Research Paper

Studies on Buccoadhesive Tablets of Terbutaline Sulphate

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An attempt has been made to develop buccoadhesive bilayered tablets comprising of drug containing bioadhesive layer and drug free backing layer to release the drug for extended period of time with reduction in dosing frequency. Tablets of terbutaline sulphate were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, Methocel K4M, Methocel K15M and sodium carboxy methyl cellulose either alone or in combinations with backing layer of ethyl cellulose. The physical characteristics, swelling index, surface pH, *in vitro* bioadhesion strength, and *in vitro* release of formulated tablets were shown to be dependent on characteristics and composition of bioadhesive materials used. The modified in vitro assembly was used to measure and compare the bioadhesive strength of tablets with fresh porcine buccal mucosa as a model tissue. The maximum bioadhesive strength was observed in tablets formulated with Carbopol 934P alone and strength decreases with decrease in its content. The tablets were evaluated for *in vitro* release in pH 6.8 phosphate buffer for 10 h using a standardized dissolution apparatus. In order to determine the mode of release, the data was subjected to Korsmeyer and Peppas diffusion model. All the formulations followed non-Fickian release mechanism. Carbopol 934P and Methocel K4M in the ratio of 1:1 could be used to design effective and stable buccoadhesive tablets of terbutaline sulphate.

Key words: Buccoadhesive tablet, terbutaline sulphate, swelling, bioadhesion, *in vitro* release

Buccal drug delivery 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].

Terbutaline sulphate is a selective β_2 adrenergic agonist. Because of its selectivity for β_2-adrenoceptors, it produces less cardiac stimulations[3]. Terbutaline sulphate is variably absorbed from the gastrointestinal tract and about 60% of the absorbed dose undergoes first-pass metabolism by sulphate conjugation in the liver and the gut wall[4]. The oral bioavailability of terbutaline is 14.8% and half-life is 3 to 4 h[5]. Hence, it was considered as suitable candidate for administration via buccal route. There are two situations in which oral β adrenergic agonists are used frequently. First, in young children (< 5 years old) who cannot manipulate metered does inhalers yet have occasional wheezing with viral upper respiratory infections, brief courses of oral therapy are well tolerated and effective. Second, in some patients with severe asthma exacerbations, any aerosol, whether delivered via a metered does inhaler or a nebulizer can be irritating and cause a worsening of cough and bronchospasm. In this circumstance, oral therapy with β_2 adrenergic agonists can be effective[6].

The aim of the present study was to design buccoadhesive bilayered tablets to release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first-pass metabolism for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.

MATERIALS AND METHODS

Terbutaline sulphate (TS) was procured from Wardex Pharmaceuticals Ltd. (Mumbai, India). Carbopol 934 P (CP) was obtained as gift sample from Ruger Chemical Co. Inc (Irvington, NJ). Methocel K4M and K15 M (HPMC K4M and HPMC K15M) were obtained as gift samples from Colorcon Asia Pacific Pvt. Ltd. (Singapore). Sodium carboxymethylcellulose (NaCMC) was procured from Loba Chemie Pvt. Ltd. (Mumbai, India). All other materials were of analytical or pharmacopoeial grade and used as received.

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Preparation of buccoadhesive bilayered tablets:
The buccoadhesive bilayered tablets were prepared using different polymers either alone or in combinations with varying ratios as summarized in Table 1. Bilayered tablets were prepared by direct compression procedure involving two consecutive steps. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium stearate (MS) was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 8 mm flat faced punch using single punch tablet compression machine (Cadmach, Ahmedabad), the upper punch was then removed and backing layer material ethyl cellulose was added over it and finally compressed at a constant compression force.

Evaluation of buccoadhesive bilayered tablets:
All the tablet formulations were evaluated for uniformity of weight, drug content and content uniformity as per IP method. Friability was determined using Roche friabilator while hardness was measured by Pfizer hardness tester.

***In vitro* swelling studies of buccoadhesive tablets[7,8]:**
The swelling rate of buccoadhesive tablets of terbutaline sulphate was evaluated using a 1% w/v agar gel plate. The swelling index was determined using the formula, % Swelling index = $[(W_2-W_1)/W_1]\times100$

Surface pH of the buccoadhesive tablets[9]:
Buccoadhesive tablets were left to swell for 2 h on the surface of an agar plate. The surface pH was measured by means of a pH paper placed on the core surface of the swollen tablet. A mean of three readings was recorded.

