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Exploring the Effect of Polyox on the Release Kinetics of a Model Antihypertensive Drug from a Cellulose Derivative Based Buccal Patch.

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ABSTRACT

Drug release from matrix dosage form is affected by polymer swelling, it's erosion, drug distribution inside the matrix and polymeric combination. To prepare buccal controlled release patches hydrophilic, swellable, porous polymeric material alone or in optimum combination along with their buccoadhesive strength is essential. Here a plant derived gum like Gum karaya (GK) , a cellulose derivative-HPMCK15M and Polyox have been used to prepare buccal buccal patches of Carvedilol phosphate . The effect of Polyox and gum karaya on the release kinetics of drug from the buccal patches have been studied.The buccal patches were evaluated for it's physico-mechanical characteristics. The buccal patches revealed satisfactory physic-mechanical results. Buccoadhesive strength was found to be in the range of 31-35 gm, which is good enough to hold the buccal buccal patches inside the buccal cavity. Percent Swelling of the buccal patches were in the range of 449-529%.Swelling is maximum in the buccal patches where Polyox is present along with HPMCK15M and GK. Drug dissolution from the buccal patches has been described by kinetic models. The release data were fitted in different kinetic models, like zero order, first order and Higuchi. Release study of Buccal patches made up of only HPMCK15M followed zero order kinetics.. Buccal patches with GK along with HPMCK15M provided Higuchi kinetics over 8 hours of drug release.Further incorporating Polyox along with HPMCK15M and GK showed mixed order kinetics. Initially drug release followed Higuchi kinetics followed by zero order in the last phase.

INTRODUCTION

Among the various routes of drug delivery, the oral route can be considered as preferred route for patients and clinicians. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism, many drugs, cannot be delivered effectively through the conventional oral route, because after administration are subjected to pre-systemic clearance extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability. Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time.

Carvedilol is a poorly water-soluble oral antihypertensive agent, with problems of variable bioavailability and bio-in equivalence. It is an alpha and a beta adrenoreceptor-blocking agent used in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrhythmia and hypertension.

Hyroxypropyl methylcellulose (HPMC) is one of the most widely used polymers in the preparation of oral controlled drug delivery systems [1]. Hydroxypropyl methylcellulose (HPMC) products vary chemically and physically. HPMCK15M has been selected for the experiment here. To achieve controlled release through the use of a water-soluble polymer like HPMC, the polymers generally hydrate on the outer surface to form a gelatinous layer. A rapid

formation of a gelatinous layer is critical to prevent wetting of the interior and also prevent rapid release of drug from the matrices [2].

Once the protective gel layer is formed, it also controls the penetration of additional water into the matrix. When the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. It has been observed that mechanism of release and the release profiles from matrices depend on the type and ratio of the quantity of the polymers used in combination. One plant derived bio compatible gum, Gum karaya has been selected for the study .Gum karaya (GK), also called sterculia gum, is the dried exudation of the Sterculia urens tree and other species of Sterculia, which belong to the family Sterculiaceae [3].

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 salt [4].

The general utility of GK is based on its viscosity. GK showed its suitability in the preparation of hydrophilic matrices [5] mini-matrices, microcapsules and transdermal buccal patches. It has been used here in combination with HPMCK15M to prepare matrix buccal patches for buccal administration and to observe its influence on the release profile of drug and the buccoadhesive strength of the dosage form. A suitable buccal drug delivery system should be flexible with good bio adhesion, so that it can be retained in the oral cavity for the desired duration releasing the drug in a predictable manner to elicit the required therapeutic response. Gum karaya, is good buccoadhesive in nature. It swells in water and has profound effect on the release kinetics of controlled release dosage form. Polyox has been extensively studied as a matrix-forming polymer. This can be utilized for modulating drug release. POLYOX in Wide range of molecular weights offers formulation flexibility, fast hydration and gel formation for use in hydrophilic matrices.

