 to 40 %) there is an increase in tensile strength (Patel and Poddar 2009, as shown in formulation F4, F3 and F5. The mean value of tensile strength of patch containing different concentration of plasticizer was found to be 4.33±1.27, 7.72±0.40 and 8.28±0.65 kg/mm² for formulation F4, F3 and F6, respectively. Presence of a plasticizer in the formulation helps in imparting strength to the films

by lubrication effect of the plasticizer and reduction of the cohesive force between chain molecules of polymer. As a result, tensile strength of the films will be reduced. The formulation F3 showed optimum tensile strength which indicates less probability of rupture. The values for folding endurance varied from 32±3.87 to158±4.37, as shown in [table 3]. The value depends on hydrophilic polymer as well as plasticizer concentrations used. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. *In vitro* residence time studies showed that all patches adhered immediately to the buccal mucosa and showed residence times above 30 min. HPMC K 15 M is a non-ionic polymer having unique gelling characteristics, which in turn are responsible for its adhesive properties. It exhibits strong bioadhesive behavior either because of hydrogen bonding due to hydroxyl groups or because of significant chain penetration or both (Thakur and Ratnaparkhi, 2014).

Table 3: Tensile strength, folding endurance, % moisture absorption and Moisture loss of developed formulations of betamethasone sodium phosphate

Formulation	Percentage moisture absorption±SD	Percentage moisture loss±SD	Folding endurance±SD	Tensile strength Kg/cm²±SD	*In vitro* residence time
F1	3.90±0.19	3.48±0.23	32±3.87	4.11±1.51	>30
F2	4.09±0.32	5.73±0.39	59±2.83	5.34±0.95	>30
F3	5.50±0.21	5.81±0.50	93±3.58	7.72±0.40	>30
F4	5.71±0.33	6.63±0.33	158±4.37	8.55±0.98	>30
F5	4.45±0.53	4.20±0.31	76±2.01	4.33±1.27	>30
F6	5.23±0.43	5.33±0.42	135±4.02	5.28±0.65	>30

mean±SD (n=3)

In vitro drug release studies

In vitro release of all formulation were performed and results are shown in fig. 2 and 3. The maximum percentage of drug released from the formulations F1 to F4 was found to be 95.88±3.03, 92.29±2.72, 90.18±2.59, and 75.88±2.43 at the end of 480 min. It was found that increase in the concentration of polymer significantly decreased the drug release. The slow drug release mechanism for higher polymer concentration can be explained by the reduction in permeability due to change in the morphology of the polymer. Improved polymer concentration may have providing the matrix with greater tortuosity and deprived water porosity for diffusion of drug [20,21]. *In vitro* release of drug also depends on nature of plasticizer. As the concentration of hydrophilic plasticizer was increased, the release of drug was also found to be increased, asshown in fig. 2. It may be due to quick absorption of water by formation of large number of hydrogen bonds and helped in faster diffusion of drug from the system. Formulation F5, F3 and F6 were contained different concentrations of plasticizer i.e. 20, 30 and 40 % respectively and maximum drug release at the end of 480 min was found to be 62.15±2.39, 90.18±2.59 and 93.18±1.19 respectively.
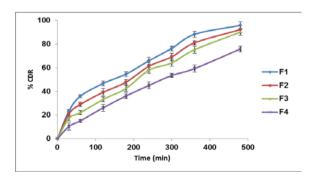
release was best fitted to zero order as the plot indicates highest linearity regression coefficient (R^2) when compared to first-order kinetic model. The mechanism of drug release from buccal patches was studied by fitting the data into Higuchi model and korsmeyer peppa's exponential model. The corresponding *in vitro* release plot of Korsmeyer–peppa's equation indicated good linearity of regression coefficients (Patel and Poddar 2009). Release exponent (n) was found to be more above 0.45, so that the release can be characterized by non–fickian (anomalous) diffusion, which may indicate that the drug release rate is controlled by more than one mechanism i.e. Diffusion coupled with erosion mechanism [22, 23].
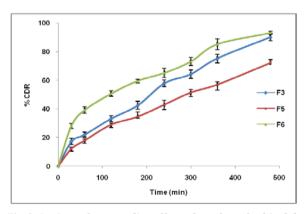

Fig. 3: *In vitro* release studies of buccal patches of nebivolol contains different concentration of propylene glycol [mean±SD (n=3)]

Fig. 2: *In vitro* release studies of buccal patches of nebivolol contains a different concentration of HPMC K15 M[mean±SD (n=3)]

Drug release kinetics

For the investigation of drug release kinetics, release data were fitted to various kinetic models and results shown in table 4. *In vitro* drug

Based on physicochemical properties, *in vitro* residence time and *in vitro* drug release studies, formulation F3 was found to be optimized. Tensile strength of formulation F3 was sufficient to maintain the integrity of the film and it showed adequate residence time to keep the film at the site of administration. From *in vitro* drug release study, it was found that F3 showed maximum release (90.18±2.59) at the end of 30 min which was the prerequisite for the achievement of therapeutic action. However, formulations F1 and F2 containing lower concentration of HPMC K 15 M showed more

release compared to F3 at the end of 480 min, but tensile strength was lesser than F3. But formulations F4 containing high concentration of HPMC K 15 M showed less release and high tensile

strength compare to F3. Formulation F6 also showed more drug release compared to F3, since it content higher amount of plasticizer, but it was rejected because of its sticky nature.

