

Research Article



Development and Evaluation of Buccal Mucoadhesive Patches of Diclofenac Potassium

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ABSTRACT

For the preparation of buccal controlled release patches hydrophilic, swellable, porous polymeric material alone or in optimum combination and optimum mucoadhesive strength is essential. The use of naturally occurring biocompatible polymers has been the area of interest of recent research activity for designing controlled release dosage forms. Diclofenac causes gastro-intestinal irritation and ulceration upon oral administration. Hence an approach has been adopted to prepare buccal mucoadhesive patches of Diclofenac potassium to overcome the above mentioned problem and avoidance of hepatic "first-pass" effect. Buccal patches of Diclofenac potassium were prepared with Carbopol 974P, HPMCK4M, Ethyl cellulose and Gum karaya. HPMCK4M and Ethyl cellulose were used to prepare all the patches whereas Carbopol 934P and Gum karaya were incorporated in the patches as 1:0 (F1), 1:1 (FGK1) and 0:1 (FGK2). The patches were evaluated for their mucoadhesive strength, folding endurance, surface pH, in vitro release, in-vitro skin permeation and ex-vivo residence time. Mucoadhesive strength was found to be 25 ± 1.15 g, 35.5 ± 1.67 g and 41.28 ± 1.23 g for F1, FGK1, and FGK2 respectively. Release of drug in 8 h was found to be almost 64.45% and 62.13% from the formulations with gum karaya (5% and 10%) and 44.71 % from the formulations without gum karaya. The drug release data were fitted in different kinetic models, like zero order, first order and Higuchi. It has been found that drug release pattern from the formulations obeyed Higuchi kinetics.

Keywords: Diclofenac potassium, buccal mucoadhesive patch, Mucoadhesion, Release Kinetics.

INTRODUCTION

Drug delivery systems are now receiving considerable attention from pharmaceutical Companies. The main objective is to develop alternative drug delivery technologies to gain efficiency and safety of drug delivery for providing more convenience to the patient. Some drugs have an optimum concentration range within which maximum benefit can be expected. Concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to target in tissues. Drug delivery systems (DDS), are combination of polymer science, pharmaceutics, bioconjugate chemistry and molecular biology. To prevent harmful side-effects and to increase drug bioavailability and the fraction of drug accumulated in the required zone different approaches are tried.

Among the various routes of drug delivery, oral route is still the most preferred route to the patient. However, peroral administration of drugs has some disadvantages of hepatic first pass metabolism and enzymatic degradation within the GI tract that resists the oral administration of certain classes of drugs. Transmucosal route of drug delivery offers distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of the first pass effect, avoidance of presystemic elimination within the GI tract. Within the oral mucosal cavity the buccal region offers an attractive route of administration for systemic

drug delivery. Buccal mucosa has rich blood supply and it is relatively permeable¹. It is a good alternative, amongst the various routes of drug delivery. Buccal cavity has a wide variety of functions and it acts as an excellent site for the absorption of drugs². Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) used for the treatment of rheumatoid arthritis and other rheumatic disorders. The long-term use causes gastro-intestinal irritation and ulceration. The physico-chemical properties of Diclofenac and its short half-life make it a suitable candidate for administration by buccal route. Potassium salt of Diclofenac has good solubility and fewer problems to be included in buccal patches.

Gum Karaya is a negative colloid and a high-molecular-weight complex, acidic polysaccharide. It is a partially acetylated complex polysaccharide composed of galacturonic acid, beta-D-galactose, glucuronic acid, L-rhamnose, and other residues obtained as the calcium and magnesium salt³. It is used as a thickener and emulsifier in foods, as a laxative, and as a denture adhesive. It is also used to adulterate Gum Tragacanth due to their similar physical characteristics⁴.

MATERIALS AND METHODS

Materials

Diclofenac potassium (Windlas Biotech Ltd. Dehradun, Uttaranchal), gum karaya powder # 150 (Nutriroma, Hyderabad, India), were gift samples. Carbopol 974P (Corel Pharma-Chem, Ahmadabad, India), HPMCK4M, disodium hydrogen orthophosphate anhydrous, potassium dihydrogen phosphate and sodium chloride



(Process Chemical Industries, Kolkata, India), ethyl cellulose (S.D Fine-chem. Ltd., Boisar, India) and chloroform were obtained commercially.