MATERIALS AND METHODS

Materials

Carvedilol phosphate was obtained as a gift sample from Macleods Pharmaceuticals Ltd, Mumbai, India. HPMCK15M was obtained from Colorcon India Ltd, India, Polyox was obtained from Colorcon India Ltd,India., Gum karaya was obtained from Nutriroma, Hyderabad, India.

Methods

Preparation of buccal patch

Bu8ccoadhesive buccal patches were prepared by solvent casting method. All ingredients were accurately weighed and mixed by triturating in glass pestle and mortar. The mixture was then added gradually to magnetically stir solvent system containing the plasticizer. Stirring was continued until a clear solution was obtained. The Solution was then transferred quantitatively to aluminum foil. The aluminum foil was covered with inverted funnels to allow controlled evaporation of the solvents. These were lefts undisturbed upon temperature (20-25°C) for one to two days depending upon the solvent system used.

Drug-Excipient Interaction Study Using FTIR Spectroscopy

Drug polymer interaction one of the most essential parameter is studied before development of formulation. An infrared spectrum was recorded on Fourier Transform Infrared (FT-IR) spectrometer (ALPHA T, Bruker) using potassium bromide (KBr) pellet method. IR spectra of Carvedilol phosphate alone, physical mixture of polymers and drug-polymers combination is shown Figure 1.

Differential Scanning Calorimetry (DSC)

The DSC analysis of pure drug, polymers, physical mixture of polymer and drug was carried out separately using Pyris Diamond TG/DTA Thermo gravimetric /Differential Thermal Analyzer (Perkin Elmer Inc, PerkinElmer SINGAPORE) to study any possible drug-polymer interaction at the molecular level [6]. The ratio of drug to polymer chosen was same as that in the final formulation. Platinum crucible was used with alpha alumina powder as reference.

About 6 to 10 mg sample were kept in platinum pans at a rate of 12°C/min from 10oC to 300°C temperature range under a nitrogen flow of 150 ml/min. The changes in the DSC curves were evaluated both with the positions of peak maxima and minima. The peak areas represent the phase-transition enthalpies.

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Evaluation of buccal patches

Mass uniformity and Thickness

The assessment of weight and patch thickness was done in 6 different randomly selected buccal patches from each batch. For determination of mass, buccal patches were directly weighed on a digital balance and the patch thickness was measured at 6 different randomly selected spots on buccal patches using a screw gauge.

Folding endurance

Folding endurance of buccal patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times without breaking [7].

Drug content uniformity

The amount of drug contained in the patch was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 8 hr under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45µm Whatman filter paper. The drug content was then determined after proper dilution by UV spectrophotometer (Shimadzu-1700 Japan) at λmax of 285 nm. The experiments were carried out in triplicate.

Percent Swelling

The buccal patches were weighed (W1) and placed separately in petri dishes containing 25 ml of Phosphate buffer pH-6.8.. The dishes were stored at room temperature. After 60 minutes and 420 mins the patches were removed and the excess water on their surface was carefully removed using filter paper. The swollen patches were weighed (W2) and the percentage of swelling was calculated by the following formula

$$\text{Swelling index} = W2 - W1/W1*100$$

The Figure 3 represents data related to the percent swelling of the buccal patches.

Surface pH Determination

The surface pH was determined by the method similar to that used by Bottenberg. A combined glass electrode was used for this purpose. The buccal patches were allowed to swell by keeping them in contact with 1 ml of distilled water for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the buccal patches was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of the patch close to the neutral pH.

Moisture content

For moisture content first buccal patches were properly dried then kept in a dessicator which was filled with fused silica gel , after that dessicator was vacuumed with help of pump .After 24 hrs, 48 hrs, 72 hrs the Weight of buccal patches were recorded.

Buccoadhesive strength

To determine buccoadhesive strength of the experimental patch, it was attached to goat buccal mucosa fixed on the back of a Petridis . Small physical balance having two circular pans hanged from a road was used as a buccoadhsive test assembly. The lower portion of the circular pan was attached to the buccal patch. The buccal patch was made wet before attaching the buccal membrane with phoshphate buffer pH 6.8. Immediately after the attachment weights were placed on the other pan . Placing of weight were continued till pan got detached [8].

