THE PHARMA RESEARCH
E-mail: thepharmaresearch@sudarshanonline.co.in
Website: www.thepharmaresearch.info
E-ISSN 0975–8216 (Online)
Dr. Sayeed Ahmad
Editor-In-Chief,
The Pharma Research
1455, Krishan Ganj, Pilkhuwa Ghaziabad,
U.P. 245304 India

INFLUENCE OF THE POLYMERS AND CO-EXCIPIENTS ON THE PERFORMANCE OF BUCCAL BIOADHESIVE TABLETS CONTAINING MICONAZOLE NITRATE

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Abstract

Background and purpose of the study: The purpose of this research was to study the influence of Carbopol® 71 G and Noveon® AA-1 as mucoadhesive polymers for the buccal delivery of Miconazole Nitrate (MN). The formulations were developed with varying concentrations of Carbopol® 71G or Noveon® AA-1 as well as composed by the combination of both polymers in 1:1 ratio, using microcrystalline cellulose (MCC) or lactose as fillers.

Methods: Twelve different types of tablets were prepared using blends of either Carbopol® 71G or Noveon® AA-1 and a mixture of both polymers at 1:1 ratio with either MCC or lactose as fillers. Accurate quantity of MN and co-excipients were weighed. They were passed through 30 mesh sieve and thoroughly mixed using mortar and pestle. The blend was lubricated and compressed into tablet on a hydraulic press with 8 mm diameter flat-faced tooling.

Results: All the formulations exhibited satisfactory pharmaceutical properties. Cumulative percentage of the drug released in 10 hrs from the ten formulations were about 90% for F1,F3 and F5 formulation .The microcrystalline cellulose and lactose included in the formulations slightly modifies the swelling capacity. The mucoadhesive strength increase as the concentration of polymer increases. However there is no correlation between swelling and mucoadhesion strength of compacts.

Conclusion: The optimal balance between a combination of Carbopol® 71G and Noveon® AA-1 polymers showed satisfactory mucoadhesive characteristics and drug controlled release over 10 h, which in turn reduces dosing frequency and improved patient compliance in oral candidiasis patients.

Keywords: Noveon® AA-1, Carbopol® 71G, Miconazole nitrate, buccal mucoadhesion, fillers.

Introduction

Conventional solid oral dosage forms, such as tablets and capsules, have been limited in use because of short resident time and insufficient therapeutic effect like rapid salivary concentration after application and rapid clearance. As a consequence, bioadhesive polymers have been used in the development of controlled drug delivery systems to improve buccal, nasal and oral administration of drugs. In general, bioadhesion (or mucoadhesion) is the ability of a polymeric material to bind to a biological membrane for a certain period of time [1]. Particularly, anionic polymers are the most widely employed mucoadhesive excipients due to their high adhesive properties and low toxicity, such as, Carbopol® and Noveon® derivatives [2, 3]. Particularly, Carbopol® 71 G, a water-swellable high molecular weight polyacrylic acid crosslinked with allyl ethers of pentaerythriol, has been incorporated into controlled-release tablets and mucoadhesive microspheres [4, 5]. On the other hand, buccal tablets prepared using Noveon® AA1 has shown high bioadhesive force and prolonged residence in human buccal mucosa [6]. In addition, this polymer has been used for delivering bioactive substances for local application to gingival and periodontal area [7]. Although a considerable attention has been focused on the evaluation of mucoadhesive polymers, the influence of common tablet excipients on the performance of mucoadhesive formulations was not deeply investigated, suggesting that much work remains to be done in this area. Miconazole nitrate (MN) is a broad-spectrum antifungal compound extensively used in the treatment of buccal, dermal and vaginal candidiasis, a fungal infection caused primarily by *Candida albicans*. Attempts have been made to prepare MN mucoadhesive devices including chewing gum, mucoadhesive lozenges, and bioadhesive tablets [8, 9 and 10]. Recently, 50 mg MN tablets have been shown to be effective for cancer patients with oral candidiasis [11].