***In vitro* bioadhesion studies[10,11]:**
Bioadhesive strength of the tablets was measured using modified physical balance. Bioadhesion studies were performed in triplicate and average bioadhesive strength was determined. From the bioadhesive strength, force of adhesion was calculated, force of adhesion (N)= (bioadhesive strength/100)×9.81

Stability of terbutaline sulphate buccoadhesive tablets in human saliva[12]:
The human saliva was collected and filtered. The tablets from each batch were immersed in 5 ml of human saliva for 4 h and taken out of saliva at predetermined time intervals. The stability of the terbutaline sulphate buccoadhesive tablet was then evaluated by its appearance, such as color and shape, and terbutaline sulphate concentration.

***In vitro* drug release studies:**
The influence of technologically defined condition and difficulty in simulating *in vivo* conditions has led to development of a number of *in vitro* release methods for buccal formulations; however no standard *in vitro* method has yet been developed. Standard USP or BP dissolution apparatus have been used to study *in vitro*

TABLE 1: COMPOSITION OF TERBUTALINE SULPHATE BUCCOADHESIVE TABLETS

Formulation code	Ingredients (mg)						
	Terbutaline sulphate	Cabopol 934P	HPMC K4M	HPMC K15M	NaCMC	Magnesium stearate	Ethyl cellulose
F1	5	95	---	---	---	1	50
F2	5	47.5	47.5	---	---	1	50
F3	5	23.75	71.25	---	---	1	50
F4	5	71.25	23.75	---	---	1	50
F5	5	47.5	---	47.5	---	1	50
F6	5	23.75	---	71.25	---	1	50
F7	5	71.25	---	23.75	---	1	50
F8	5	47.5	---	---	47.5	1	50
F9	5	23.75	---	---	71.25	1	50
F10	5	71.25	---	---	23.75	1	50
F11	5	---	95	---	---	1	50
F12	5	---	47.5	---	47.5	1	50
F13	5	---	23.75	---	71.25	1	50
F14	5	---	71.25	---	23.75	1	50
F15	5	---	---	95	-	1	50
F16	5	---	---	47.5	47.5	1	50
F17	5	---	---	23.75	71.25	1	50
F18	5	---	---	71.25	23.75	1	50
F19	5	---	---	---	95	1	50

Formulae for the preparation of buccoadhesive tablets of terbutaline sulphate.

release profile using both rotating paddle and basket[13]. *In vitro* release rate study of buccoadhesive tablets of terbutaline sulphate was carried out using the USP XXIV rotating basket method at 37±0.5° and 100 rpm. Study was conducted in triplicate.

Each tablet was inserted in a metal die having a central hole of 8 mm in diameter so that the drug could be released only from the upper face of the tablet. Medium used for the release rate study was 500 ml of phosphate buffer pH 6.8. Samples were withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered (Whatman filter paper no. 42) and assayed spectrophotometrically at 276 nm (Shimadzu UV 2401 PC, Japan).

Stability studies:

The optimized formulation (F2) was subjected to stability testing at 40±2°, 75±5% RH for three months. Tablets were evaluated periodically for bioadhesion strength and *in vitro* drug release. Results were analyzed by One-way ANOVA followed by Dunnett test. Differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The main aim of this work was to develop buccoadhesive bilayered tablets to release the drug at mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. CP, HPMC K4M, HPMC K15M and NaCMC were selected as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness while ethyl cellulose, being hydrophobic, as backing material. Ethyl cellulose has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility[14].

All the formulations passes test for weight variation content uniformity and showed acceptable results with respect to drug content (98.91-101.10%) and % friability (0.15-0.75%). Buccoadhesive tablets containing CP showed hardness in the range of 8.98 to 10.98 kg/cm^2 and it decreased with increasing amounts of HPMC. The hardness of the tablets containing NaCMC was much lower, ranging from 2.20 to 8.98 kg/cm^2 and increased with increasing amounts of HPMC or CP. The difference in the tablet strengths are reported not to affect the release of the drug from hydrophilic matrices. Drug is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet[15].

