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Original Article

DESIGN AND EVALUATION OF BUCCOADHESIVE CONTROLLED RELEASE FORMULATIONS OF PROCHLORPERAZINE MALEATE

SONIA PANDEY*[1], RITESH R. SHAH[1], ARTI GUPTA[1], B. ARUL[2]

[1]Department of Pharmaceutics, Maliba Pharmacy College, Bardoli, India, [2]Vinayaka Mission College of Pharmacy, Salem, Tamilnadu
Email: sonia.pandey@utu.ac.in

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ABSTRACT

Objective: The Purpose of this work was to design mucoadhesive tablets of prochlorperazine maleate to release the drug in buccal cavity for an extended period of time in order to avoid the first-pass metabolism.

Methods: Six formulations were prepared using different polymer like Xanthan gum, Locust bean gum, Carbopol 974P NF, HPMC K100MCR, Polyox-WSR301 and Gantrez AN139 as a mucoadhesive and controlled release agents. The formulations were tested for content uniformity, thickness, weight variation, friability, *in vitro* drug release, in-vitro bio-adhesion, swelling index and residence time.

Results: Drug excipient compatibility studies performed using DSC. The DSC studies revealed endothermic peak at 200°–205°C for Prochlorperazine maleate. Similarly endothermic peaks were obtained for separate excipient when heated in the range of 50-300 °C indicating their melting points. There was no separate peak observed when the drug was mixed with the different polymers like Xanthan gum, locust bean gum, Carbopol 974 P, HPMC K100 MCR, Gantrez AN139 and Polyox-WSR301 in ratio (1:1) indicating that no interaction took place between drug and polymers used in the study. Dissolution studies of the tablets of the optimized batch (BDS-6) containing Carbopol 974P (CP) and HPMC K100 MCR showed extended release 90.65% up to 24 hr. The bioadhesive force of optimized formulation is 12.18±.011 gm and the maximum swelling index was observed in 3.87±.0057 h.

Conclusion: From the study it can be concluded that formulation BDS-6 containing Carbopol and HPMC K100 MCR give a promising result for sustained release action of PrM.

Keywords: Buccoadhesive tablets, Prochlorperazine maleate, Mucoadhesive polymer.

INTRODUCTION

Buccal drug delivery system (BDS) has been considered as an alternative to oral dosing for compounds subjected to degradation in the gastrointestinal tract or to hepatic first pass metabolism [1]. Buccal drug delivery offers a safer mode of drug utilization since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity [2]. The advances in bioadhesive and controlled release technology have stimulated a renewal of interest in the delivery of drugs to, or via, the buccal route. Buccal drug delivery (BBD) devices can now be designed to remain in contact with the oral mucosa while providing controlled release characteristics over a prolonged period of time. A combination of these two attributes can be achieved by the use of suitable bioadhesive materials. Appropriate materials for the bioadhesive drug delivery consist mainly of hydrogel-forming polymers [3].