In vitro release study

The In-vitro dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The dissolution medium was consisted of 900 ml of phosphate buffer pH 6.8. The release of drug from the buccal patches was performed at 37 ± 0.5 °C, at a rotation speed of 50 rpm. One side of the buccal patch was attached to a glass disk with instant adhesive (cyanoacrylate). The disk was put in the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples (5 ml) were withdrawn by using calibrated pipette

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at pre-determined time (30mins) intervals and replaced with fresh medium. The samples were filtered through 0.45 µm Whatman filter paper with appropriate dilutions with phosphate buffer pH 6.6 and were assayed spectro photo metrically at 285 nm. The graphical representation of the release pattern of the drug from the buccal patches is reflected in Figure 4.

Microscopic view

Before and after the drug release study the microscopic view of the buccal patches were photographed under projection microscope (Figure 5).

In vitro permeation study [9]

Franz diffusion cell of 70 ml capacity was used for in vitro skin permeation study. A round section of goat buccal mucosa skin was tripped of adhering fat and was tied with an adhesive tape on a donor part of Franz Diffusion cell. A portion of major buccal patch was placed on the skin. The donor compartment containing skin and the buccal patch was placed on the receptor compartment of the diffusion cell containing Phosphate buffer pH 6.8 and the temperature was maintained at 37°± 0.5°C. The phosphate buffer in the receptor compartment was continuously stirred using magnetic beads during the experiment, 5ml of sample was withdrawn at a specific time interval and it was replaced with 5ml of fresh phosphate buffer pH 6.8. Absorbance of the sample was measured in UV- visible spectrophotometer (UV-1800 Shimadzu) at 285 nm against Blank. The data is represented in Figure 6.

RESULTS AND DISCUSSIONS

Drug-excipient interaction is a very important pre-formulation study to develop a new formulation. Among the various methodologies available to understand the drug excipient interaction, common approaches are FTIR spectroscopy, DSC, IR-spectra etc. Here FTIR-spectroscopy shows the interaction between the molecules at the level of functional groups. IR spectra of Carvedilol phosphate and its formulations were obtained by KBr pellet method using ALPHA T, BRUKER spectrometer in order to rule out drug-carrier interaction occurring during the formulation process. Figure 1 shows the overlayed IR spectra of a mixture of Drug, mixture of polymers (HPMCK15M + Gum karaya + Polyox) and drug-polymers mix. In IR-spectra of drug-polymers mix, between 3300 cm^{-1} and 1600 cm^{-1} and between 1500 cm^{-1} and 900 cm^{-1} wave numbers, variations at transmission spectroscopy data were noted. Alkanyl (-CH-) (2950 cm^{-1}- 2800 cm^{-1}), alkenyl C=C (3100-3010 cm^{-1}) ,acetylenic (-3300 cm^{-1}), aldehyde (2850-2750 cm^{-1}) , carboxyl (3400-2400 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 for those regions. It can be concluded from the above findings that there may be physical interactions related to the formation of weak to medium intensity bonding as there was no major shifting of peaks [10].

DSC measurement was carried out to provide better evidences whether predicted physical interaction would lead to drug amorphous formation in the formulations. Figure 2 shows the overlayed thermogram of Carvedilol phosphate, HPMCK15M, Polyox, Gum karaya, drug-polymeric combination according to the formulations (Table-1). Figure 2 shows the overlayed thermogram of the polymers individually and the physical mixture of polymers along with drug according to the formulation selected. The pure drug Carvedilol phosphate is having the endothermic peak at 157.11 °C. That peak is present in the HPMCK15M-GK mixture along with drug (HGD) but the peak is quite shortened. In HPD(HPMCK15M-Polyox combination with drug) and HD (HPMCK15M-drug combination)the peak of the drug are superimposed. The endothermic peak of Polyox (76.22 °C) is light shifted in HPD (75.81°C). The changes in all the DSC thermograms correspond to the changes at the respective TGA shown in the Figure 2 depict the DSC and TGA of the polymeric mixture.