The bioadhesion and drug release profile are dependant upon swelling behavior of the tablets. Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration as shown in Table 2. Swelling index measurements could be done

TABLE 2: SWELLING INDEX OF TERBUTALINE SULPHATE BUCCOADHESIVE TABLETS

Formulation code	% Swelling index*				
	Time (h)				
	0.5	1	2	4	6
F1	50.01±0.098	90.71±1.10	210±0.098	260.06±0.78	275.00±1.89
F2	42.12±0.084	77.04±1.51	170.96±1.99	200.10±2.12	220.05±2.22
F3	36.98±1.01	65.14±1.33	135.96±1.33	175.59±1.12	180.07±1.11
F4	46.14±0.088	82.96±0.52	185.58±1.01	225.54±1.23	250.20±1.99
F5	38.36±0.99	72.16±1.05	162.04±1.21	193.66±1.34	213.16±2.01
F6	34.31±0.65	59.53±0.78	130.42±1.57	171.33±0.95	177.00±0.00
F7	42.61±0.95	77.96±1.01	179±0.58	217.18±1.04	240.01±1.11
F8	55.66±1.16	100.56±1.47	219.84±1.99	267.53±2.01	280.00±1.66
F9	60.12±0.69	110.03±0.77	225.17±0.49	283.19±1.41	295.00±1.59
F10	57.34±0.28	105.16±0.95	221.08±0.27	277.50±2.26	289.02±0.00
F11	30.98±0.57	59.42±0.87	125.41±0.087	160.57±1.04	167.57±1.21
F12	49.33±0.59	85.60±2.56	184.17±1.66	215.18±2.95	230.18±2.45
F13	54.28±1.03	90.59±2.11	190.37±0.58	231.71±3.26	269.77±3.57
F14	40.12±1.07	79.75±2.06	177.27±1.37	200.03±2.76	218.31±3.05
F15	21.12±0.044	45.31±0.24	118.55±2.20	149.27±1.05	155.16±0.37
F16	45.99±1.43	83.45±1.74	169.99±3.14	204.95±2.25	222.01±2.55
F17	49.85±0.88	87.11±2.11	180.88±3.36	227.11±3.45	265.40±3.16
F18	33.07±0.49	69.99±1.46	160.17±3.14	185.01±3.04	211.19±1.49
F19	68.35±1.26	121.11±2.56	250.50±3.36	---	---

*Each value represents mean ± S.D. (n=6).

upto 2 h with the tablets containing 95 mg NaCMC alone, since it looses its shape at the end of 2 h. The swelling indices of the tablets with CP and HPMC increased with increasing amounts of CP. Maximum swelling was seen with the formulations (F9, F10, F8, and F1) containing NaCMC and/or CP, the values increased with increasing amounts of NaCMC and/or CP[15].

Tablets of all the formulations except F1 had shown a surface pH values in the range of 5 to 7 that indicates no risk of mucosal damage or irritation. Tablets of formulation F1 had shown lower surface pH which is due to presence of higher amount of polyacrylic acid. These observations reflect that CP alone can not be incorporated in the designing of buccoadhesive tablets.

The bioadhesive property of buccoadhesive tablets of terbutaline sulphate containing varying proportions of polymers was determined with an insight to develop the tablets with adequate bioadhesiveness without any irritation and other problems. The bioadhesion characteristics were found to be affected by the nature and proportions of the bioadhesive polymers used as seen from fig. 1. The highest adhesion force i.e. highest strength of the mucoadhesive bond was observed with the formulation F1 containing only CP, this followed by F4 and F7 formulations containing CP:HPMC K4M and CP:HPMC K15M, respectively. The reason for such findings might be ionization of CP at salivary pH which leads to improved attachment of the device to mucosal surface. Adhesion force decreased as another polymer is mixed with CP. Tablets of formulation F19 containing NaCMC alone showed least adhesion force than tablet of all other formulations, which might be due to low viscosity of the NaCMC. These observations indicate that the bioadhesive strength of CP is much more than NaCMC.

The stability of terbutaline sulphate buccoadhesive tablets in human saliva was evaluated by their appearance, such as color and shape, and TS concentration. The tablets of all the formulations except F19, prepared with NaCMC alone, did not disintegrate for at least 4 h. The tablets of F19 were disintegrated during study period owing to low hardness of the tablets. All of the tablets were acceptable with respect to color and TS concentration.