In this context, it was decided to develop novel mucoadhesive extended-release formulations containing 50 mg MN by using Carbopol® 71G and Noveon® AA-1 at different ratios and compacted with different amounts of microcrystalline cellulose (MCC) or lactose. It was evaluated if and how polymer concentrations affect the mucoadhesive properties and drug release of the prepared compacts. The influence of the fillers, as well as, the swelling capacity and bioadhesion strength of the polymeric systems were also analyzed. To the best of our knowledge it is the first attempt made to prepare 50 mg MN mucoadhesive compacts using a combination of Carbopol® 71G and Noveon® AA-1.

Experimental

Carbopol® 71G and Noveon® AA-1 (Arihant Trading Co, Mumbai, India), MN (Bhavani-Pharmaceuticals, Hyderabad, India), MCC, lactose, and talc (Zydus Cadila, India) were used.

Preparation of buccal tablets

Twelve different types of compacts were prepared using blends of either Carbopol® 71G or Noveon® AA-1 and a mixture of both polymers at 1:1, 0.5:1 and 1:0.5 ratios with either MCC or lactose as fillers. Accurate quantity of MN and co-excipients were weighed. They were passed through 30 mesh sieve and thoroughly mixed using mortar and pestle. The blend was lubricated and compressed into tablet on a hydraulic press with 8 mm diameter flat-faced tooling. The tablets were compressed at compression forces of 2 ton and dwell time of 20 s. The detailed composition of all the formulations is shown in Table 1.

Table 1. Composition of 50 mg Miconazole Nitrate compacts.

Formulation code	Carbopol® 71 G (mg)	Noveon® AA-1 (mg)	MCC (mg)	Lactose (mg)	Talc (mg)	MN (mg)
F1	40	---	55	---	5	50
F2	60	---	35	---	5	50
F3	---	40	55	---	5	50
F4	---	60	35	---	5	50
F5	20	20	55	---	5	50
F6	10	20	65	---	5	50
F7	40	---	---	55	5	50
F8	60	---	---	35	5	50
F9	---	40	---	55	5	50
F10	---	60	---	35	5	50
F11	20	20	---	55	5	50
F12	20	10	---	65	5	50

Evaluation of buccal Tablets

All the formulations were evaluated for uniformity of weight, and drug content as per Pharmacopoeial method. The average weight was obtained for at least 20 units. The MN quantification was analyzed at 272 nm by UV spectrophotometer (UV-1700 Shimadzu, Japan). The thickness was measured using Mitotoyo screw gauge (Mitotoyo, Japan). Hardness was determined for at least 10 tablets using Erweka hardness tester (Erweka, India) and friability was evaluated for a sample of 20 tablets using Electrolab EF-2 friabilator (Electrolab, India). Technological parameters of the formulations are shown in Table 2

Swelling studies

Swelling index for buccal compacts was determined according to Desai and Kumar 2004[12]. At predetermined time intervals (from 2 to 8 hours), hydrated samples were removed and weighted after blotting the surface water with a parchment paper (Himedia, India). The swelling ratio was calculated by (W2 – W1)/W1 equation where W1 and W2 are dry and wet weights of the tablets, respectively. The experiment was done in triplicates.

Microenvironment pH

The microenvironment pH of the prepared buccoadhesive compacts was determined to evaluate the possible irritation effects on the mucosa. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, an attempt was made to keep the surface pH close to neutral pH. The compacts were left to swell in 5 mL of distilled water (pH 6.8) in 25 mL beakers and the pH was measured by placing the electrode in contact with the microenvironment of the swollen compacts [13]. The average pH of 3 determinations was reported.