Prochlorperazine maleate (PrM) is a piperazine phenothiazine derivative with antipsychotic, antiemetic and weak sedative activity. PrM is well absorbed from the gastrointestinal tract PrM distributes to most body tissues with high concentrations being distributed into both liver and spleen. PrM enters the enterohepatic circulation and is excreted chiefly in the feces. The low oral bioavailability 16% is due to the high first pass metabolism [4]. Since buccal route bypasses first pass effect, the dose of the drug could be decreased by 50%. The drug dosage regimen is usually three to four times a day because of it's short half-life [5] which makes it a good candidate for buccal and controlled drug delivery. The Proper combination of suitable mucoadhesive polymer would allow the desired mucoadhesion and extended release of the drug. The various polymers considered alone and in combination suitable for the development of bioadhesive extended release delivery like cellulosic and polyacrylates derivatives (hydroxypropyl-methylcellulose and Carbopol) natural gums (xanthan gum and locust bean gum) Gantrez A139 and Polyox-WSR301 (PEO). PEO is the fastest hydrating water soluble polymer among hydrophilic polymers [6]. Xanthan gum is a hydrophilic, anionic heteropoly-saccharide whereas Locust bean gum is a nonionic polysaccharide and its hydration process is independent of pH. The drug release was slower from the matrices which were composed of both xanthan gum and locust bean gum compared with the tablets whose composition was only locust bean gum and xanthan gum [7]. Hydroxypropyl methylcellulose (HPMC), a semisynthetic derivative of cellulose, has its popularity for the formulation of controlled release (CR) dosage forms as a swellable and hydrophilic polymer. Carbopol polymers have been used as mucoadhesives. Carbopol polymers are high molecular weight, crosslinked, acrylic acid-based polymers and carbopol 974P are cross-linked with allyl pentaerythritol that are polymerized in ethyl acetate [8]. Gantrez AN-139 copolymer of methyl vinyl ether and maleic anhydride and methyl vinyl ether and maleic acid, respectively (PMVE/MAH) and PMVE/MA, with molecular masses of 1,080,000 [9]. Effect of polymer concentration on mucoadhesion and release pattern was also studied. The purpose of this work is to design mucoadhesive tablets to release the drug in buccal cavity for an extended period of time in order to facilitate the intimate contact with the underlying absorption surface, to avoid the first-pass metabolism, for better bioavailability, to reduce the dosing frequency and to improve patient compliance.

MATERIALS AND METHODS

Materials

Prochlorperazine maleate (PrM), HPMC K100MCR, Carbopl 974P, locust bean gum and Xanthan gum were obtained as a gift sample from Alembic pharmaceutical Vadodara. PEO WSR 205 was purchased from Dow chemicals, India. Gantrez AN-139 was purchased from Sigma-Aldrich. All other chemicals and reagents used were of analytical grade.

Drug excipient compatibility study

Differential scanning calorimetry (DSC)

The samples were sealed in aluminum pans, and DSC thermo grams were recorded at a heating rate of 10C/min from 50 °C to 300 °C

temperature range. A nitrogen purge was maintained throughout runs and baseline optimization was performed before each run.

Preparation of mucoadhesive tablets

Various mucoadhesive tablet formulations of PrM were formulated with different water soluble polymers like Xanthan gum, Locust been gum, Carbopol 974P NF, HPMC K100MCR, Polyox-WSR301, Gantrez AN139 as a mucoadhesive agent, polyvinylpyrrolidone in Isopropyl alcohol (IPA) as a binder solution, sucrose as a diluent as well as sweetener, magnesium stearate as a lubricant and talc as a glidant. Tablets weighing 60 mg containing 5 mg of PrM were compressed using tableting machines (rimek minipress) employing a 5.5 mm flat punch without brake line. Compression force was adjusted to the hardness of 4-5 kg/cm^2.

After ejection, the tablets were stored over silica gel in a desiccator for 24 h to allow for elastic recovery and hardening. Different mucoadhesive agents were studied to check the effect on the mucoadhesive force, swelling index and % drug release. The different batches were prepared as mentioned in table 1. Prepared mucoadhesive tablets were evaluated for their physical and mechanical properties like weight uniformity, content uniformity, hardness, friability, diameter, thickness, bio-adhesion force, swelling index and *in vitro* drug release study.

Table 1: Composition of mucoadhesive tablets with different mucoadhesive agents

Ingredient*	BDS-1	BDS-2	BDS-3	BDS-4	BDS-5	BDS-6
Xanthan gum	4.5	-	-	-	-	-
Locust been gum	4.5	-	-	-	-	-
Carbopol 974P	-	5	-	-	-	5
HPMC K100 MCR	-	-	5	-	-	5
Gantrez AN139	-	-	-	5	-	-
Polyox-WSR301	-	-	-	-	5	-
Prochlorperazine maleate	5	5	5	5	5	5
PVP K29/30	3	3	3	3	3	3
Sucrose	41.5	45.5	45.5	45.5	45.5	40.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1	1	1	1	1	1
Total wt	60	60	60	60	60	60

*Indicates the quantity in mg.