In vitro drug release studies revealed that the release of TS from different formulations varies with characteristics and composition of matrix forming polymers as shown in figs. 2-6. The release rate of terbutaline sulphate decreased with increasing concentration of HPMC K4M and HPMC K15 M in F2 to F7 and F11 to F18, respectively. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to delay in release of drug from the device. CP is more hydrophilic than HPMC; it can swell rapidly, therefore decrease of CP content delays the drug release in F2 to F7[15]. Drug release rate was increased with increasing amount of hydrophilic polymer. The

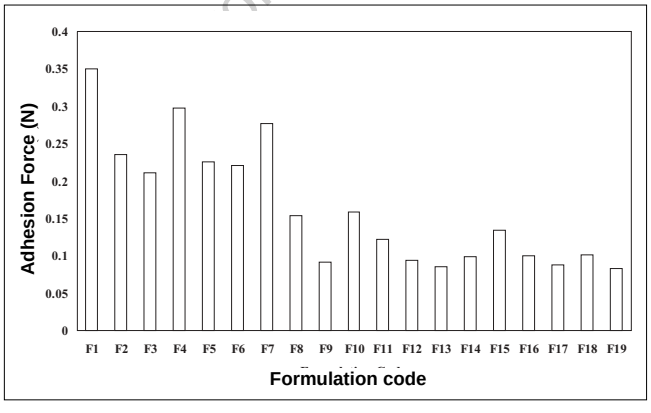

Fig. 1: *In vitro* bioadhesion profile of terbutaline sulphate buccoadhesive tablets
Bioadhesive strength of various formulations of terbutaline sulphate

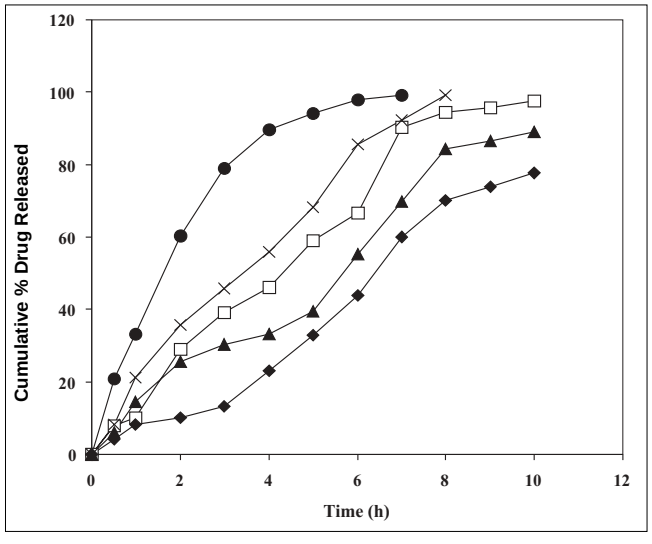

Fig. 2: *In vitro* release profile of terbutaline sulphate buccoadhesive tablets
Release profiles of terbutaline sulphate from buccoadhesive tablets, F1 (—●—), F2 (—□—), F3 (—▲—), F4 (—×—) and F11 (—♦—).

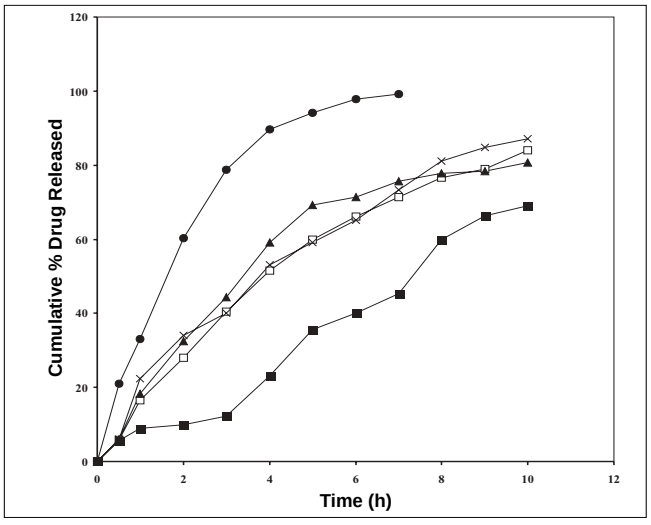

Fig. 3: *In vitro* release profile of terbutaline sulphate buccoadhesive tablets
Release profiles of terbutaline sulphate from buccoadhesive tablets, F1 (—●—), F5 (—□—), F6 (—▲—), F7(—×—) and F15 (—■—).

