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Formulation and Evaluation of Mucoadhesive Buccal Patch of Timolol Maleate

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ABSTRACT

The present study includes the Formulation and Evaluation of Mucoadhesive Buccal Patch of Timolol Maleate for this study work timolol maleate selected as model drug and using either ionic polymers (SCMC) or non-ionic polymers (carbopol, HPMC).The fabricated patches were prepared by solvent casting method. The mean thicknesses of the buccal patch formulations were 0.34 – 0.43 mm. Moisture uptake of transdermal patches were found to be 2.94-4.13.which prevents the patches from microbial growth and bulkiness. As amount of PVP increased in every polymer blend, tensile strength and elongation at break were increased. Addition of PVP predominantly decreased the swelling characteristics of the buccal patches, except for SCMC. The drug content of the prepared bioadhesive buccal patches were found in the range of 91.4 - 98.54 %.Bioadhesive strength of buccal patches in following order SCMC >Carbopol>HPMC. The release of Timolol maleate from HPMC patches was slower than SCMC and CP 934.As PVP concentration increased, dissolution rate increases among all polymers. For determination of λmax the solution of the timolol maleate was subjected to ultraviolet scanning in the rage 200 to 400 nm. The λmax was found to be at 294 nm .The pH of formulations was found to be 6.8 - 7.5 which is within the limit of semisolid specifications. The folding endurance of BP formulations was found to be 296 – 325.The results indicated that all formulations were flexible and soft. Bioadhesive buccal patches containing SCMC, HPMC and Carbopol showed a zero order drug release.

Keywords: Timolol Maleate, Mucoadhesion, Buccal Patch, PVP, HPMC.

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INTRODUCTION

The oral route of drug administration is the most common route of delivering active pharmaceutical ingredients (APIs) to the human body [1]. In comparison with other routes of drug administration, the oral route is considered the safest, simplest and most convenient. The buccal mucosa is somewhat less permeable than the sublingual mucosa and is generally not the perfect delivery side for rapid absorption and docs not exhibit as good a bioavailability as sublingual. However the buccal route provides the opportunity for drug absorption through the buccal epithelial lining of the oral cavity (mucosa and cheek) for local or systemic action[2]. Buccal mucosa allows drug delivery for both local and systemic therapies. Local delivery to tissue of the oral cavity has a number of applications, including treatment of local conditions such as periodontal disease, bacterial and fungal infections, aphthous stomatitis and vesiculo bullous diseases, toothache, and in facilitating tooth movement with prostaglandin .[3-5]

Buccal patches laminates consisting of an impermeable backing layer, a drug-containing reservoir layer, a bioadhesive surface for mucosal attachment. Film forming polymer Plasticizer,Penetration enhancer,Active Pharmaceutical ingredient,Sweetening agents,Saliva stimulating agent, Flavoring agents,Coloring agents. The objective of present work was to develop the mucoadhesive patches of timolol maleate using solvent casting technique by using different polymers like hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Carbopol, PVP and evaluated for different parameters.

MATERIALS AND METHOD

Materials:

Timolol Maleate was gift sample of Micro lab Pvt Ltd. Bangluru. The entire all polymers were purchased from Loba chemicals Pvt Ltd. Mumbai.

Methods: Preparation of bioadhesive drug free buccal patch

Bioadhesive buccal patch were prepared using a solvent evaporation method. Plasticizer as dissolved in 10 ml of solvent system then stirred and heated to 80 °C. Polymers were slowly added into the solution to make all the polymer molecules dispersed (1 to 2 min). The dispersion was stirred for one hour to dissolve the polymers. The solution was continually stirred at room temperature for 30 minutes after other excipient was added. The solution was left to stand overnight to remove all the entrapped bubbles, poured into an aluminum petridish and dried at room temperature for 2 days.

The bioadhesive patches were prepared using either ionic polymers (SCMC) or non-ionic polymers (carbopol, PVA, HPMC). To improve patch performance and release characteristics, a water-soluble hydrophilic additive, PVP, was added[6].

Preparation of Timolol maleate buccal patch

On the basis of physical and mechanical properties best polymeric patch was selected for incorporation of drug. Calculated amount of timolol maleate (30 mg/cm²) was dispersed in the polymeric solution, after the drug is completely dispersed; plasticizer was added and stirred to form a uniform dispersion. The solution was left to stand overnight to remove all the entrapped bubbles, casted into an aluminium petri dish and dried at room temperature for 2 days.