Table1: Drug and Polymers combination

Ingredients / Formulation	P1	P2	P3
Drug (mg)	6.25	6.25	6.25
HPMCK15M(mg)	200	50	50
Gum karaya(mg)	-	150	100
Polyox(mg)	-		50
Distilled water(ml)	5	5	5
Glycerol (drop)	1	1	1

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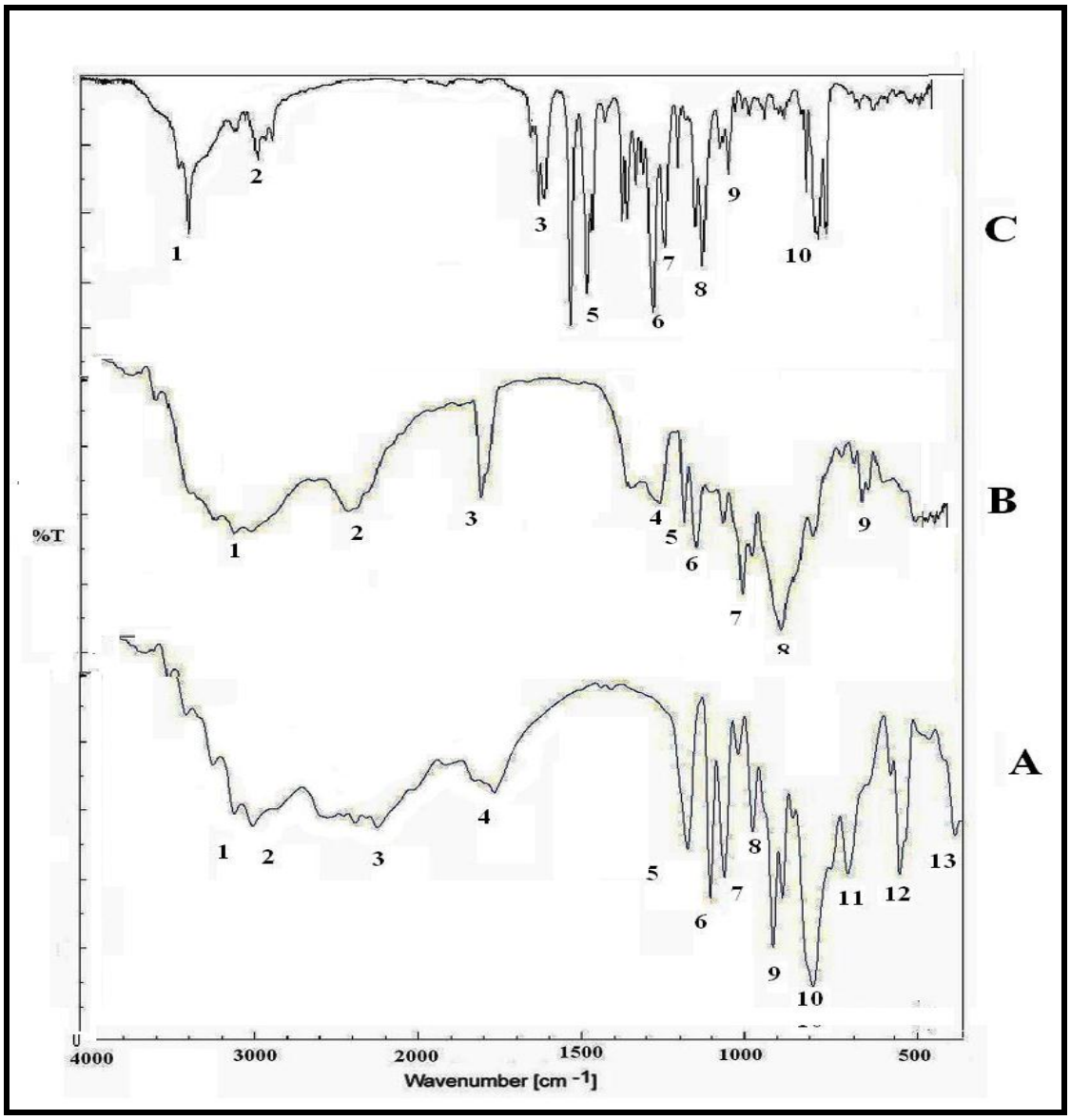
Figure 1: Overlayed FTIR spectra of A. Carvedilol phosphate (CAR-P) B.Physical mixture of polymers (Gum karaya , HPMCK15M and Polyox) C. Drug and polymers