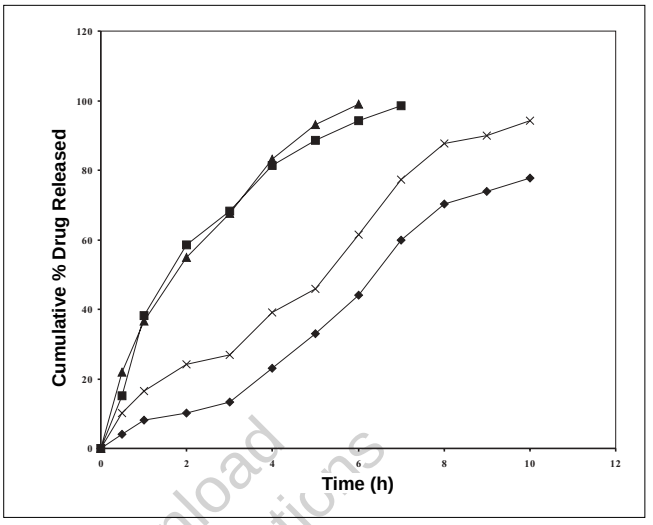

Fig. 5: *In vitro* release profile of terbutaline sulphate buccoadhesive tablets
Release profiles of terbutaline sulphate from buccoadhesive tablets, F11 (—♦—), F12 (—■—), F13 (—▲—) and F14 (—×—).

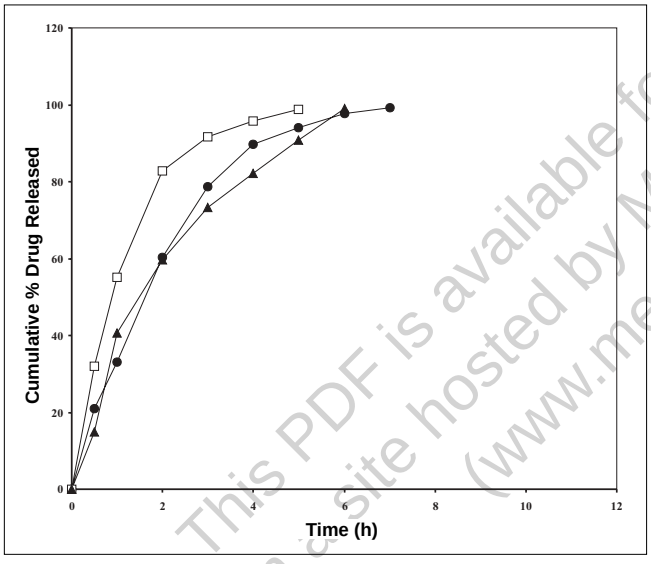

Fig. 4: *In vitro* release profile of terbutaline sulphate buccoadhesive tablets
Release profiles of terbutaline sulphate from buccoadhesive tablets, F1 (—●—), F8 (—□—) and F10 (—▲—).

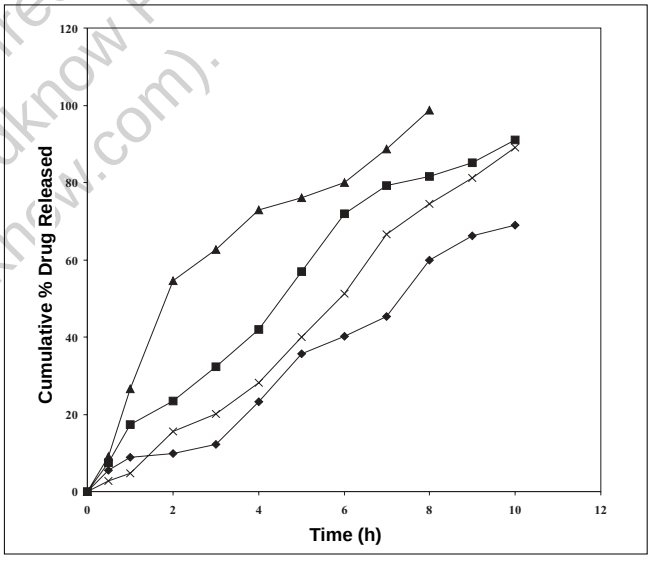

Fig. 6: *In vitro* release profile of terbutaline sulphate buccoadhesive tablets
Release profiles of terbutaline sulphate from buccoadhesive tablets, F15 (—♦—), F16 (—■—), F17 (—▲—) and F18 (—×—).

maximum cumulative percent release of terbutaline sulphate from formulation F1 could be attributed to ionization of CP at pH environment of the dissolution medium. Ionization of CP leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counterion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the high water uptake. This water uptake leads to the considerable swelling of the polymer. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate[8]. Formulations F8, F10, F12, F13 and F17 showed relatively high rate of release of terbutaline sulphate which is due to rapid swelling and erosion of NaCMC. Further, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water soluble drug. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse

out of the device[2]. Formulation F19 which contains NaCMC alone and F9 with CP and NaCMC gets eroded during dissolution study before stipulated study period. Thus higher concentration of NaCMC can not be incorporated into such formulations for sustaining the release.