Table 1 Formulation design and appearance of buccal patch containing SCMC and PVP

Formulation	SCMC (%)	PVP (%)	DBP (%)
BP 1	5	1	20
BP 2	5	1	30
BP 3	5	1	40
BP 4	5	2	30
BP 5	5	3	30
BP 6	5	4	30

Table 2: Formulation design and appearance of buccal patch containing HPMC and PVP

Formulation	HPMC (%)	PVP (%)	DBP (%)
BP 7	10	1	20
BP 8	10	1	30
BP 9	10	1	40
BP 10	10	2	40
BP 11	10	3	40
BP 12	10	4	40

Table 3 Formulation design and appearance of buccal patch containing carbopol and PVP

Formulation	Carbopol (%)	PVP (%)	DBP (%)
BP 13	2.5	0.5	20
BP 14	2.5	0.5	30
BP 15	2.5	0.5	40
BP 16	2.5	1.0	40
BP 17	2.5	1.5	40
BP 18	2.5	2.0	40

Table 4: Formulation design and appearance of buccal patch containing PVA and PVP

Formulation	PVA (%)	PVP (%)	DBP (%)
BP 19	10	1	20
BP 20	10	1	30
BP 21	10	1	40
BP 22	10	2	30
BP 23	10	3	30
BP 24	10	4	30

Evaluation of buccal patch:

Physical Appearance and Surface Texture:

Physical Appearance and Surface Texture includes visual inspection of patches and evaluation of texture by feel or touch.

Thickness:

Thickness the patch was measured using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken and SEM was calculated [7}]

Appearance of buccal patches

All formulations were transparent, soft and easily removed from surface (fig.5.9 & table 5.3-5.6).

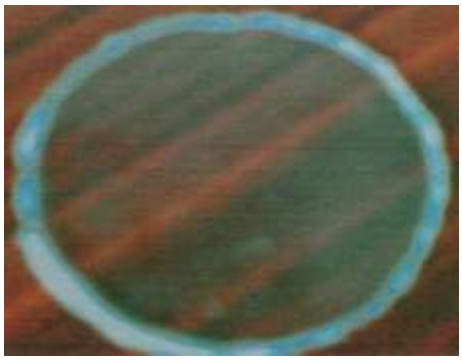


Figure 1: Bioadhesive buccal patch

Surface pH:

Buccal patches 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 surface

Percent Swelling Index:

The polymeric patches cut into 1 x 1 cm were weighed accurately and kept immersed in 50 ml of water. The patches were taken out carefully at 5, 10, 20, 30 and 60 minutes intervals blotted with filter paper to remove the water present on their surface and weighed accurately, the percent swelling is calculated using formula [8]

$$Swelling\ (\%) = \frac{(wet\ weight - dry\ weight)}{dry\ weight} X\ 100$$

Moisture Uptake:

A modification of the ASTM method was used. Specimens were subjected to desiccation over sodium hydroxide at room temperature for 48 hours. This weight was recorded as the initial weight. These samples were then exposed to 74.9%, 52% and 98%.Relative humidity (RH) using sodium chloride (NaCl), sodium bisulfate and potassium dichromate respectively in their saturated

solution at room temperature. These specimens were weighed periodically until no further increase in weight was recorded. The moisture uptake was calculated at each RH as given below:

$$Moisture\ uptake\% = \frac{(W_1 - W_2)}{W_2}\ X\ 100$$

Where W_1= Final weight and W_2= Initial weight

This test is of great significance as variation in moisture content causes a significant variation in mechanical properties of the film especially when film comprises of hygroscopic components, it is also important to assess such polymers, which are of humidity-dependent diffusiveness. The capacity of the film to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of drug through mucous membrane [6].

Folding Endurance:

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance. [9]

Mechanical properties: [9]

Tensile Strength:

Tensile strength of buccal patch refers to tension or forced required to tear of the patch apart into two pieces. This was determined with an instrument assembled in the laboratory based on the American Standard for Testing Material (ASTM) standard tests principles . The specimen was held between two clamp in such a way that the marking towards the fixed clamp as just inside it, whereas marking towards the movable clamp was measured. The change in length of the specimen that occurred with increase in weight was measured. The rate of change of stress was keep constant by increasing the load on the pan at the rate of 10 g/2 min because stress strain relationship changes with rate of change of stress.