The buccal tablets show satisfactory physical-mechanical properties. In the entire three formulations drug content is above 97% and the low values of standard deviation and coefficient of variation (<1) indicate uniform distribution of the drug within the buccal patches. Surface pH obtained (Table 2) in this study were within the limits and showed hardly any variation from time to time which omits the chances of irritation in the buccal mucosa upon application.

Table 2 : Physico-mechanical properties of Buccal patches

Formulation	Thickness (mm) ±SD(N=3)	Weight (mg) ±SD(N=3)	Folding endurance	Content uniformity (%) ±SD(N=3)	Surface PH ±SD (N=3)	Buccoadhesive strength(gm) ±SD(N=3)
P1	0.16±0.02	192.8±1.5	>300	97.98 ± 0.5	6.6 ±0.05	30.25 ± 2
P2	0.28±0.05	195.32±1.6	>300	98.26 ±.02	6.68 ±.0.06	33.50 ±1.4
P3	0.35±0.03	198.86± 0.3	>300	98.83 ±.0.35	6.74 ±0.07	35.15 ±1.6

All the three types of buccal patches exhibited good buccoadhesive strength; those were found to be 30.25, 33.50 and 35.15 g respectively. In case of the mucoadhesive polymers desired strength was reported to be about 30 g [11]. Hence the buccoadhesive strengths were found to be satisfactory to hold the buccal patches inside

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the oral cavity. That strength of buccal patches was found to be a function of the nature of polymers used and polymeric combination.

Figure 2 Overlayed DSC thermogram of Carvedilol phosphate (CAR-P), Gum karaya (GK), HPMCK15M+Drug (HD), HPMCK15M+GK+DRUG (HGD), HPMCK15M+Polyox+Drug (HPD), Polyox (POLX), HPMCK15M

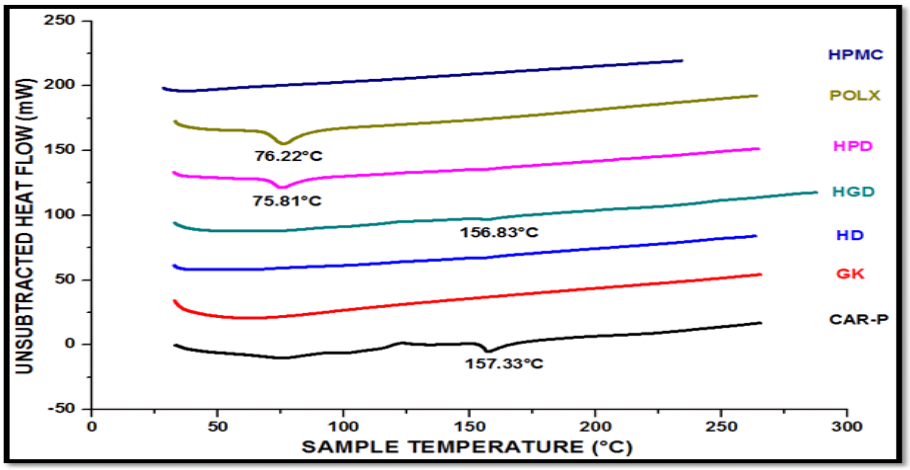

Figure 3: Percent swelling of the buccal patches in phosphate buffer pH-6.8 (±SD, N=6)