In vitro drug release

The drug release from buccal compacts was studied using the orbital shaking incubator (Remi CIS 24, Mumbai, India) using 30 mL of phosphate buffer pH 6.8 as dissolution medium, for 10 h. The temperature was maintained at 37°C ± 0.5°C. At predetermined interval, 3 mL of dissolution medium was withdrawn and replenished by 3 mL of fresh medium to maintain the sink condition. The amount of MN released was analyzed at 272 nm by UV spectrophotometer (UV-1700 Shimadzu, Japan) [14].

In vitro bioadhesion

Bioadhesive strength of the compacts was measured using modified physical balance as recently discussed [15]. *In vitro* bioadhesion studies were carried out using sheep buccal mucosa and modified two-armed balance. The phosphate buffer pH 6.8 was used as the moistening fluid. A glass stopper was suspended by a fixed length of thread on one side of the balance and was counter balanced with the weights on the other side. Fresh sheep buccal mucosa was collected

from the slaughter house. It was scrapped off from the connective tissues and a thin layer of buccal mucosa was separated which was stored in Tris buffer until used for the bioadhesion study. A circular piece of sheep buccal mucosa was cut and fixed to the tissue holder and was immersed in phosphate buffer pH 6.8 and the temperature was maintained at 37 °C ± 1°C. Then the tablet was fixed to a glass stopper with the help of cyanoacrylate adhesive and it was placed on the buccal mucosa by using a preload of 50 gm and kept it aside for 3 min to facilitate adhesion bonding. After preloading time, the preload was removed and the weights were added on the other side of the balance until tablet detaches from the sheep buccal mucosa. The weight required to detach tablet from buccal mucosa was noted.

Infrared Absorption spectroscopy (IR)

To investigate any possible interactions between the drug and the utilized buccoadhesive material, the IR spectra of pure MN and its physical mixture (1:1) with Noveon® AA-1 and Carbopol® 71G were carried out using FTIR-8400S (Shimadzu, Japan). The samples were prepared as KBr disks compressed under a pressure of 6 tons.

Kinetic analysis

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Equation to find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model. The n value is used to characterize different release mechanisms as given in table 1 for matrix tablets [16].

Table 1: Diffusion exponent and solute release mechanism

Diffusion Exponent(n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n>0.89	Anomalous(non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Stability studies

The optimized formulation (F5 and F11) was subjected to stability testing as per ICH guidelines at 30°C ± 2°C, 65 % ± 5 % RH and 40°C ± 2°C, 75 % ± 5% RH for three months. Compacts were evaluated periodically for drug content and *in vitro* drug release studies by means of UV spectroscopy (UV-1700 Shimadzu, Japan).

Results and discussion

Pharmaceutical properties of the tablets

Tablets containing various ratios of Carbopol® and Noveon® loaded with 50 mg of MN, were prepared and their pharmaceutical properties (weight variation, drug content, friability and hardness) were examined. All the formulations showed satisfactory values (Table 2) within the limits of conventional oral tablets stated in the *Indian Pharmacopoeia* [17].

The IR spectra of pure MN and its physical mixture with Noveon® AA-1 and Carbopol® 71G did not show any significant differences (data non shown). Evaluation of the surface pH of the compacts prepared with Carbopol® 71G showed a pH value in the range of 6.55-6.65, probably due to high concentration of carboxylic acid in the Carbopol® 71 G. Similarly, Noveon® AA-1 containing formulations showed microenvironment pH of about 6.6, due to the polyacrylic acid. These results reveal that all the compacts provide a pH value in the range of salivary pH (5.5 to 7.0) [18].

Table 2. Technological characterization of the compacts.

