ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD

Volume - 02 Issue - 01 JAN-FEB 2014

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

FORMULATION AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL TABLETS OF METOPROLOL SUCCINATE BY USING XANTHUM GUM

V.Kalyani*, V.Sai Kishore, G.Padmini, R.K.V.Nagasudha, M.Kalyan Kumar

Bapatla College of Pharmacy, Bapatla, **Guntur (D), Andra Pradesh**

Received: February 2014 ***Revised and Accepted: March 2014***

ABSTRACT

In the present work, the mucoadhesive tablets of Metoprolol succinate were prepared by using xanthum gum as a binder. The four tablet formulation were prepared by using drug xanthum gum ratios of 1:0.5, 1:0.75, 1:1, 1:1.25 by direct compression technique. Tablets were subjected for evaluation of uniformity of weight, hardness, friability, drug content uniformity, Swelling studies, Surface pH study, Ex-vivo mucoadhesion time, Ex-vivo Bio adhesive strength and In vitro drug release study. Drug polymer interactions were evaluated by Fourier Transform Infrared Spectroscopy. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesive strength increases. Based on the results F4was found to be optimized formulation. The in-vitro drug release of all formulations exhibits complete release of Metoprolol succinate with zero order release kinetics and followed by Higuchi mechanism. From the study it can be conclude that the Aegle marmelos gum used as a binding agent in mucoadhesive buccal tablet.

Key words: *Metoprolol, Buccal, xanthum gum, Mucoadhesive.*

INTRODUCTION:

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Other advantages such as low enzymatic activity painless administration, easy drug withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions. Mucoadhesion is not new; there has been increased interest in recent years in using mucoadhesive polymers for drug delivery. Substantial effort has recently been focused on placing a drug or a formulation in a particular region of the body for extended periods of time [1].

Xanthum gum a gum produced by fermentation of a carbohydrate with Xanthomonas camoestris. It is used in pharmaceutical manufacturing as a suspending, stabilizing, thickening, retarding and emulsifying agent [2]. In the present investigation mucoadhesive property *of* xanthum gum has been evaluated using Metoprolol succinate (as model drug) used in the treatment of anti-hypertension and cardiovascular diseases and it is known to have low oral bioavailability (50%) due to an extensive high first-pass effect. Hence, it is suitable for buccal drug delivery. The aim of

***Corresponding Author**
V.Kalyani
Department Pharmaceutics, Bapatla
Bapatla College of Pharmacy, Guntur (D),
Andhra Pradesh, India.
E-mail: Kalyanineyutha@gmail.com
Ph.no:9603799044

the present study was to design and develop mucoadhesive buccal tablets of Metoprolol succinate that could be applied to the buccal mucosa to release the drug unidirectionally in buccal cavity in order to decrease gastric irritation and avoid first pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.

MATERIALS AND METHODS:

Materials: Metoprolol succinate (It is obtained as gratis sample from Hetero pharmaceuticals). All other materials used in this study were of A.R. grade purchased from S.D. fine chemicals Mumbai.

Method:

Preparation and evaluation of Tablet:

Buccal tablets were prepared by direct compression procedure involving two consecutive steps. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15mins. Magnesium stearate was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 9mmflat punched using sixteen station tablet compression machine (Cadmach), the upper punch was then removed and backing material ethyl cellulose was added over it and finally compressed at a constant compression force. The tablets composition was shown in the Table I. All ingredients were dried, passed through 100 mesh sieve and mixed manually in mortar. The tablet formulation was developed for 250 mg tablet weight using 50 mg of Metoprolol succinate (drug) and varying concentration of xanthum gum [3]. The tablets were compressed by using sixteen station tablet machine fitted with flat faced punches.

Table I: Composition of mucoadhesive buccal tablets of metoprolol succinate

Content of tablet	1:0.5 (F1)	1:0.75 (F2)	1:1 (F3)	1:1.25 (F4)
Metoprolol succinate	50	50	50	50
Xanthum gum	25	37.5	50	62.5
Microcrystalline cellulose	121	108.5	96	83.5
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Ethyl Cellulose	50	50	50	50
Total weight (mg)	250	250	250	250

Evaluation of the prepared buccal tablets:

All the tablets were evaluated for different parameters such as hardness, weight variation and friability [4].

Drug content:

Twenty tablets were collected and powdered. The powder equivalent to 50 mg of drug was weighed accurately, dissolved in 100ml of phosphate buffer pH 6.8. The solution was filtered, suitably diluted and an aliquot was analyzed at 224nm [5].