Measurement of bio-adhesion force

The force of adhesion for each formulation was measured by a specially designed apparatus by referring to the literature [10]. Apparatus is shown in fig. 1. A string was wound over two pulleys and connected to a pin stuck to the surface of the mucoadhesive tablet. The other surface of each tablet was stuck to sieve no (120) by the wetting procedure. An empty bottle was connected to the other side of the string. The adhesion force was measured by addition of water to this bottle. The weight of water as a measure for the force of adhesion was determined.

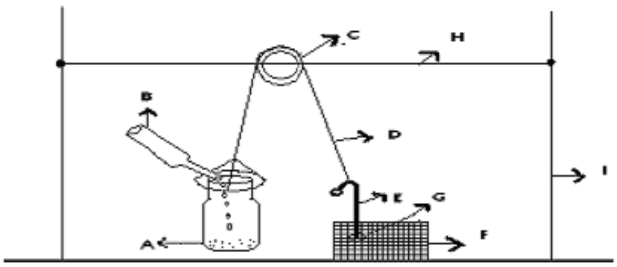


Fig. 1: Measurement of bioadhesion force, A= Plastic bottle B= Pipette C= Pulley D= Thread E= Pin F= 120 No Sieve, G= Buccal tablet H= stainless steel I= Stand

Measurement of swelling index (SI)

Tablets were weighed individually along with the Petri dish (W_1).10 ml of phosphate buffer (pH6.8) was added to each Petri dish. At a regular interval (0.5, 1, 2, 3, & 4 h) the excess amount of phosphate buffer was removed by using tissue paper. The swollen tablets were reweighed (W_2) and SI was calculated using the following formula.

$$S.I = \frac{W2 - W1}{W1}$$

Where, S. I = swelling index, W_1= initial weight of tablet, W_2= weight at time't' [11]

Determination of residence time

The in-vitro residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was 800 ml isotonic phosphate buffer solution pH 6.8, maintained at 37 °C±1 °C. A segment of goat buccal mucosa was glued to glass slide, attached to glass slab which is vertically attached to the apparatus. The tablet was hydrated from one surface using a little amount of isotonic phosphate buffer solution, and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed move up and down so that the tablet was completely immersed into the solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface were recorded [12].

***In vitro* drug release study**

The USP V (Disc cover paddle) method was employed for the in-vitro dissolution studies. The dissolution medium was, 500 ml of isotonic phosphate buffer solution pH 6.8. The rate of stirring was 100 rpm. The temperature was maintained at 37 °C±0.5 °C for a period of 24 h. At appropriate time interval (1, 2, 4, 6, 8, 12, 16 and 24 hr), 10 ml of sample was taken and filtered. In the dissolution media, 10 ml of fresh dissolution fluid was added after each withdrawal in order to maintain a constant volume. The samples were assayed at 262 nm by 1st Derivative Spectroscopy [13-15].

Drug release kinetics

Release data were analyzed using the following equation:

$$\frac{Mt}{M\infty} = kt^n$$

Where, M_t/M_∞: is the fractional release of drug,

t: Denotes the release time,

K: Constant incorporating structural and geometrical characteristics of the device

n: Diffusional exponent that characterized the type of release mechanism during the dissolution process.

For non-fickian release, the value of n falls between 0.5 and 1.0; while, on the case of fickian diffusion, n = 0.5; for Zero order release (case II transport), n = 1; and for super case II transport, n is greater than 1. The values of 'n' were estimated by linear regression of log (M_t/M_∞) versus log (t) of different formulations are shown in table 2. This model used, when the release mechanism is not known or when more than one type of release phenomenon could be involved [11, 16-17].

RESULTS AND DISCUSSION

Compatibility studies of drug: polymer

The DSC thermo grams are represented as fig. no 2(a-e). According to the functional category, the drug and excipient are mixed in an appropriate ratio in a mortar for 5-10 min and then transferred the amount in amber colored glass vials. Samples in amber glass vials were loaded in the 60 ºC chamber. Initial samples were evaluated for incompatibility studies by differential scanning calorimetry (DSC). The samples were checked for physical changes such as lump formation and color change after two weeks.