The definition of tensile strength as per ASTM standards is the maximum load during the tensile strength test divided by the original minimum cross-sectional area of the specimen. Thus, tensile strength:

$$T = \frac{MX\ g}{w\ X\ l}\ kg/cm2$$

Where,

m = mass in grams

g = acceleration due to gravity 980 cm/sec^2

w = breadth of the specimen in cm

l = thickness of sample in cm.

Percent Elongation at Break:

The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100.

$$EB\ (\%) = \frac{L_1 - L_0}{L}$$

L1 = length of the specimen in cm when it breaks.

L0 = original length of the specimen in cm.

Drug Content Uniformity:

The patch of known weight (dimension 1 x 1cm) was extracted with 100 ml of phosphate buffer by shaking. The solution was suitably diluted with phosphate buffer and the absorbance was measured in UV-spectrophotometer at 294 nm against the same phosphate buffer. [10]

Bioadhesion studies:

In evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In present study, sheep buccal mucosa was used as a model mucosal surface for bioadhesion testing. Immediately after slaughter, the buccal mucosa was removed from the sheep and transported to laboratory in tyrode solution.

The Mucoadhesive forces of the patch were determined by modified balance method. The sheep buccal mucosa was cut into strips/pieces and washed with tyrode solution. At time of testing a section of sheep buccal mucosa (c) was secured keeping the mucosal side out, on the upper glass slide (B) using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1 cm. Then one glass slide with section of sheep buccal mucosa (C) and another glass slide were fixed on height adjustable pan (E). To a lower glass slide a film was placed with the help of bilayered adhesive tap, adhesive side facing downward. The height of the lower glass slide was adjusted so that a patch could adhere to the sheep buccal mucosa on the upper glass slide. A constant force was applied on the upper slide for 2 min, after which it was removed and the upper slide was then connected to the balance. Then the weight added on right side pan till the two glass slide separated from each other [10].

In Vitro release study:

A buccal strip of 1 cm² (containing 30 mg of drug) affixed with the backing membrane was held at the centre of a microscope slide by means of rubber band. The slide was placed at an angle of 45º in a 150 ml beaker containing 100 ml of pH 6.6 buffer preheated to 37ºC. The beaker was kept in 37ºC water bath. A non-agitated system was selected to eliminate any effect of turbulence on the release rate to assure that no disruption of strip occurred. Periodic assay of samples were obtained by removing the slide, stirring the medium and pipetting a 1 ml sample with graduated pipette, whose tip was covered with a piece of muslin cloth. The volume of the sample was immediately replaced with 1 ml of fresh buffer. The slide was quickly reinserted, making sure that the slide remained completely immersed throughout the release rate studies. The beaker was kept covered throughout the run to prevent evaporation. All samples were analyzed spectrophotometrically at 294 nm. [9].

In Vitro drug release kinetic study of buccal patch [11-14]

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order Log(Q0-Q) v/st, Higuchi's square root of time (Q v/s t1/2) and Krosmeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t.

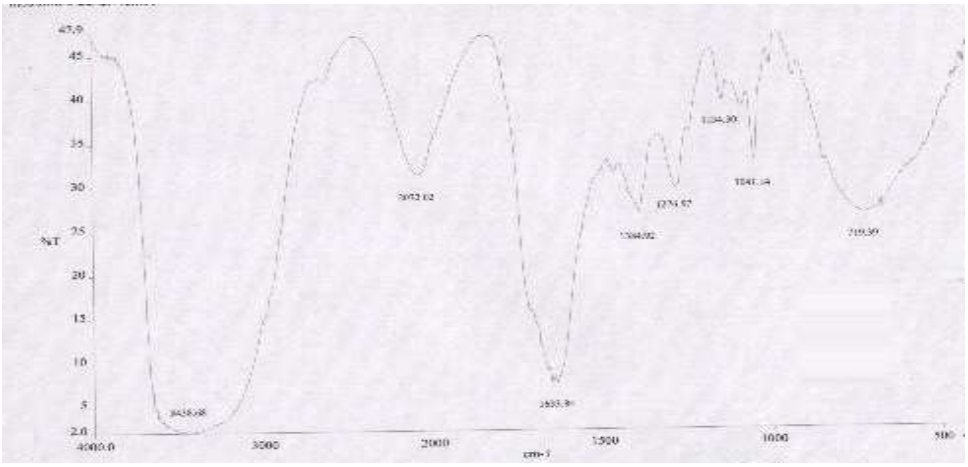
In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