Preparation of the buccal patch

A. Backing Membrane Preparation

Backing Membrane of the buccal patches was prepared by dissolving Poly Vinyl Alcohol (PVA) in the distilled water at 70 – 100 °C by the help of Magnetic Stirrer with hot plate (1 MLT Magnetic Stirrer REMI). 1.5 gm Poly Vinyl Alcohol (PVA) was dissolved in 30 ml of distilled water. The concentration of the PVA solution was 5% w/v and it was poured into small aluminum foil to prepare backing membrane.

B. Preparation of drug containing layer on the backing membrane

Buccal mucoadhesive patches of Diclofenac potassium were prepared by solvent casting technique using film forming polymers like HPMCK4M, Ethyl cellulose, Carbopol 974P and Gum karaya. The amount of different polymers has been mentioned in the table 1. The polymers are dispersed in chloroform and it was stirred continuously keeping on a magnetic stirrer. One drop of glycerin was added to it. Then the calculated amount of drug was mixed with it. Whole solution was casted on backing membrane.

Drug-Excipient Interaction Study Using FTIR Spectroscopy

Drug-excipient interaction, one of the most essential parameters, was studied before development of the formulations. Pure drug Diclofenac potassium, drug with polymeric combination and polymeric combination alone were mixed separately with IR grade KBr in the ratio 1:100 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. Polymers were HPMCK4M, Carbopol 974 P, Ethyl cellulose and Gum karaya. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} in Magna IR 750 Series II (Nicolet, USA) FTIR spectroscope.

Evaluation of the patches

Thickness uniformity of the patches

The thickness of each patch was measured by screw gauge. At six different positions of the patch the thickness was observed and the average was noted.

Folding endurance

Folding endurance of the patches was determined⁵ by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to evaluate good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on six patches.

Mass uniformity

The assessment of mass uniformity was done by weighing six randomly selected patches from each batch. Then the mean and standard deviation were determined.

Drug content uniformity

Buccal mucoadhesive patches were weighed and dissolved in 100 ml isotonic phosphate buffer pH 6.8 using magnetic stirrer. The solution was filtered and after suitable dilution analyzed for drug Diclofenac sodium spectrophotometrically at 276 nm.

Surface pH

The surface pH of the patches was determined in order to investigate the possibility of any side effects in- vivo. As an acidic or alkaline pH may irritate the buccal mucosa, it is expected to keep the surface pH as close to neutral as possible. For determination of surface pH six patches of each formulation were allowed to swell for 2 h on the surface of an agar plate. Then the surface pH was determined by touching the electrode of a pH meter (Toshniwal Instruments, Ajmer, Rajasthan, India) in the excess phosphate buffer pH-6.8 present at the surface of the buccal mucoadhesive patches. A mean of three readings was recorded⁶.

Mucoadhesive strength

To determine mucoadhesive strength of the experimental patch, it was attached to goat buccal mucosa fixed on the back of a Petri dish. Small physical balance having two circular pans hanged from a rod was used as a mucoadhesive test assembly. The lower part of the circular pan was attached to the buccal patch. The buccal patch was made wet before attaching the buccal membrane with phosphate buffer pH 6.8. Immediately just after the attachment weights were placed on the other pan. It was continued until pan got detached.

Ex -Vivo Residence Time

The ex-vivo mucoadhesion time was observed (n=6) after application of buccal mucoadhesive patches on freshly cut goat buccal mucosa⁷. The fresh goat buccal mucosa was fixed to the inner side of a beaker, about 3 cm from the bottom, with cyanoacrylate glue. A portion of buccal mucoadhesive patch was cut and wetted with phosphate buffer (pH 6.8) and attached to the goat buccal mucosa by applying a light force. The beaker was filled with 200 mL of phosphate buffer (pH 6.8) and kept at 37°C \pm 1°C. The beaker was kept on a magnetic stirrer and around 50-rpm stirring rate was applied to mimic the buccal cavity environment. Adhesion of the buccal mucoadhesive patches were monitored for 12 hours⁸. The time taken for dislodgment of the patches from the goat buccal mucosa was recorded.