The DSC studies revealed endothermic peak at 200º–205 ºC for PrM. Similarly, Endothermic peak were obtained for separate excipient when heated in the range of 50-300 °C indicating their melting points. There was no separate peak seen when the drug was mixed with the polymer in a ratio indicating that there is no interaction between drug and polymers used in the study. No significant change in onset values in the DSC curve indicates that the PrM is stable with all polymer investigated.

Evaluation of mucoadhesive tablets

Physicochemical characterization of PrM revealed that the drug is a slightly bitter, off-white amorphous powder, with a melting point range from 200º–205 ºC. The assay was found to be 97% w/w and the percentage loss on drying was 1.55%w/w. The bulk density and tapped density of the drug was found to be 0.309 gm/ml and 0.486 gm/ml respectively. The compressibility index and Hauser's ratio of the drug were found to be 36.419% and 1.572 respectively, which showed that the compressibility of the PrM was poor. The particle size analysis was done by sieve method which revealed that higher % of the particles were of the size 180 µm retained. All the tablet parameters as weight variation, thickness, hardness, friability were found within the limits and comply as per official limits (wherever applicable) results are shown in table 2. The bioadhesion force of all the formulations is shown in table 3. The bioadhesion force of optimized formulation is 12.18±.011 gm. The swelling index of the optimized batch was found to be 3.27±.0057 and results are shown in fig. 3. Residence time of the optimized batch was found to be 9.45 hr and values of all the formulation shown in table 4. The kinetic studies showed the non-fickian diffusion. The results are listed in table 5.