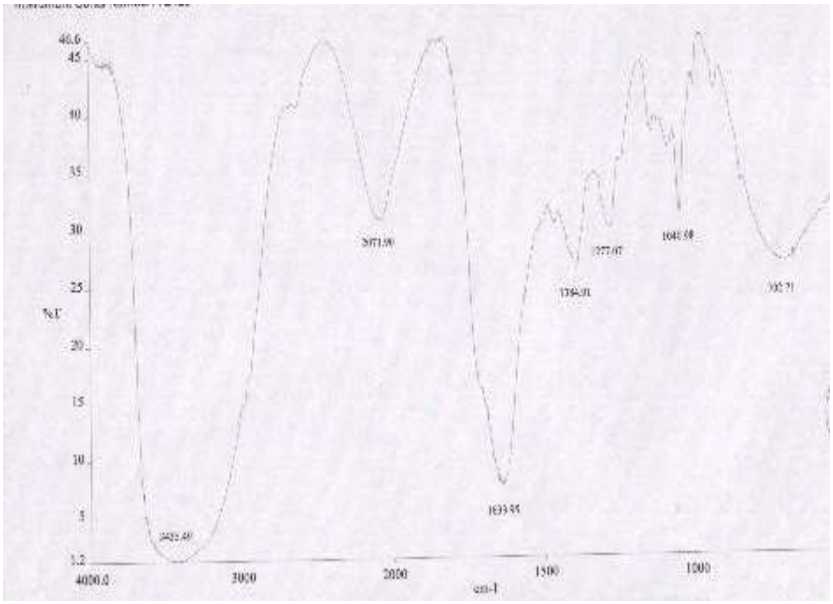
RESULTS AND DISCUSSION:

Drug polymer compatibility study:

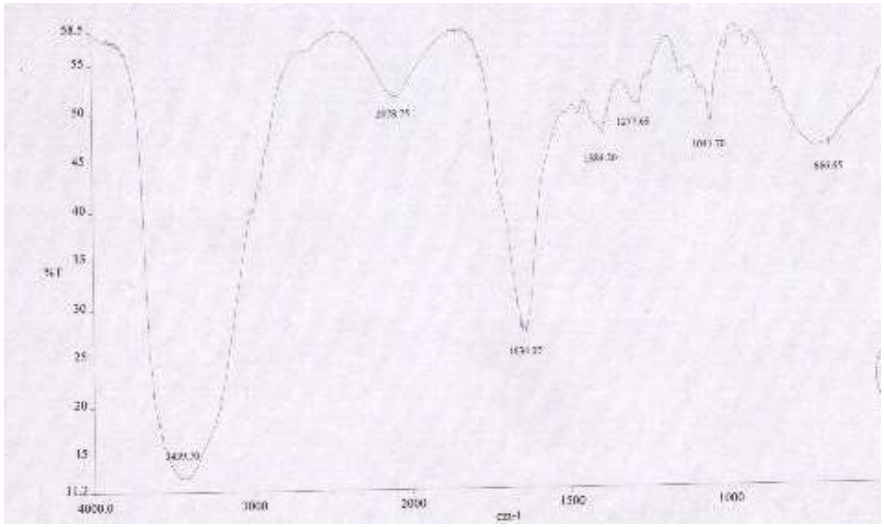
No incompatibility was seen between timolol maleate and excipients.



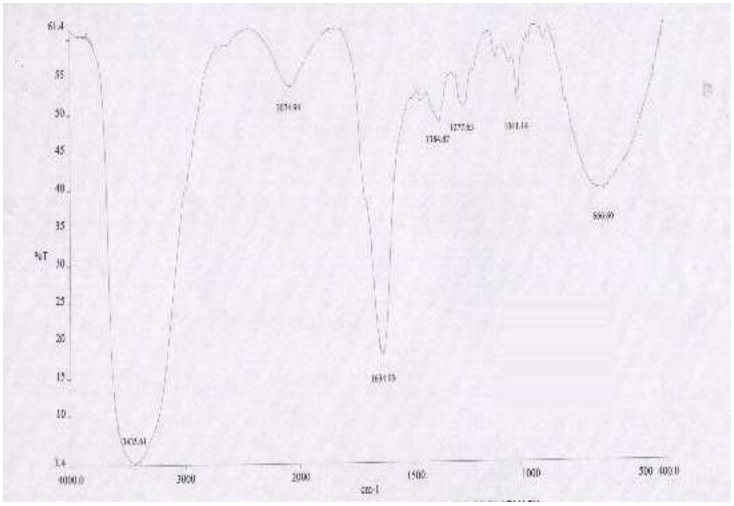
Graph 1: FTIR spectra of binary mixture of (timolol maleate: PVP)