Formulation code	Weight variation (%)	Drug content (%)	Hardness (kg/cm2)	Microenvironment pH
F1	0.72±0.12	99.91±0.05	5.11±0.01	6.55±0.12
F2	0.82±0.11	99.91±0.01	5.13±0.06	6.65±0.12
F3	0.74±0.17	99.84±0.05	5.23±0.01	6.66±0.13
F4	0.76±0.09	99.8±0.152	5.16±0.06	6.66±0.14
F5	0.81±0.16	99.80±0.10	5.23±0.05	6.84±0.14
F6	0.82±0.15	99.90±0.13	5.21±0.04	6.72±0.12
F7	0.81±0.14	99.82±0.18	5.12±0.01	6.53±0.11
F8	0.79±0.12	99.90±0.08	5.14±0.04	6.62±0.13
F9	0.77±0.11	99.91±0.09	5.18±0.03	6.64±0.12
F10	0.80±0.14	99.92±0.13	5.15±0.03	6.65±0.13
F11	0.83±0.13	99.87±0.11	5.20±0.04	6.82±0.15
F12	0.82±0.11	99.89±0.12	5.21±0.06	6.52±0.21

Swelling Studies

Formulations F1 and F7 (27% of either Carbopol or Noveon) presented higher swelling index than F2 and F8 (40% of polymers), in the opposite way to the literature data [19]. Interestingly, formulations F5 and F11 (containing 13.5% of each polymer) exhibited higher swelling index than those prepared with a single polymer. Water influx weakens the network integrity of the polymer, the structural resistance of the swollen matrices is thus greatly influenced and release of MN through gel layer is more pronounced, as discussed later on.

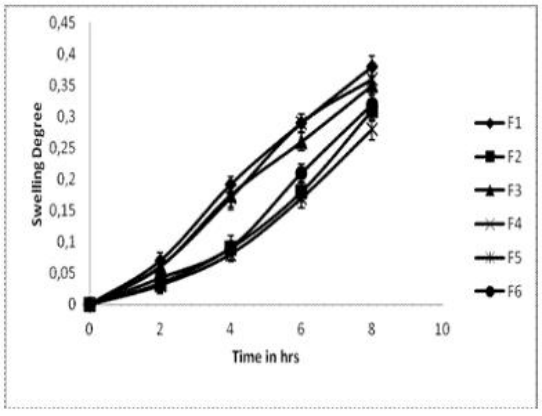

Fig 1. Swelling studies for formulation F1-F6.

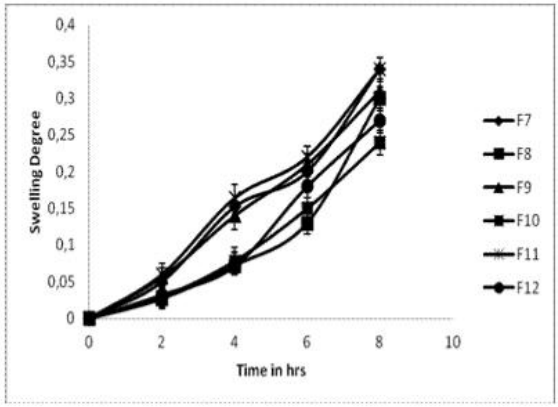

Fig 2. Swelling studies for formulation F7-F12.

In vitro release of MN

The mechanism of drug release from swellable matrices is ruled by several physicochemical characteristics. Among them, polymer water uptake, gel layer formation and polymeric chain relaxation are currently regarded as primarily involved in the modulation of drug release.

Drug release patterns can be greatly either increased or decreased by increasing the amount of the polymers [20, 21]. Herein, drug release profiles of the polymeric compacts containing Carbopol® and/or

Noveon® and formulated with MCC (Fig. 3) and lactose (Fig. 4) are described. In all formulations (Table 1), the MN release was gradually increased up to 10 h, without any detected burst release. When Carbopol® was used at 27%, (F1) MN was released within 10 h. On the other hand, when the content of this polymer was increased to 40%, a lower amount of MN (60%) was released at 10 h. it should be considered that at higher concentration of the polymer the gel layer is thicker and stronger and, as a consequence, the time for the drug to diffuse to the surface is also greater. On the other hand and contrary to other work [20], when Noveon® was used at low amount (F3) the drug release rate was more than 80%. By increasing its amount to 40% (F4), the release rate of MN decreased to 60%. The 0.5:1 ratio of Carbopol 71G and Noveon AA-1(F6) released around 88% of drug; this may be due to the fewer amounts of polymers. Gel layer from this ratio of polymer perhaps forms less thick and weaker layer around the compact. Whereas the 1:0.5 of Carbopol 71 G and Noveon AA-1 ratio(F12) released around 89% of drug. Both the ratio forms less thick gel layer as a consequence, more drug is diffuse to the surface.