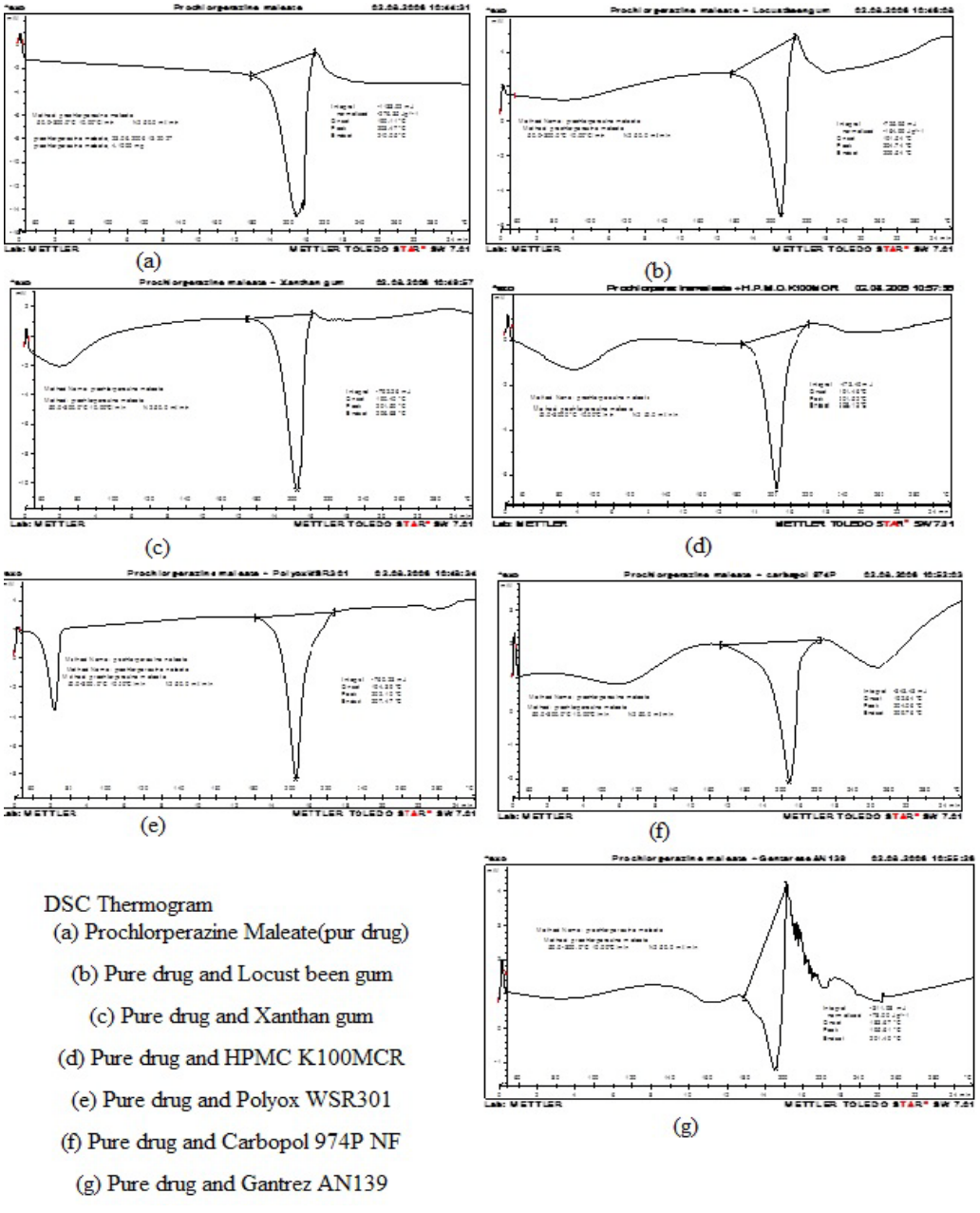


Fig. 2(a-g): DSC thermograms of pure grams of pure drug and along with the polymer

Table 2: Physical parameter of buccoadhesive tablets

Batch no.	Weight of tablet (mg) (n=20)	Hardness (kg/c. m²) (n=20)	Thickness (mm) (n=6)	Friability (%)(n=20)	% Assay(w/w) (n=20)
BDS-1	60.05±0.73	4.41±0.66	2.16±0.03	0.15±0.5	100±0.31
BDS-2	60.26±0.65	4.37±0.61	2.17±0.04	0.09±0.39	93.47±0.45
BDS-3	60.06±0.77	4.57±0.46	2.18±0.05	0.09±0.56	93.47±0.03
BDS-4	60.13±0.77	4.54±0.59	2.19±0.03	0.12±0.13	93.47±0.01
BDS-5	60.32±0.95	4.61±0.51	2.17±0.05	0.09±0.02	95.65±0.18
BDS-6	60.42±0.80	4.43±0.56	2.18±0.06	0.09±0.03	95.65±0.04

All Value expressed as mean±SD

Table 3: Bioadhesion force

Formulation	Bioadhesive force (gm)
BDS-1	16.00±.12
BDS-2	11.92±.06
BDS-3	Not obtained
BDS-4	Not obtained
BDS-5	7.60±.18
BDS-6	12.18±.011

All Value expressed as mean±SD (n=3)

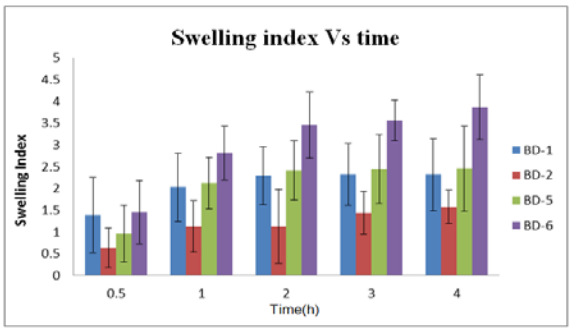
Table 4: Residence time (h) of all the batches

Residence time(h)						
Batch no.	**BDS-1**	**BDS-2**	**BDS-3**	**BDS-4**	**BDS-5**	**BDS-6**
	9.45±0.10	9.67±0.42	Not performed	Not performed	8.88±0.39	>10

All Value expressed as mean±SD (n=3)

Table 5: Kinetic coefficients estimated values of n (Diffusional Exponent) and r² (Correlation coefficient) M_t/M_∞ Vs Log (T)

Batch code	Kinetic parameters for peppas model	
	n (Diffusional exponent)	r² (Correlation coefficient)
BDS-1	0.7399	0.9726
BDS-2	0.7053	0.9858
BDS-3	0.6698	0.9978
BDS-4	0.5886	0.9940
BDS-5	0.5945	0.9853
BDS-6	0.5258	0.9935