Graph 2: FTIR spectra of binary mixture of (timolol maleate: HPMC



Graph 3: FTIR spectra of binary mixture of (timolol maleate: SCMC)



Graph 4: FTIR spectra of binary mixture of (timolol maleate: Carbopol)

Thickness:

The mean thicknesses of the buccal patch formulations were 0.34– 0.43mm. There was no statically significant difference (P > 0.05) in thickness among the bioadhesive patch formulations**.**

pH of formulation: The pH of formulations were found to be 6.8 - 7.5 which is within the limit of semisolid specifications.

Folding Endurance:

The folding endurance of BP formulations were found to be 296 - 325 The results indicated that all formulations were flexible and soft. This was also supported by mechanical properties of formulations.

Moisture uptake:

Moisture uptake (%) behaviour of buccal patches was found to be 2.94 - 4.13. moisture uptakes of buccal patches were found to be low, which prevents the patches from microbial growth and bulkiness.

Mechanical property of patch:

The tensile strength and percent elongation could be used to describe how the mechanical properties are related to their chemical structure. The tensile strength indicates the maximum tensile stress that the film can sustain. Percent elongation is the maximum change in length of a test specimen before breaking. As amount of PVP increased in every polymer blend, tensile strength and elongation at break were increased. It may be due to formation of inter hydrogen bonding between PVP and HPMC/ SCMC/CP.

Swelling Index:

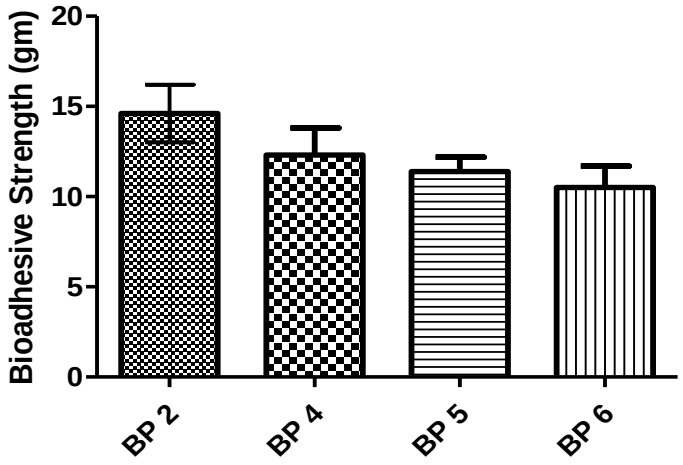
The result showed that addition of PVP predominantly decreased the swelling characteristics of the buccal patches, except for SCMC.

Drug content:

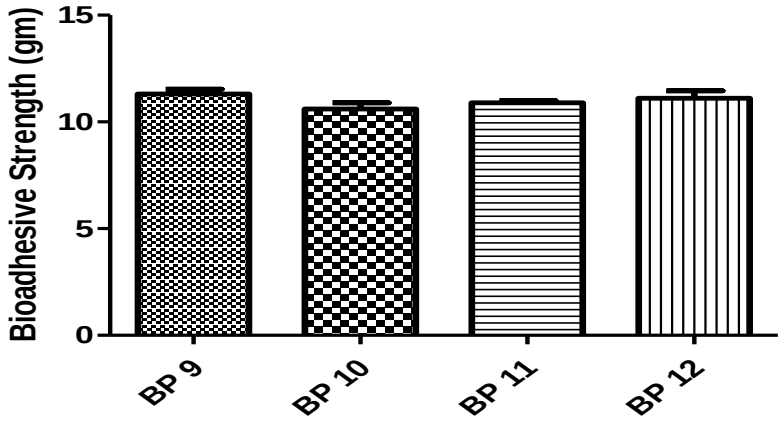
The drug content of the prepared bioadhesive buccal patches were found in the range of 91.456-98.54 % indicating that all formulations with high drug content with no significant difference.