To examine further the release mechanism of terbutaline sulphate from buccoadhesive tablets, the results were analyzed according to the equation[8,11], $Mt/M_{\infty} = Kt^{n}$

The obtained values of n lie between 0.5 and 1.0 in all formulations for the release of terbutaline sulphate, indicating non-Fickian release kinetics, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation. No statistically significant differences were observed in bioadhesion strength and release rate of optimized formulation (P>0.05).

In light of aforementioned discussion it can be concluded that formulation F2 could be used to release the terbutaline sulphate unidirectionally in buccal cavity for extended period of time without the risk of mucosal irritation.

ACKNOWLEDGEMENTS

The authors wish to thanks Management, Vidarbha Youth Welfare Society, Amravati for providing all possible facilities at IPER, Wardha. Also thanks to AICTE, New Delhi for providing junior research fellowship to one of the author.

REFERENCES

1. Jacobsen J. Buccal iontophoretic delivery of atenolol hydrochdrochloride employing a new *in vitro* three chamber permeation cell. J Control 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. Lee TJF, Stitzel RE. Adrenomimetic drugs. *In*: Craig CR, Stitzel RE, editors. Modern Pharmacology with clinical applications. 5th Ed. Little Brown and Company: Boston;1997. p. 119.
4. Sweetman SC. Martindale - The complete drug reference. 33rd Ed. Pharmaceutical Press: London; 2002.
5. Reynolds JE. Martindale - The extra pharmacopoeia. 31st Ed. The Royal Pharmaceutical Society: London; 1996.
6. Undem BJ, Lichtenstein LM. Drugs used in the treatment of asthma. *In*: Hardman JG, Limbird LE, Gilman AG, editors. Goodman and Gilman's-The pharmacological basis of therapeutics. 10th ed. McGraw–Hill Medical Publishing Division: New York; 2001.p. 736.
7. Ahuja A, Dogra M, Agarwal SP. Development of buccal tablets of diltiazem hydrochloride. Indian J Pharm Sci 1995;57:26-30.
8. Agarwal V, Mishra B. Design, development and biopharmaceutical properties of Buccoadhesive compacts of pentozocine. Drug Develop Ind Pharm 1999;25:701-9.
9. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Muccoadhesive buccal patches of miconazole nitrate – *in vitro/in vivo* performance and effect of ageing. Int J Pharm 2003;264:1-14.
10. Gupta A, Garg S, Khar RK. Measurement of bioadhesive strength of muccoadhesive buccal tablets: Design of an *in vitro* assembly. Indian Drugs 1992;30:152-5.
11. Singh B, Ahuja N. Development of controlled release Buccoadhesive hydrophilic matrices of diltiazem hydrochloride: Optimization of bioadhesion, dissolution, and diffusion parameters. Drug Develop Ind Pharm 2002;28:431-42.
12. Yong C, Jun JH, Rhee JD, Kim CK, Choi HG. Physicochemical characterization and evaluation of buccal adhesive tablets containing omeprazole. Drug Develop Ind Pharm 2001;27:447-55.
13. Devarajan PV, Gandh AS. *In vitro* and *in vivo* models for oral transmucosal drug delivery. *In*: Jain NK editor. Advances in controlled and novel drug delivery. CBS Publishers and Distributors: New Delhi; 2001. p. 71.
14. Lopez CR, Porteo A, Vila-Jato JL, Alonso MJ. Design and evaluation of chitosan/ethyl cellulose muccoadhesive bilayered devices for buccal drug delivery. J Control Release 1998;55:143-52.
15. Dortunc B, Ozer L, Uyanik N. Development and *in vitro* evaluation of a Buccoadhesive pindolol tablet formulation. Drug Develop Ind Pharm 1998;24:281-8.

Accepted 6 July 2007
Revised 18 April 2007
Received 6 March 2006
Indian J. Pharm. Sci., 2007, 69 (4): 505-510