Patch swelling

The Patch swelling studies were conducted using two media, namely, distilled water and phosphate buffer pH-



6.8. The buccal mucoadhesive patches were weighed and placed in a pre-weighed wire mesh with sieve opening 800 μm . The mesh containing a patch sample was submerged into 15 ml medium. Increase in weight of the patch was determined at preset time intervals until a constant weight was observed. The degree of swelling was determined for six patches of one type of formulation.

In vitro Drug Permeation Studies

The goat buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with internal diameter of 2.1 cm (3.46 cm^2 area) with a receptor compartment volume of 70 ml.

The donor compartment contained a solution of 3ml of phosphate buffer pH 6.8. Buccal mucoadhesive patch was placed over it. It was fixed with a cello tape so that it will not get dislodged from the skin. 5 ml sample was collected at predetermined time intervals from the receptor compartment and replaced with an equal volume of phosphate buffer pH 6.8.

In vitro Release Study from Diclofenac potassium loaded mucoadhesive buccal patches

Drug release from the buccal mucoadhesive patches was studied by using Lab India dissolution test apparatus. The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug release from the buccal mucoadhesive patches. The dissolution medium consisted 900 ml of phosphate buffer pH 6.8. The release was performed at $37^\circ\text{C} \pm 0.5^\circ\text{C}$, with a rotation speed of 50 rpm. In this study sinker was used to prevent the float of the patch and retain at the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution (1ml of Sample in 10 ml) by UV spectrophotometer (UV – 1800 Shimadzu) at 276 nm (pH- 6.8) ⁹. The experiment was performed in six patches.

RESULTS AND DISCUSSIONS

Prior to development of drug containing layer an impermeable backing membrane is made so that it can reduce the patch deformation and disintegration ¹⁰. The buccal mucoadhesive patches with HPMCK4M, EC, Carbopol 974P and another with the earlier mentioned polymer and Gum karaya have been reported here as F1 and FGK1 (Carbopol 934p: Gk; 1:1) and FGK2 (Carbopol 934P: GK; 0:1) respectively. The drug (Diclofenac Potassium)-polymer ratio by weight was taken 1:10 for the formulations.

Drug-excipient interaction is one of the major steps in pre-formulation study for the development of a new formulation. Among the various methodologies to study the drug excipient interaction, common techniques are FTIR spectroscopy, DSC, IR-spectra etc. Here FTIR-spectroscopy has been carried out which shows the

interaction between the molecules at the level of functional groups ¹¹. IR spectra of Diclofenac potassium and its formulations were obtained by KBr pellet method using ALPHA T, BRUKER spectrometer. Figure 1 shows the IR spectra of Drug, mixture of polymers (HPMCK4MM + Gum karaya + Ethyl cellulose, Carbopol 934P) and drug-polymers mix. Between 3500 cm^{-1} and 2400 cm^{-1} and between 2000 cm^{-1} and 1000 cm^{-1} wave numbers, variations at transmission spectroscopy data were observed. Alkenyl (C=C) (3020 cm^{-1} - 3100 cm^{-1}), amide (-NH) (1000 cm^{-1} - 1250 cm^{-1}) ketonyl (-C=O) (1710 cm^{-1} - 1720 cm^{-1}), phenolic (-OH) (970 cm^{-1} - 1250 cm^{-1}) stretches are mainly responsible functional groups for those regions. It is suggested by the FTIR spectra that there may be some physical interactions due to generation of weak to medium intensity bonds as no major shifting of peaks was marked ¹².