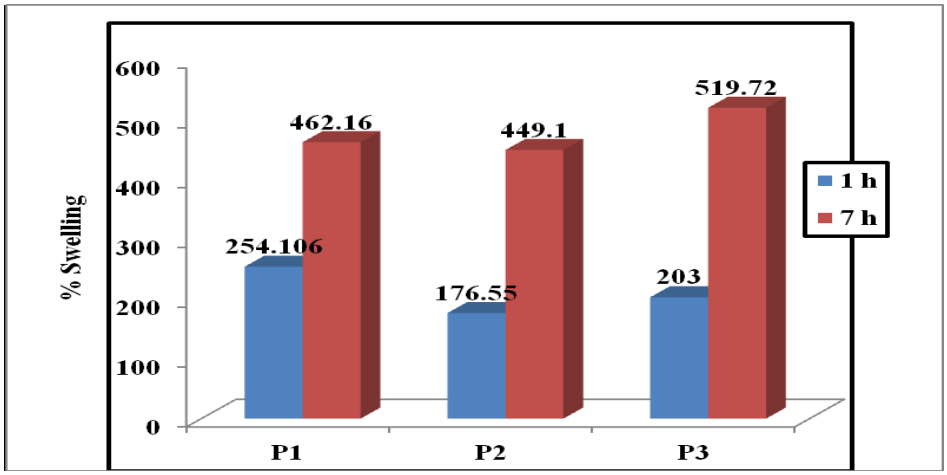

Figure 4: Release profile of Carvedilol phosphate from Buccal patches in phosphate buffer pH-6.8 (±SD, N=6)

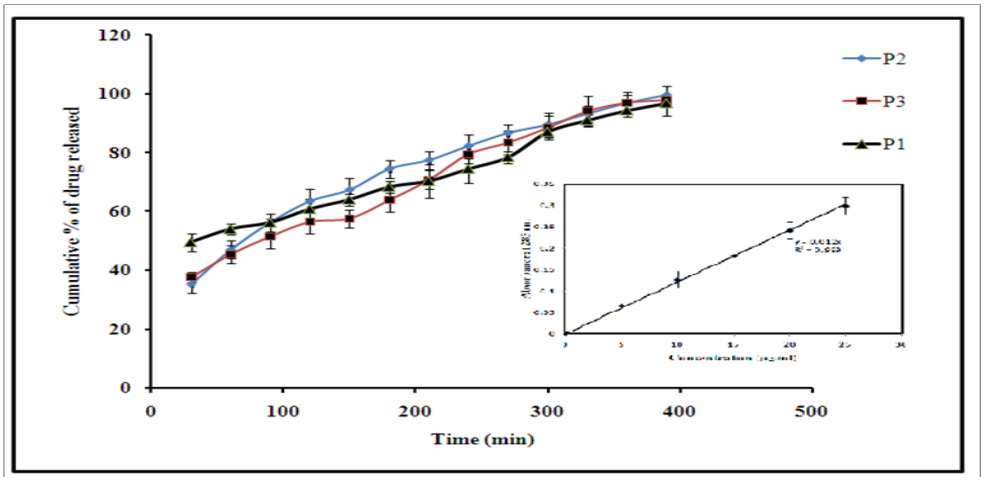

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Figure 5: Projection Microcopic view of buccal patches before and after of 7h drug release