(n=3)

Fig. 3: Graphical representation of swelling index of prepared buccoadhesive Prochlorperazine maleate tablets (BDS-1 to BDS-6)

The result of bioadhesive force study as presented in table no.3 showed 16 gm, 11.93 gm, 7.60 gm, and 12.18 of BDS-1, BDS-2, BDS-5 and BDS-6 respectively. BDS-1 formulation containing xanthan gum and locust been gum showed highest bioadhesive force (16 gm) may be due to the high interlocking property of xanthan gum and locust been gum because Locust bean gum is a galacto mannan composed of a 1-4-linked-b-D-mannan backbone with 1-6-linked-a-D-galactose side groups so Xanthan gum interacts with galacto mannans to form mixed gels with high viscosity at low-total-polysaccharide concentrations [18]. The sufficient bio-adhesion value was not observed in BDS-3 and BDS-4 that may be due to the presence of HPMC K100MCR and Gantrez AN139 respectively, so these formulation are not considered for further studies The least bioadhesive force value was proposed by BDS-5 formulation containing only Polyox-WSR301.

The swelling behavior of differently formulated tablets as a function of time was shown in fig. 3. The appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and prolonged drug release. The swelling index increased with time as the weight gain by the tablet was increased proportionally with the rate of hydration. The maximum swelling was obtained in 4 h (BDS-6), after which polymer starting eroding slowly in the medium. During the swelling study, two phases such as swelling phase (increase in weight) and the degradation phase (reduction in weight) were observed [19]. The maximum swelling was observed in formulation BDS-6 containing Carbopol 974P NF and HPMC K100 MCR. BDS-5 formulation showed least swelling index in comparison to other formulation. The linearity in the swelling index shows the sustained release of the drug. The tablets of all batches except BDS 6-BDS 1, BDS 2 and BDS 5 showed the moderate residence time (around 8.8 h). Tablets of batch BDS 6 showed residence more than 10 hr; reason might be the presence of carbopol 934P and HPMC K100 MCR [19]. The in-vitro release study did not showed the satisfactory sustained release of PrM from all formulation. Comparative dissolution profiles of all batches BDS-1 to BDS-6 were shown in fig. 4.

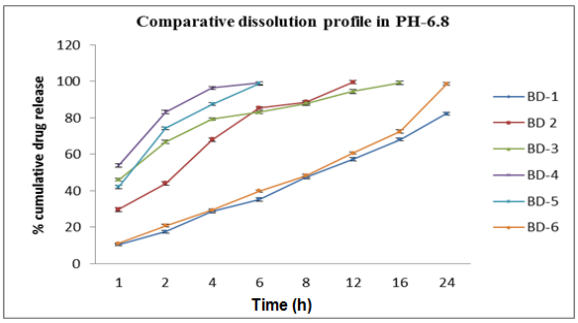


Fig. 4: Comparative drug release profile prepared buccoadhesive PrM tablets of all batches (BDS-1 to BDS-6)

The burst release was observed in tablets of batches BDS-4 and BDS 5 containing Gantrez AN139, Polyox WSR 301 respectively because these polymers did not show sufficient bioadhesive and swelling properties as reflected from results, so drug release cannot be controlled with these polymers. From the *in-vitro* release study, it was also concluded that formulation BDS-2 and 3 showed slower release compared to batch BDS-4 and 5 but not extendable up to 24 h. BDS-2 and 3 containing CP and HPMC released the whole drug within 16 hr. BDS-6 considered as optimized batch release was slow and extendable up to 24 h because CP and HPMC are hydrophilic swellable polymer matrices; they are able to form a viscous gel layer; which controls the drug release via diffusion through the gel and erosion of the gel layer [19]. Batch BDS-6 was considered for further studies based on swelling study, bio-adhesion force, mucoadhesion time and drug release study. The data obtained from the release kinetic study shows all the 'n' values in between 0.5 to 1; indicating non-fickian release kinetics.

CONCLUSION

The mucoadhesive tablet formulation BDS-6 containing CP and HPMC give a promising result for sustained release action of PrM with adequate swelling, bio-adhesion force, suitable residence time, and, it reduces the polymer loss, along with sustained release of drug from the mucoadhesive tablets.