However, the most interesting result was observed by mixing both polymers at 1:1 ratio, using 13.5% of each one. About 85% of the drug was released within 10 h from mucoadhesive F5 and F11 compacts. Clearly, drug release rate from the polymeric compacts could be controllable by the ratio and combination of polymers. Despite of the low amount of the polymeric mixture, its ability to absorb water promotes the dissolution, and hence the drug release. It should be mention that up to 13.5% of Carbopol® may be used without causing any sign of mucosal irritation, consequently, F5 and F10 formulations could be the more suitable formulations for the buccal cavity in comparison with F1 and F6 [22].

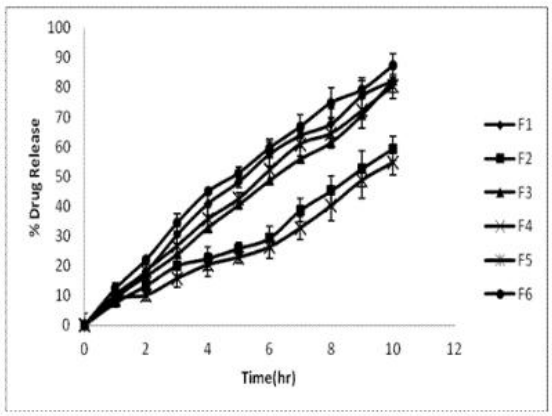

Fig 3. Percentage drug release for formulation F1-F6

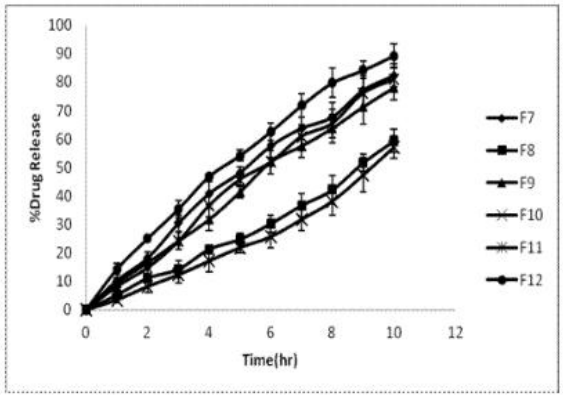

Fig 4. Percentage drug release for formulation F7-F12.

Influence of MCC and lactose

Usually, the addition of fillers is necessary to replace the portion of polymer as well as to obtain solid dosage forms with desirable technological properties. However, these additives can have significant effect on the water uptake of the formulations and dissolution properties of drugs. In this context, it was reported that water absorption behavior of polymers might be influenced by the presence of different co-excipients [21]. It is well known that MCC is one of the most commonly used direct compression excipient as a binder/filler. In addition to its use as a

binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. On the other hand, lactose is the most useful filler used for tablet and capsule formulation. Since it is water soluble, upon contact with the release medium, lactose diffuses out of the device, thereby increasing the porosity of the resulting polymer network. As a consequence, the pores allow the solvent front penetration to increase drug dissolution rate, although the initial burst effect may be also increased [23]. It is observed that drug release rate of the compacts were slightly modified by replacing swellable MCC by the non-swellable lactose (Fig. 3). Thus, the dissolution process would be mainly affected by the water absorption, positively correlated with the gel forming of the mucoadhesive polymers, working as a diffusion barrier. Moreover, it should be mention that the incorporation of the highly water-soluble lactose is not always an effective tool to increase drug dissolution rates [24].