Swelling studies:

Three buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates and incubated at 37±1^{0}c. After every 2h time interval until 6h the tablet was removed from the petri dish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W2) and the swelling index were calculated by using the formula given in equation [6].

Swelling index = (W2-W1)/W1 X 100.

Where,
W1 = initial weight of the tablet
W2 = final weight of the tablet

Surface pH study:

The tablet was allowed to swell by keeping in contact with 1 ml, of distilled water for 2h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min [7].

Ex-vivo mucoadhesion time:

The ex vivo residence time was found using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800-ml pH 6.8 phosphate buffer maintained at 37°C.The sheep buccal tissue was glued to the surface of a glass slab using cyanoacrylate adhesive, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5-ml of pH 6.8 phosphate buffers and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted [8].

Ex-vivo Bio adhesive Strength:

Ex-Vivo Bio adhesive strength of the buccal tablet was measured on the modified physical balance method. The fresh goat buccal mucosa obtained from slaughter house was cut in to pieces and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH6.8. The tablet was stuck to the lower side of second glass slide with glue. The both pans were balanced by adding an appropriate support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right hand pan and water (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface it give the mucoadhesive strength [9].

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.81}{1000}$$

In vitro drug release study:

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 500ml, of phosphate buffer pH 6.8 of 50 rpm. The buccal tablets were allocated to the bottom of the dissolution vessel. 5ml sample were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were analysed after appropriate dilution by UV spectrophotometer at 224nm [10].

Drug-excipient interaction studies:

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with A.marmelos gum, diluents and lubricants used in tablet formulations. In the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies [11].

RESULT AND DISCUSSION:

The swelling behavior of gum reveals, it was suitable candidate for sustained release. Mucoadhesive buccal tablets of Metoprolol succinate with xanthum gum were prepared by using different drug: gum ratios. The results of the physical characterization of tablets are summarized in Table II. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeial limits. The swelling behavior is important for bio adhesion. Water sorption increases with increase in the concentration of hydrophilic polymers. Swelling index, Mucoadhesive strength and Ex-vivo residence time were shown in Table III.

The xanthum gum swells slowly and dissolves in presence of water. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH was bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.32 to 6.84 which were nearer to the salivary pH 6.8 Hence it was assumed that these formulations do not cause any irritation to the mucous layer of oral cavity.

Table II: Evaluation of mucoadhesive buccal tablets of metoprolol succinate

Formulation	Hardness(kg/cm^2)	Friability (%)	Drug content (%)	Weight variation
F_1	3.5 ± 0.2	0.41	98.62	248 ± 0.21
F_2	3.7 ± 0.3	0.48	99.75	249 ± 0.17
F_3	3.8 ± 0.5	0.56	98.37	250 ± 0.14
F_4	4.0 ± 0.3	0.53	99.75	251 ± 0.28

Table III: Mucoadhesion strength, swelling index, retention time, surface pH of buccal tablets

Formulation	Swelling index	Ex-vivo mucoadhesion time	Ex-vivo bioadhesive strength	Surface pH
F_1	8.13 ± 3.68	4 hours 45 minutes	16.09 ± 0.28	6.32 ± 0.07
F_2	8.95 ± 3.07	6 hours 20 minutes	16.78 ± 0.31	6.55 ± 0.05
F_3	10.17± 7.62	8 hours 15 minutes	17.12 ± 1.25	6.84 ± 0.09
F_4	11.75 ± 6.85	10 hours 50 minutes	18.19 ± 1.36	6.73 ± 0.06

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulation F1-F4 shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F4 shows maximum mucoadhesive strength this is due to tremendous increase in viscosity.

The ex-vivo residence time was determined using USP disintegration apparatus. Among the four formulations subjected for this study F4 showed maximum residence time of 10.5 hrs. It was found that an increase in concentration of polymer increases the residence time. This was mainly due to the strong mucoadhesion nature of the polymer used. The results of in vitro drug release studies of different formulation are depicted in Fig 1.Tablet formulations prepared by using drug and gum in ratios of 1:0.5, 1:0.75, 1:1, and 1:1.25 shown drug release for a period of 7 hours, 8 hours, 10.5 hours and 12 hours respectively. The initial burst release decrease with increase in concentration of gum. The dissolution kinetics values were shown in Table IV. The in-vitro drug release of all formulations exhibits complete release of Metoprolol succinate with zero order release kinetics and followed by Higuchi mechanism. IR spectroscopic studies indicated that there were no drug-excipient interactions. All the principle peaks observed for the drug alone were also observed in the tablet formulation also.