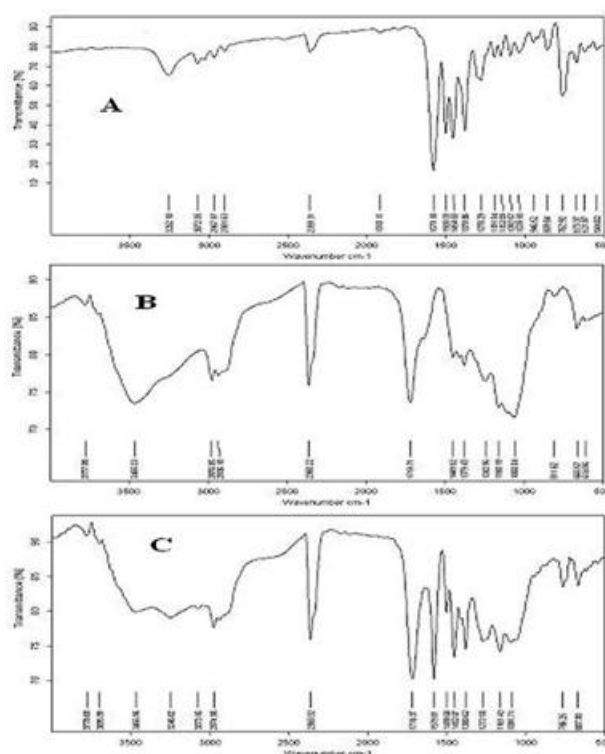


Figure 1: FTIR spectra of a. Diclofenac potassium b. mixture of HPMCK4M, Carbopol 934P, Gum karaya, Ethyl cellulose c. Mixture of polymeric blend and drug

The buccal patches show satisfactory physical-mechanical properties. In the entire three formulations drug content is above 98 % and the low values of standard deviation and coefficient of variation (<1) indicate uniform distribution of drug in the buccal mucoadhesive patches.

Buccal mucoadhesive patches did not show any cracks even after folding for more than 300 times. Hence it was considered as the end point. Folding endurance did not vary between the patches.

Surface pH obtained (Table 1) in this study were within the limits and showed no such variation from time to time which avoids the chances of buccal irritation upon application.

Table 1: Physicochemical evaluation of Diclofenac potassium loaded buccal mucoadhesive Patches (N=6)

Formulation	Composition HPMCK4M : EC : Carbopol 974P: GK	Thickness (mm) ±SD	Weight (mg) ±SD	Folding endurance	Content uniformity (%) ±SD	Surface PH ±SD	Mucoadhesive strength(gm) ±SD	Ex-vivo residence time (min) ±SD
F1	1.5:2.0:0.5:0	0.324 ±0.045	0.48 ±1.5	>300	97.18 ± 0.5	6.75 ± 0.03	25 ± 2.1	310 ± 1.80
FGK1	1.5:2.0:0.25:0.25	0.363 ±0.058	0.52 ±1.6	>300	98.26 ± 0.02	6.68±.06	35.50 ± 1.4	370± 2.70
FGK2	1.5:2.0:0: 0.5	0.366 ±0.058	0.55 ± 0.3	>300	98.13 ±0.35	6.74±.07	45 ±1.6	410 ± 2.74

* EC- Ethyl Cellulose, GK- Gum karaya

In this study, the mucoadhesive strength was determined by measurement of the force of detachment or force of adhesion¹³. All the three types of buccal mucoadhesive patches exhibited good mucoadhesive strength; those were found to be 25, 35.50 and 41.28 g respectively. In case of the mucoadhesive polymers, required strength was reported to be about 30 g¹⁴. Due to presence of gum karaya, mucoadhesive strength was good enough in FGK1 and FGK2 to hold the buccal patches attached to the buccal region and again, the tackiness was such that it was easy to be removed from the buccal area with a little effort. Hence the mucoadhesive strengths for FGK1 and FGK2 were found to be sufficient to hold the buccal patches inside the oral cavity.

For F1 the swelling was 369.15 % and for FGK1 and FGK2 they were 512.60 % and 640.50 % respectively. The highest hydration (swelling) was observed with the formulation FGK2, where Gum karaya is more in concentration. Mucoadhesion occurs after swelling but the bond formed between mucosal layer and polymer is not very strong initially. The adhesion will increase with the degree of hydration¹⁵ but the bond formed between polymer and mucosal layer is not so strong initially. The mucoadhesion will increase with the degree of hydration. Results indicate that swelling is more where GK is 10% in concentration.