Mucoadhesion study

Fig. 5 shows bioadhesive strength for all formulations (F1- F12). It is known that polymer concentration has a significantly influence the strength of mucoadhesion [25]. In this work, as expected, increasing the concentration of either Carbopol® 71G or Noveon® AA-1 from 27% to 40% (w/w) resulted in increasing mucoadhesion values [26]. In agreement with previous data, it was found that formulations containing Carbopol exhibited weak adhesion strength in comparison with the Noveon® AA-1 formulations [27]. It could be due to the non-ionized carboxylic acid groups of Noveon® AA-1 would improve the binding to the mucosal surfaces via hydrogen bonding interactions [28]. In addition, it has been discussed that adhesiveness increases with the degree of hydration up to certain limit. Then, adhesive properties decrease due to disentanglement at the polymer/tissue interface produced by higher water uptake [29]. In contrast to a previous report [30], no correlation between swelling and mucoadhesion strength of the Carbopol®-Noveon® compacts was observed, as shown in Table 3. Despite of the water uptake behavior of these formulations, an increased of either Carbopol ratio or Noveon ratio resulted in an increased adhesion of the compacts. However, Carbopol® 71G-Noveon® AA-1 mixtures containing 13.5% of each polymer (1:1 ratio) showed a higher work of adhesion values, probably due to the synergistic combination of its particular physicochemical properties. At the same time, another important factor affecting the mucoadhesive strength of dosage forms is the presence of different co-excipients. There are numerous reports in the literature reporting the influence of excipients on the strength of adhesion of such systems [31, 32]. In this it were reported that the addition of highly water soluble excipient, such as lactose, reduces the water content when the material dissolves, and subsequently decreases mucoadhesion. Then, mucoadhesion characteristics were found to be affected by the nature and proportions of the polymers used, as well as the type and amount of the fillers. The highest strength was observed in the compacts containing MCC (F1-F6) followed by those made with lactose (F7-F12).

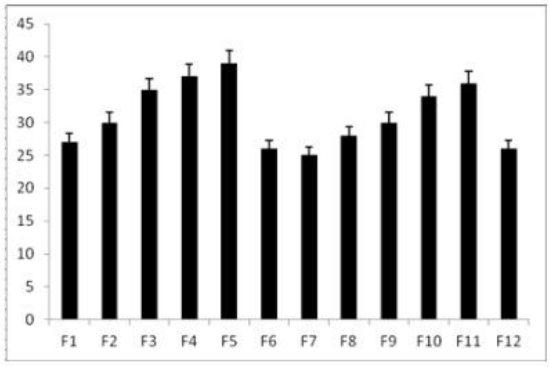

Fig 5. Mucoadhesive strength for formulations F1-F12.

Table 3. Comparison between mucoadhesive properties and swelling index of formulations.

Formulation code	Mucoadhesion strength (gms)	Swelling index (8h)
F1	28 ± 0.67	0.38 ± 0.01
F2	30 ± 0.45	0.31 ± 0.01
F3	35 ± 0.90	0.35 ± 0.03
F4	37 ± 0.89	0.28 ± 0.01
F5	39 ± 0.78	0.38 ± 0.03
F6	37±0.81	0.32±0.014
F7	25 ± 0.65	0.34 ± 0.07
F8	29 ± 0.87	0.30 ± 0.01
F9	30 ± 0.69	0.31 ± 0.01
F10	34 ± 0.54	0.24 ± 0.01
F11	37 ± 0.34	0.34 ± 0.02
F12	34±0.24	0.27±0.014

Kinetic analysis

To examine further the release mechanism of MN from buccal compacts, the results was analyzed according to the Peppas model fitting. Most of the prepared compacts exhibited *n* values greater than 0.9 indicating non-Fickian transports. Therefore, the values of diffusion release exponent *n* (slope) and coefficients of correlation *r* following linear regression of dissolution data indicated near zero order release. It may be indicative of drug release by both diffusion and chain relaxation mechanism. Therefore the drug release from the prepared compacts is controlled by swelling of the polymer followed by drug diffusion through the swollen polymer.