Table IV: Drug release kinetic studies of tablet formulation

Formulation	Zero order	First order	Higuchi	Peppas	T_{50} (hr)	T_{90} (hr)
F1	0.992	0.954	0.994	0.940	3.0	5.4
F2	0.994	0.967	0.997	0.961	3.9	6.9
F3	0.997	0.974	0.993	0.972	4.9	8.8
F4	0.995	0.989	0.998	0.986	6.2	11.2

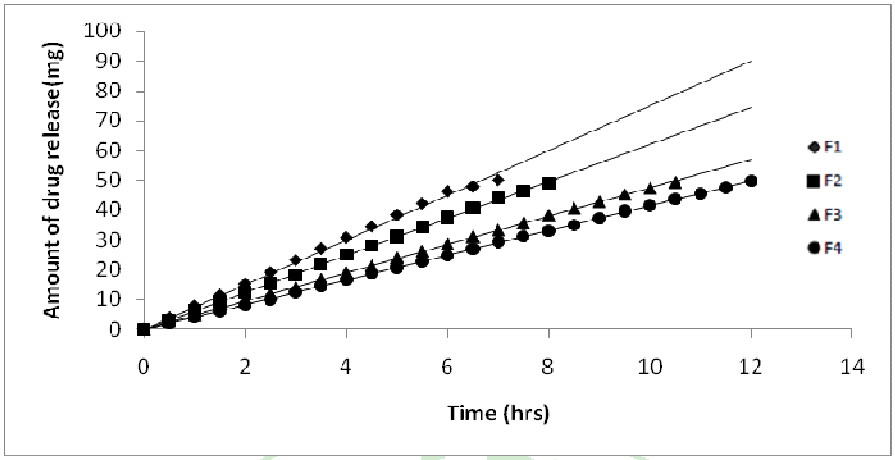

Fig-1: Zero order plot Mucoadhesive tablets of Metoprolol succinate

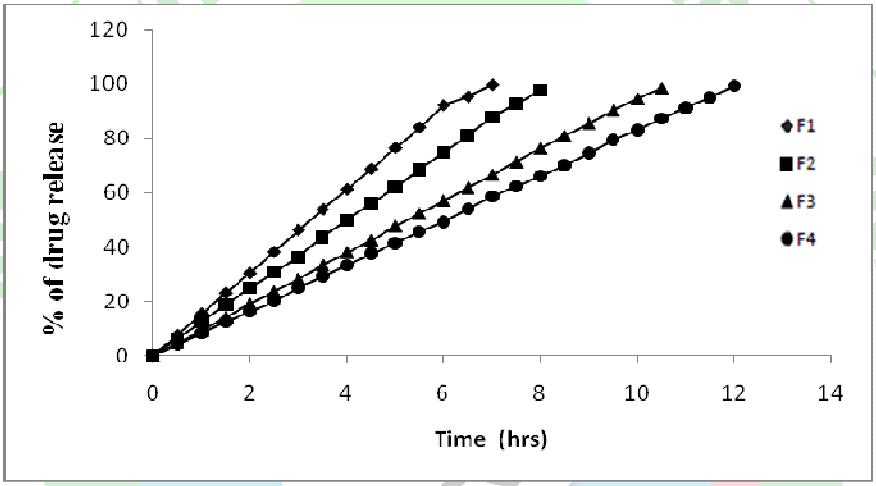

Fig-2: % Drug release of Mucoadhesive buccal tablets of Metoprolol succinate

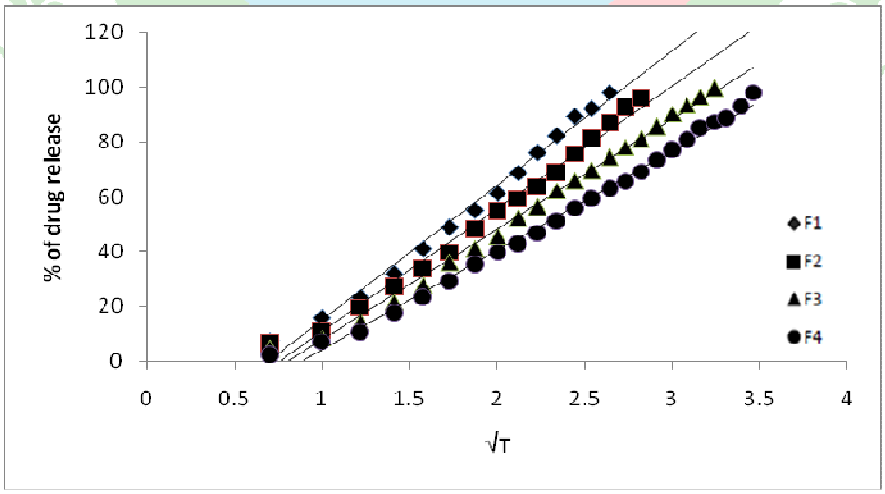

Fig-3: Higuchi plot of Mucoadhesive buccal tablets of Metoprolol succinate

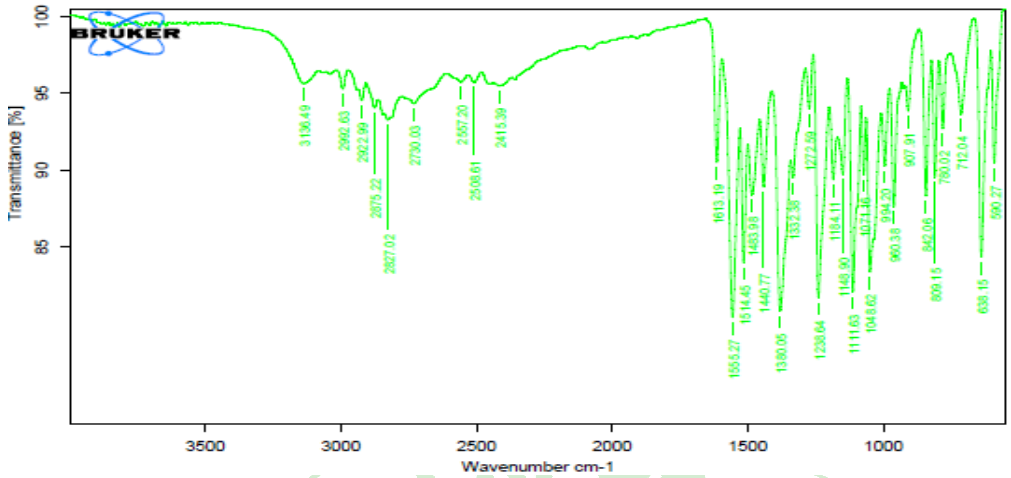

Fig -4: FTIR of Metoprolol succinate pure drug

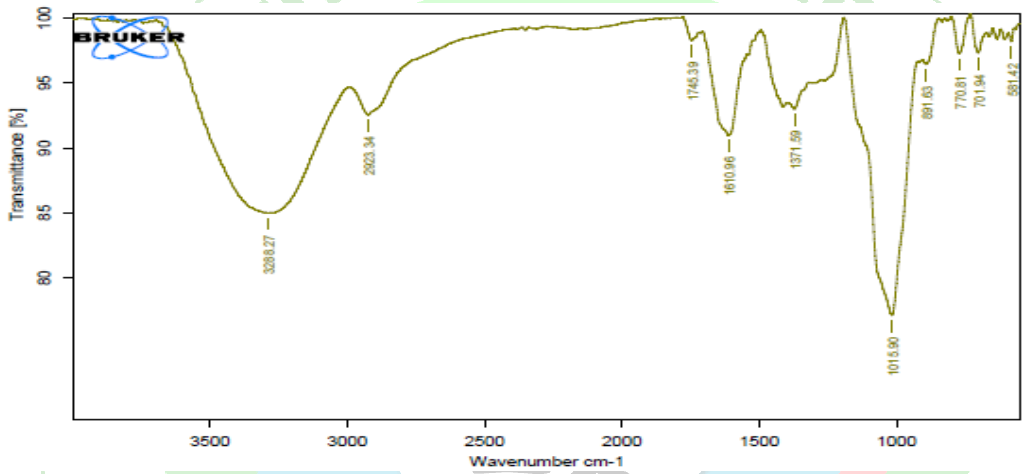

Fig-5: FTIR of xanthum gum

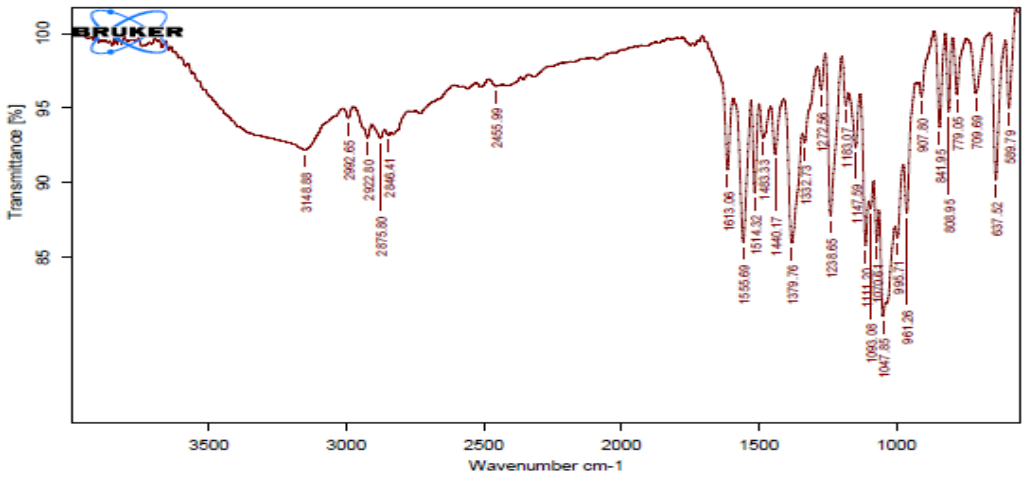

Fig-6: FTIR of Optimized formulation (F_4)

CONCLUSION:

The present study revealed that xanthum gum appears to be suitable for use as a release retardant in the manufacture of matrix tablets because of its good swelling, good flow rate and suitability for mucoadhesion formulations. As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesive strength increases. Ex-vivo residence test