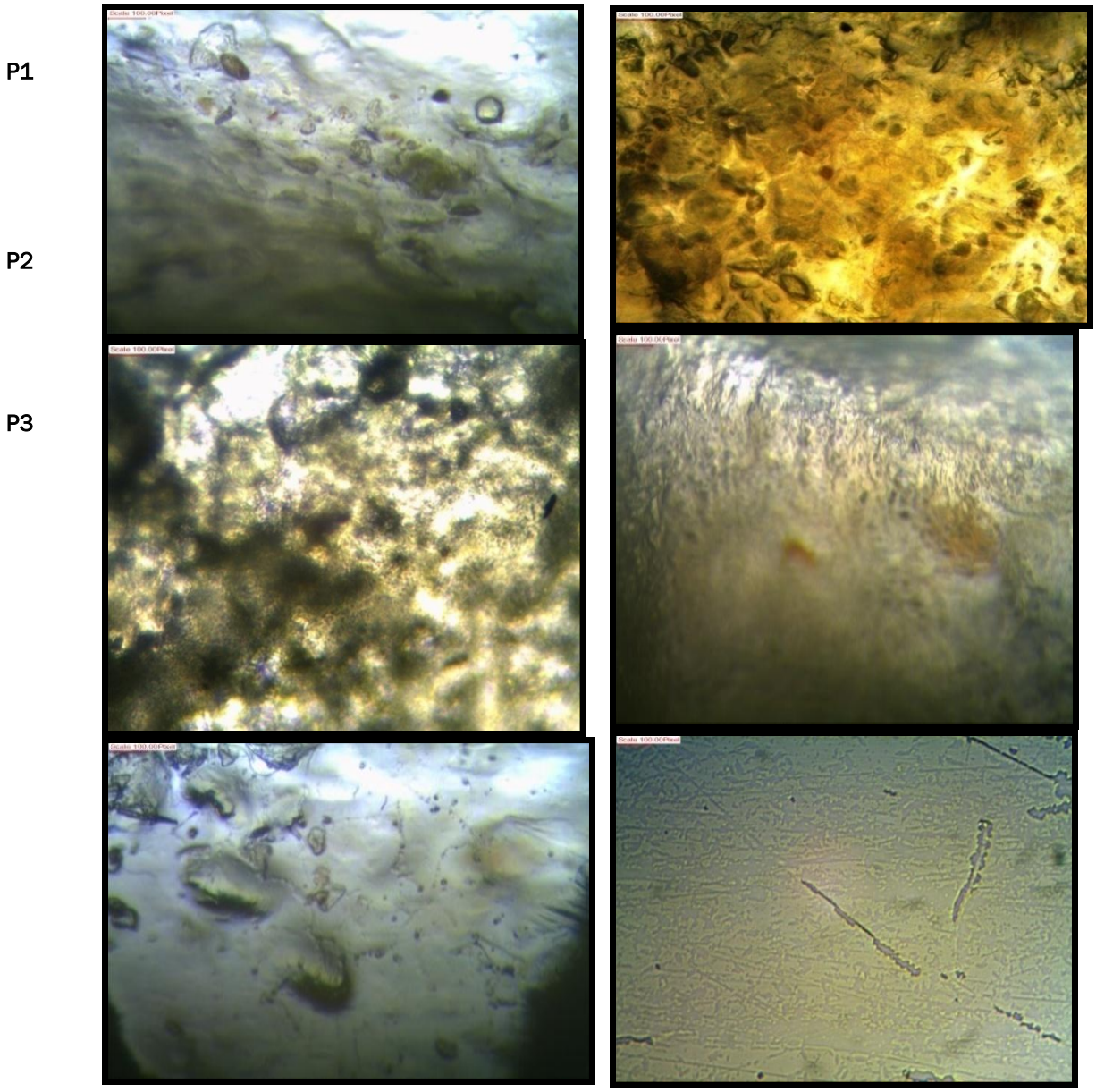
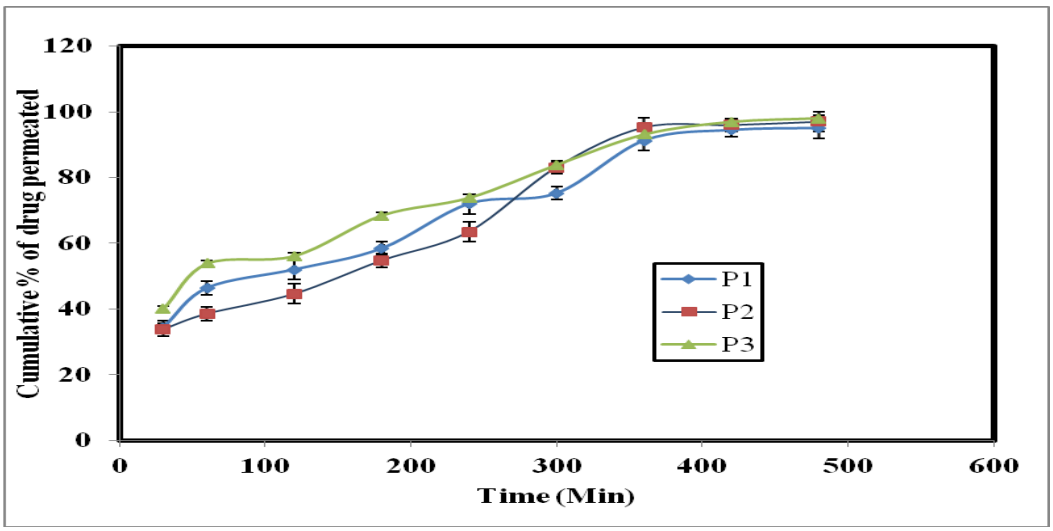