CONFLICT OF INTERESTS

The authors report no conflict of interest. Authors alone are responsible for the content and writing of paper

REFERENCES

1. Jacobsen J. Buccal iontophoretic delivery of atenolol hydro-chdrochloride employing a new *in vitro* three chamber permeation cell. J Controlled Release 2001;70:83-95.
2. Wong FC, Yuen KH, Peh KK. Formulation and evaluation of controlled release eudragit buccal patches. Int J Pharm 1999;178:11-22.
3. Tiwari D, Sause R, Madan PL. Evaluation of polyoxymethylene homopolymers for buccal bioadhesive drug delivery device formulations. AAPS Pharm Sci 1999;1:50-7.
4. SC Sweetaman. Martindale the complete drug reference. 33rd. edition; 2012.
5. Nagasamy D, Venkatesh SS, Meyyanathan SN, Elango K, Suresh B, Santhi K. Design and evaluation of prochlorperazine maleatae sustained-release tablets: influence of hydrophilic polymers on the release rate and *in-vitro* evaluation. Int J Pharm Sci Nanotechnol 2010;3:965-77**.**
6. Shah R, Patel S, Patel H, Pandey S, Shah S, Shah D. Formulation development of Carvedilol compression coated tablet. Pharm Dev Technol 2013;18:906-15.
7. Dey P, Maiti S, Biswanth SA. locust bean gum and its application in pharmacy and biotechnology: an overview. Int J Curr Pharm Res 2012;4:7-11.
8. Sharmin N, Elias-Al-Mamun, Saiful Islam MD, Reza-ul Jalil. Preparation and characterization of lidocaine double layer buccal tablet using mucoadhesive carbopol® polymers. Dhaka Univ J Pharm Sci 2011;10:29-34.
9. Ryan F Donnelly, Maelıosa TC Mc C, Ahlam Zaid A, Eneko L, Emma Mc, Aaron JC. Hydrogel-forming microneedles prepared from "Super swelling" polymers combined with lyophilised wafers for transdermal drug delivery. PLOS One 2014;9:1-12.
10. Manivannan R, Balasubramaniam A, Prem Anand DC, Sandeep G, Rajkumar N. Development and *in vitro* evaluation of novel buccoadhesive tablet formulation of prednisolone. Acta Pharm 2002;52:121–7.
11. Desai KG, Kumar TM. Preparation and evaluation of a novel buccal adhesive system. AAPS PharmSciTech 2004;5:1-9.
12. Noha Adel N, Ismail FA, Boraie NA. Mortada LM. Mucoadhesive drug delivery systems. Evaluation of mucoadhesive polymers for buccal tablet formulation. Drug Dev Ind Pharm 2004;30:985-99.
13. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi Shadbad RM, Saeedi M. Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulation: effect of fillers. II Farmaco 2004;59:155-61.
14. Noha Adel N, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive drug delivery systems. II. Formulation and in-vitro/in-vivo evaluation of mucoadhesive buccal tablets containing water soluble drugs. Drug Dev Ind Pharm 2004;30:995-1004.
15. Fabregas JL, Garcia N. *In-vitro* studies on buccoadhesive tablet formulation of hydrocortisone hemisuccinate. Drug Dev Ind Pharm 1995;21:1689-96.
16. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Balsi P, *et al.* Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J Controlled Release 2005;95:521-33.
17. Fergany A, Khedr MH. Preparation and *in-vitro/in-vivo* evaluation of the buccal bioadhesive properties of slow release tablets containing miconazole nitrate. Drug Dev Ind Pharm 2003;29:321-37.
18. Higiro J, Herald TJ, Alavi S, Bean S. Rheological study of xanthan and locust bean gum interaction in dilute solution: effect of salt. Food Res Int 2007;40:435–47.
19. Pandey S, Gupta A, Yadav JS, Shah DR. Formulation and *in-vitro* evaluation of bilayered buccal tablets of carvedilol. Indian J Pharm Edu Res 2010;44:259-66.