for mucoadhesion indicated good mucoadhesive property of the prepared tablets. From the results, it was concluded that xanthum gum can be used as an excipient for making mucoadhesive buccal tablets of Metoprolol succinate.

REFERENCES

1. *H.H. Alur, T.P. Johnston, A.K. Mitra, Encyclopedia of Pharmaceutical Technology, in: J. Superbrick, J.C. Boylan (Eds.), Peptides and Proteins: Buccal Absorption, Marcel Dekker Inc., New York, 2001, 20 (3):193–218.*
2. *Gracia F, Santos VE, Casas. Xanthan gum: Production recovery and properties. Biotechnology Advances 2000:18; 549-579.*
3. *V. Sai Kishore, B Sudheer, K.Srikanth, M. Sandeep and M. Teja Krishna. Design and development of mucoadhesive buccal tablets of metoprolol succinate by using Cashewnut Tree Gum. International journal of pharmaceutical and chemical sciences 2013; 2(4): 1914-1921.*
4. *Indian Pharmacopoeia: Ministry of Health and Family Welfare, Govt. of India, Controller of Publications, New Delhi 1996:Vol.II, A100 - A111.*
5. *Chanda R, Nath LK and Mahapatra S: Formulation Development of Oral Mucoadhesive Coated Terbutaline Sulphate Tablets Using Some Natural Materials Extracted from Edible Fruits Available in India. . Iranian Journal of Pharmaceutical Sciences 2009; 5(1): 3-12.*