Table 4: Kinetic parameter for *in vitro* drug release from buccal patches of nebivolol

Kinetic model		F1	F2	F3	F4	F5	F6
Zero Order	R^2	0.9701	0.987	0.9917	0.9932	0.9939	0.9683
	K	-0.161	-0.162	-0.167	-0.145	-0.13	-0.14
First Order	R^2	0.941	0.9495	0.9444	0.9806	0.9826	0.955
	K	-0.0027	-0.0021	-0.002	-0.0012	-0.0011	-0.0022
Higuchi	R^2	0.9886	0.986	0.9806	0.9885	0.9862	0.9917
	K	4.488	4.45	4.5654	3.9959	3.5718	3.924
Korsmeyer Peppas	R^2	0.9911	0.9889	0.9831	0.9972	0.9966	0.9938
model	K	0.5059	0.5434	0.6208	0.7361	0.6341	0.4238
	n	0.6267	0.49	0.2688	0.102	0.1362	0.8256

CONCLUSION

The buccal patches are very comfortable due to nonirritating to tissue and can be easily apply and revome. The buccal patches of Nebivolol required lower doage compared to conventional tablets and able to deliver a drug over 6 hr continuously. Results illustrate the drug release was decreases with polymer and increases plastsizer.

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al.* Clinical practice guidelines for the management of hypertension in the community: a statement by the American society of hypertension and the international society of hypertension. J Hypertens 2014;32:3-15.
2. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: a systematic review. J hypertens 2004;22:11-9.
3. Gavhane YN, Yadav AV. Loss of orally administered drugs in GI tract. Saudi Pharm J 2012;20:331-44.
4. Harris D, Robinson JR. Drug delivery via the mucous membrane of the oral cavity. J Pharm Sci 1992;81:1-10.
5. Tarun P, Kumar V, Kumar A. Drug delivery via the buccal patch-a novel approach. Indo Am J Pharm Res 2013;3:3466-83.
6. Veverka A, Nuzum DS, Jolly JL. Nebivolol: a third-generation β-adrenergic blocker. Ann Pharmacother 2006;40:1353-60.
7. Shah I, Bhatt S, Yadav A. Enhancement of solubility and dissolution of nebivolol by solid dispersion technique. Int J Pharm Pharm Sci 2014;6:566-71.
8. Shah H, Shah V, Bhutani S, Parikh D, Mehta T. Dissolution improvement of nebivolol hydrochloride using solid dispersion adsorbate technique. Asian J Pharm 2015;9:49-55.
9. Hirlekar RS. Design of buccal drug delivery system for a poorly soluble drug. Asian J Pharm Clin Res 2009;2:49-53.
10. Periolia L, Ambrogia V, Angelicia F, Riccia M, Giovagnolia S, Capuccellab M, Rossi C. Development of mucoadhesive patches for buccal administration of ibuprofen. J Controlled Release 2004;9:73-82.
11. Priya S, Rathnanand M, Udupa N, Ongole R, Sumanth KN, Joshi U. Preparation and evaluation of buccal mucoadhesive patch of betamethasone sodium phosphate for the treatment of oral submucous fibrosis. J Chem Pharm Res 2011;3:56-65.
12. Patel VM, Prajapati BG, Patel MM. Design and *in vitro* characterization of eudragit containing mucoadhesive buccal patches. Int J Pharm Tech Res 2009;1:783-9.
13. Averineni RK, Sunderajan SG, Mutalik S, Nayak U, Shavi G, Armugam K, *et al.* Development of mucoadhesive buccal films for the treatment of oral sub-mucous fibrosis: a preliminary study. Pharm Dev Technol 2009;14:199–207.
14. Deshpande PB, Dandagi P, Udupa N, Shavi VG, Jain SS, Vasanth SG. Controlled release polymeric ocular delivery of acyclovir. Pharm Dev Technol 2009;15:369-78.
15. Thakur P, Ratnaparkhi MP. Formulation and evaluation of mouth dissolving film of felodipine. Res J Pharm Technol 2014;7:1145-9.
16. Wani MS, Dehghan MH, Mahendrakumar C, Polshettiwar SA, Yadav VB. Design and evaluation of terbutaline sulphate buccal patch. Res J Pharm Technol 2009;2:86-90.
17. Singhvi G, Singh M. Review: *in vitro* drug release charecterization models. Int J Pharm Sci Res 2011;2:77-84.
18. Moffat AC, Osselton MD, Brain W. Clarke's analysis of drugs and poisons overview. 3rd Edition. Pharmaceutical Press: Londom; 2009.
19. Gupta JRD, Irchhiaya R, Garud N, Tripathi P, Dubey P, Patel JR. Formulation and evaluation of matrix type transdermal patches of glibenclamide. Int J Pharm Sci Drug Res 2009;1:46-50.
20. Gawai N, Zaheer Z. Formulation and development of mucoadhesive sustained release buccal tablets and patches of 5-fluorouracil using different polymers. Asian J Pharm Clin Res 2018;11:174-85.
21. Patel RS, Poddar SS. Development and characterization of mucoadhesive buccal patches of salbutamol sulphate. Curr Drug Delivery 2009;6:140-4.
22. Ashutosh R, Prabhakara P, Akhilesh D. Design and evaluation of buccal patches containing combination of hydrochlorothiazide and atenolol. Int J Appl Pharm 2018;10:105-12.
23. Soji S, Arun JL. Development, evaluation, and characterization of Losartan potassium buccal patches using jackfruit polymer. Asian J Pharm Clin Res 2019;12:24-30.