Ex-vivo residence time (7 h) was found to have low ex-residence time of 5 h (Table-1) for the formulation without gum karaya. The combination of Carbopol 934P and GK are responsible for rapid swelling which leads to interpenetration of the polymer chains at the interface, and improved attachment of the patch to the buccal membrane. It has been observed that ex-vivo residence time of the patches is higher where gum karaya is present. The findings signify that gum karaya exhibits better mucoadhesion with respect to carbopol 934P.

Figure 2 represents the graph consisting of cumulative percentage of drug release with time. Drug release is fast in FGK1. In formulation FGK1, $t_{50\%}$ value is 140 minutes whereas in FGK2 it is 240 minutes. In F1 drug release is sufficiently slow enough, so that only 44% drug is released in 480 minutes.

The release of drug followed mixed kinetics. Drug release from a polymeric material takes place generally by the

diffusion or by polymer degradation or by a combination of the both¹⁶.

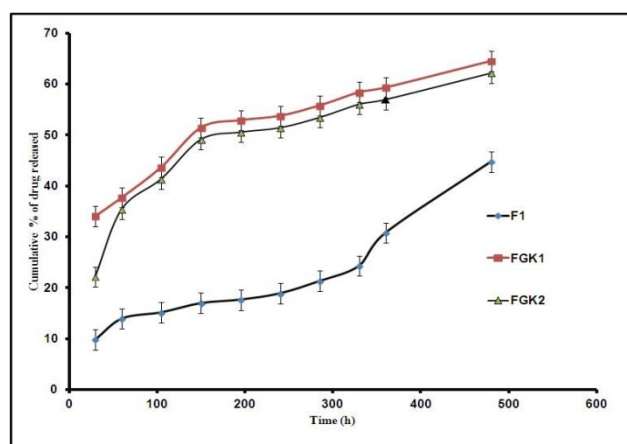


Figure 2: Drug release profile of Diclofenac potassium from buccal mucoadhesive patches in phosphate buffer pH-6.8, (\pm SD, N=6)

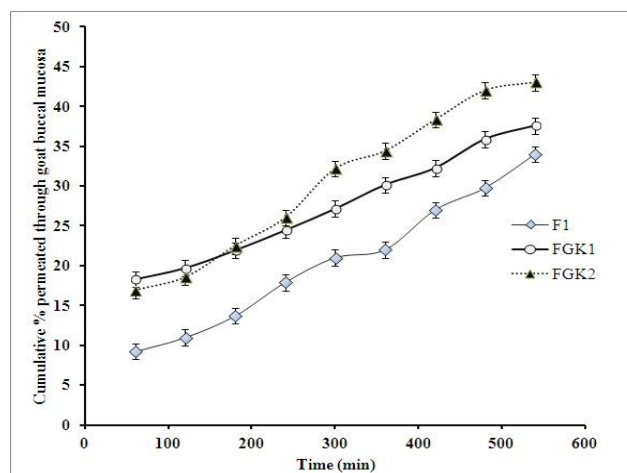


Figure 3: *In-vitro* permeation of Diclofenac potassium from buccal mucoadhesive patches in Phosphate buffer pH-6.8, (\pm SD, N=6)

At the beginning, because of the faster diffusion of the drugs from the surface; drug release from FGK1 and FGK2 provides a first-order kinetic pattern. However, with the length of time the release pattern gradually changed to Higuchi kinetic model. Drug release from F1 obeyed zero order kinetics throughout the entire study. Swelling of the polymers with the duration might vary the tortuosity of the polymeric network pathways which gradually shifted the drug release pattern¹⁷. More amount of Gum karaya is responsible to swell the patches. That swollen layer of

the formulations behaves like a complete matrix structure and controlled the drug release which is reflected in the drug release kinetics. Hence it can be well said that swelling of the polymers varied the entanglement of polymeric pathways to control the diffusion of the drugs from the formulations¹⁸.

In Franz diffusion cell *in-vitro* skin permeation of Diclofenac potassium was performed through goat buccal mucosa in phosphate buffer pH-6.8. The permeation of drug from F1 across goat buccal mucosa was found to be slower than FGK1 and FGK2. In the first few hours there was rapid release of drug from both the formulations and after that drug leached out continuously to maintain sufficient concentration gradient of the drug required for diffusion across the skin. In vitro permeation study the results are in conformity with the in-vitro drug release. It can be concluded that sufficient concentration gradient was maintained for drug diffusion across the skin throughout the experiment.