6. *Venkatchalam Raju P, Goverdhan Reddy P . Formulation and in vitro evaluation of buccal tablets of metoprolol succinate. Int. Res J Pharm. App Sci., 2013; 3(2):102-111.*
7. *Parvez N, Ahuja A, Khar RK. Development and evaluation of mucoadhesive buccal tablets of Lignocaine Hydrochloride, Ind J Pharm Sci. 2002; 64(6): 563-567*
8. *Saikat Pande, Marina Koland, Jolly R Parikh, Ajay B. Solanki, Gaurav Negi, Rahul Trivedi. Buccoadhesive Tablets of Losartan Potassium: Design and Characterization. Int J Pharm and Bio Arc.2010; 2(1); 150-154.*
9. *Satyabrata Bhanja, P. Ellaiah, Sujit Kumar Martha, Pratit Kanchan Sahu, Sandip Prasad Tiwari, Bibhuti Bhusan Panigrahi, Debajyoti Das. Formulation and in vitro evaluation of mucoadhesive buccal tablets of Timolol maleate. Int J Pharm Biomed Res 2010, 1(4), 129-134.*
10. *Sonia Pandey, Arti Gupta, Jitendra Singh Yadav D. R. Shah. Formulation and In-vitro Evaluation of Bilayered Buccal Tablets of Carvedilol. Ind J Pharm. Educ. Res.2010; 44(3): 7-11.*
11. *Nakhat PD, Kondawar AA, Rathi LG, Yeole PG. Development and invitro evaluation of mucoadhesive tablets of metoprolol tartarate. Ind J Pharm Sci.2008; 70(1): 121-125.*