Stability study

Selected mucoadhesive formulations (F5 and F11) were subjected to stability study maintained at 30°C ± 2°C, 65 % ± 5 % RH and 40°C ± 2°C, 75 % ± 5% RH for 90 days. The resulting drug content assay and drug release profiles from these formulations showed no significant differences over the period of the study.

Conclusion

All polymeric tablets showed a mucoadhesive capacity and a sustained MN release. The strength of the compacts was dependent on the concentration of either Carbopol® 71G or Noveon® AA-1 bioadhesive polymers. Particularly, an optimal balance between a combination of those polymers showed satisfactory mucoadhesive characteristics and drug controlled release over 10 h, which in turn reduces dosing frequency and improved patient compliance in oral candidiasis patients. The different characteristics of MCC and lactose did not modify the water uptake and drug dissolution rates from Carbopol-Noveon compacts. In contrast, these fillers affected the mucoadhesive properties of the compacts. The stability studies carried out during 90 days for selected preparations did not show any changes in the physical property, drug content and percent drug release.

Acknowledgement

The authors wish to thank the JSS University, Mysore, India for providing the necessary facilities to complete this work.

References

1. Lee JW, Park JH, Robinson JR. Bioadhesive based dosage forms: the next generation, J Pharm Sci, 2008; 89, 850-866.
2. Bernkop-Schnurch A, Humenberger C, Valenta C. Basic studies on bioadhesive delivery systems for peptide and protein drug,Int J Pharm, 1998, 165, 217-225.
3. Khutoryanskiy V. Hydrogen-bonded interpolymer complexes as materials for pharmaceutical applications, Int J Pharm, 2007,334, 15-26.
4. Barreiro-Iglesias R, Bromberg L, Temchenko M, Hatton TA, Alvarez-Lorenzo C, Concheiro A. Pluronic-g-poly(acrylic acid) copolymers as novel excipients for site specific, sustained release tablets, Eur J Pharm Sci, 2005, 26, 374-385.
5. Dhaliwal S, Jain S, Singh HP, Tiwary AK. Mucoadhesive Microspheres for Gastroretentive Delivery of Acyclovir: *In Vitro* and *In Vivo*

Evaluation, AAPS PharmSciTech, 2008, 10, 322-330.

6. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive delivery systems. I. Evaluation of mucoadhesive polymers for buccal tablet formulation, Drug Dev Ind Pharm, 2004,30, 985-993.
7. Jones DS, Woolfson DA, Djokic J, Coulter WA. Design, characterization and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease, J Control Rel, 2000,67, 357- 368.
8. Pedersen M, Rassing MR. Miconazole chewing gum as a drug delivery system: test of release promoting additives, Drug Dev Ind Pharm, 1991, 17, 411-420.
9. Codd JE, Deasy PB. Formulation development and in vivo evaluation of a novel bioadhesive lozenge containing a synergistic combination of antifungal agents, Int J Pharm, 1998, 173:13-24.
10. Bouckaert S, Schautteet H, Lefebvre RA, Remon JP, Van Clooster R. Comparison of salivary miconazole concentrations after administration of a bioadhesive slow-release buccal tablet and an oral gel, Eur J Clin Phamacol, 1992, 43, 137-140.
11. Bensadoun RJ, Daoud J, El Gueddari B, Bastit L, Gourmet R, Rosikon A, Allavena C, Ceruse P, Calais G, Attali P. Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500-mg gel in the treatment of oropharyngeal candidiasis: a prospective, randomized, single-blind, multicenter, comparative, phase III trial in patients treated with radiotherapy for head and neck cancer, Cancer, 2008, 112, 204-211.
12. Desai KGH, Pramod Kumar TM. Preparation and Evaluation of a Novel Buccal Adhesive System, AAPS Pharm Sci Tech, 2004, 5, 1-9.
13. Patel VM, Prajapati BG, Patel HV,Patel KM. Mucoadhesive bilayer tablets of propranolol hydrochloride, AAPS Pharm Sci Tech, 2007, 8, E203-E208.
14. Fergany MA, Hussin K. 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.
15. Deshmukh VN, Jadhav JK, Sakarkar DM. Formulation and *in vitro* evaluation of theophylline anhydrous bioadhesive tablets, Asian J Pharm, 2009, 3, 54-58.
16. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers, Int J Pharm, 1983,15, 25-35.
17. Indian pharmacopeia. The Indian pharmacopeia commission. Ghaziabad (India):2007.
18. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery -A promising option for orally less efficient drugs, J Control Rel, 2006, 114, 15-40.
19. Yoo JW, Dharmala K, Lee CH. The physicodynamic properties of mucoadhesive polymeric films developed as female controlled drug delivery system, Int J Pharm, 2006, 309, 139-145.
20. Hosny EA, Al-Gohary OMN. Release kinetics and availability of mebeverine hydrochloride from polycarbophil loaded by swelling, Drug Dev Ind Pharm, 1994, 20, 2593-2605.
21. Majid Khan G, Zhu J. Studies on drug release kinetics from ibuprofen-carbomer hydrophilic matrix tablets: influence of co-excipients on release rate of the drug, J Control Rel, 1999, 57,197-203.
22. Adriaens E, Ameye D, Dhondt MMM, Foreman P, Remon JP. Evaluation of the mucosal irritation potency of co-spray dried Amioca®/poly (acrylic acid) and Amioca®/Carbopol® 974P mixtures, J Control Rel, 2003,88,393-399.
23. Surapaneni MS, Das SK, Das NG. Effect of Excipient and Processing Variables on Adhesive

Properties and Release Profile of Pentoxifylline from Mucoadhesive Tablets, Drug Dev Ind Pharm, 2006,32, 377-387.

24. Majid Khan G, Zhu J. Formulation and in vitro evaluation of ibuprofen-carbopol® 974P-NF controlled release matrix tablets III: influence of co-excipients on release rate of the drug, J Control Rel, 1998, 54, 185-190.
25. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives, Adv Drug Deliv Rev, 2005, 57, 1640-1665.
26. Rafiee-Tehrani M, Jazayeri G, Toliyat T, Bayati K, Khalkhali K, Shamimi K, Miremadi A ,Dorkoosh FA. Development and *in-vitro* evaluation of novel buccoadhesive tablet formulation of prednisolone, Acta Pharm, 2002, 52, 123-130.
27. Das NG, Das SK. Development of mucoadhesive dosage forms of buprenorphine for sublingual drug delivery, Drug Deliv, 2004, 11, 89-95.
28. Sudhakar Y, Kuotsu k, Bandyopadhyay AK. Buccal bioadhesive drug delivery –A promising option for orally less efficient drugs, J Control Rel, 2006, 114, 15-40.
29. Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: Swelling, mechanical, and bioadhesive properties, J Pharm Pharmaceutical Sci, 1999, 2, 53- 61.
30. Nakhat PD, Kondawar AA, Babla IB, Rathi LG, Yeole PG. Studies on buccoadhesive tablets of terbutaline sulphate,Indian J Pharm Sci,2007,69: 505- 510.
31. Tobyn MJ, Johnson JR, Dettmar PW. Factors affecting in vitro gastric mucoadhesion IV. Influence of tablet excipients, surfactants and salts on the observed mucoadhesion of polymers, Eur J Pharm Biopharm, 1997, 43, 65-71.
32. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR. Saeed M. Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulations: effect of fillers, II Farmaco, 2004, 59:155-161.