CONCLUSION

The prepared buccal mucoadhesive patches of Diclofenac potassium can bypass extensive hepatic first-pass metabolism and improve bioavailability. These patches showed a mucoadhesion time of more than 7 h. Buccal mucoadhesive patches prepared with HPMCK4M, Ethyl cellulose and Carbopol 934P showed zero order kinetics of drug release when subjected to dissolution study in phosphate buffer pH-6.8, whereas patches containing Gum karaya along with the above mentioned polymers showed mixed kinetics of drug release. In-vitro permeation studies showed almost more than 50 % of drug permeation in 8 h.

REFERENCES

- Shojaei AH, Buccal mucosa as a route for systemic drug delivery: A Review, *Journal of Pharm. Pharmaceut. Sci.*, 1(1), 1998, 15-30.
- Raghuraman S, Velrajan G, Ravi R, Jeyabalan B, Benito D, Design and evaluation of propranolol hydrochloride buccal films. *Indian J. Pharm. Sci.*, 64, 2002, 32-36.
- Weiping W, "Tragacanth and Karaya, in: Philips GO, Williams PA (Eds.). *Handbook of Hydrocolloids*. Woodhead, Cambridge, 2000, 155.
- Verbeken D, Dierckx S, Dewettinck K. *Appl Microbiol Biot.*, 63, 2003, 10-21.
- Khurana R, Ahuja A, Khar RK, Development and evaluation of mucoadhesive films of miconazole nitrate, *Indian J. Pharm. Sci.*, 60, 2000, 449-453.
- Nave NA, Ismail FA, Boraie NA, Mortada LM, Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, *Int J Pharm*, 264, 2003, 1-14.
- Han RY, Fang JY, Sung KC, Hu OYP, Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. *Int J Pharm.*, 177, 1999, 201-209.
- Chinna RP, Ramesh G, Shravan KY, Vamshi VY, Madhusudan Rao Y, Development of bioadhesive bucco-matrix tablets for felodipine and pioglitazone in combined dosage form: In vitro, ex vivo, and in vivo characterization, *Drug Del*, 18(5), 2011, 344-352.
- Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A, Arora P, *Eur J Pharm Biopharm.*, 59, 2005, 475-483.
- Hoogstraate, AJ, Cullander C, Nagelkerke JF, Verhoel J, Junginger HE, Bodde HE, Diffusion rates and transport pathways of FITC-labeled model compounds through buccal epithelium, *Proceed, Int. Symp. Control. Rel. Bioact. Mater*, 20, 1993, 234-235.
- Kötting C, Gerwert K, Proteins in action monitored by time-resolved FTIR spectroscopy, *Methods Mol Biol*, 305, 2013, 261-86.
- Mukherjee B, Das S, Patra B, Layek B, Nefopam containing transdermal- matrix based on pressure-sensitive adhesive polymers, *Pharm Tech*, 30, 2006, 146-18.
- Prasanna IR, Uma SK, Design, evaluation and in vitro - in vivo correlation of glibenclamide buccoadhesive films, *Int J Pharm Investig*, 2(1), 2012, 26-33.
- Singh B, Ahuja N, Development of controlled-release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution, and diffusion parameters, *Drug Dev Ind Pharm*, 28, 2002, 431-42.
- Needleman IG, Smales FC, In vitro assessment of bio adhesion for periodontal and buccal drug delivery, *Biomater*, 16, 1995, 617-624.
- Heller J, Washington DC, Penhale, WH, Use of bioerodible polymers in self-regulated drug delivery systems in: P.I. Lee, W.R. Good (Eds.). *Contro Rel Tech. Pharm. App. Washington DC, ACS Symposium Series*, 1997, 76, 281-282.
- Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A, Arora P, A comparison between povidone-ethyl cellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation, *Eur J Pharm Biopharm*, 59, 2005, 475-83.
- Aalaie J, Ebrahim VF, Semsarzadeh MA, Rahmatpour A, Rheological and swelling behavior of semi-interpenetrating networks of polyacrylamide and scleroglucan, *Polym Adv Technol*, 20, 2009, 1102-1106.

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