Figure 6: Permeation of Carvedilol phosphate through goat buccal mucosa in phosphate buffer pH-6.8 (±SD, N=6)



For P1 the swelling was 462.16 % and for P2 and P3 they were 449.10 % and 519.72 % respectively. The highest hydration (swelling) was observed with the formulation P3, where Polyox is present. Buccoadhesion occurs shortly after swelling but the bond formed between mucosal layer and polymer is not very strong at the beginning. The adhesion will increase with the degree of hydration to an optimum value. Results indicate that swelling is maximum in P3 where Polyox is present along with HPMCK15M and GK. Buccoadhesive strength is also maximum in P3 and that supports the above findings. Fig 3 represents the graph consisting of cumulative percentage of drug release vs time. Drug release is the faster in P1 and became slowest afterwards. In formulation P1, t_{50}% value is 30 minutes whereas in P2 and P3 they are 68 and 85 minutes respectively. From all the formulations 90 % of the drug got released over 7 hours. $t_{75\%\ are}$ 4 h 15 min, 3 h and 3 h 45 min for P1, P2 and P3 respectively. All the three patches 90 % of drug released within 7 h. The release data were fitted in different kinetic models. Buccal patches P2 followed Higuchi kinetics (r^2 = 0.9968). Whereas P1 followed zero order kinetics (r^2 = 0.9895). This forms released the same amount of drug by unit of time. Formulation P3 releases drug via mixed kinetics. In first 3 hours drug release from it followed higuchi kinetics (r^2= 1) followed by zero order kinetics (r^2=0.9895) from 3 hours to 8 hours. Release of drug from the porous matrices formed will be directly proportional to the amount of drug present in the interior portion of the patch [12]. Gum karaya, HPMCK15M and Polyox containing buccal patches take up water on contact with the dissolution medium and swelled up maximum after a certain time. Initially drug leached out from the intact matrix layer which became porous on due course of time to allow dissolution of the drug present in the interior portion of the buccal patches. In P3 due to presence of Polyox it provides a much more controlled release of the drug due to its very slow erosion rate [13] and moderate swellability. Combination of HPMCK15M, Gum karaya and Polyox are responsible for hydrogel formation whose concentration limits the release of the drug [14].

CONCLUSION

It can be concluded that Polyox and Gum karaya can change the release kinetics of model antihypertensive drug (here Carvedilol phosphate) from HPMCK15M based buccal patches. Release study of Buccal patches made up of only HPMCK15M followed zero order kinetics. Buccal patches incorporating GK along with HPMCK15M provided Higuchi kinetics over 8 hours of drug release. Further incorporating Polyox along with HPMCK15M and GK show mixed order kinetics. Intially drug release followed Higuchi kinetics followed by zero order in the last phase.

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