Bioadhesive Strength:

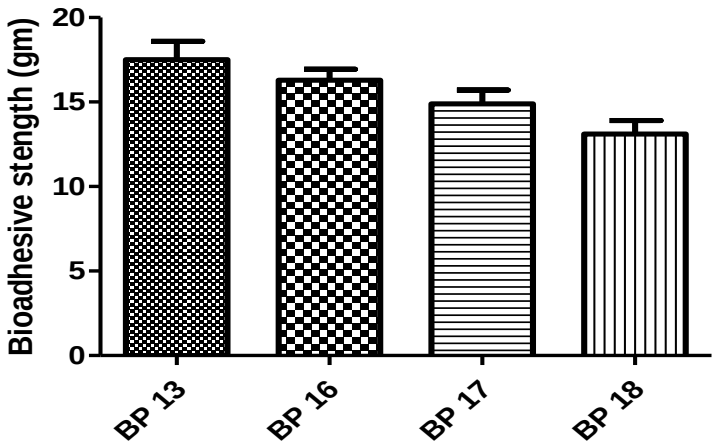
Bioadhesive strength of buccal patches in following order SCMC > Carbopol > HPMC



Graph 5: Bioadhesive strength of buccal patches containing SCMC: PVP



Graph 6: Bioadhesive strength of buccal patches containing HPMC: PVP



Graph7: Bioadhesive strength of buccal patches containing Carbopol: PVP

Bioadhesive strength of buccal patches

In Vitro drug release study:

A marked differences in the timolol maleate release are seen between PVA and the other polymers. PVA showed highest dissolution rate. During dissolution, PVA swelled forming a gel layer on the exposed patch surfaces. The loosely bound polymer molecules were easily eroded, allowing the release of drug in a higher rate compared to the polymers. SCMC and CP 934 showed comparable release behaviour. Referring to the swelling data, both polymers exhibited high swelling. Although the marked increase in surface area during swelling can promote drug release, the increase in diffusional path length of the drug may paradoxically delay the release. In addition, the thick gel layer formed on the swollen patch surface is capable of preventing matrix disintegration and controlling additional water penetration. The release of Timolol maleate from HPMC patches was slower than SCMC and CP 934. The difference in release was attributed to differences in polymer dissolution, HPMC has slower erosion rate.

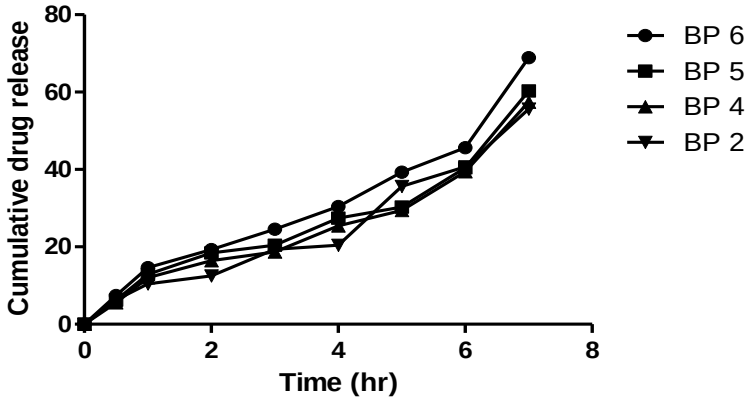


Figure 2: *In Vitro* drug release profile of buccal patches containing SCMC with PVP

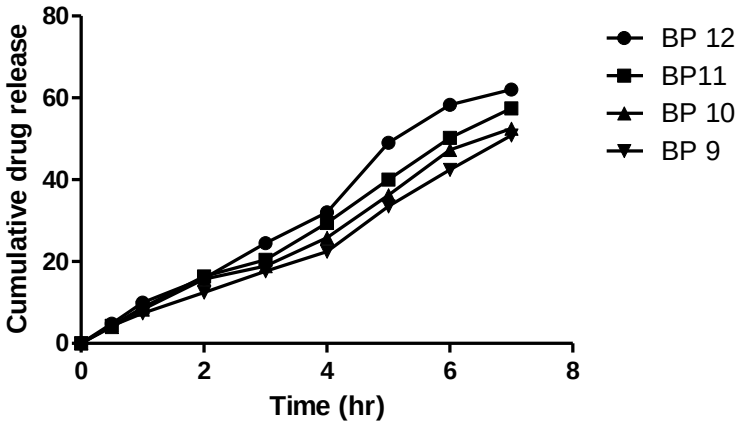


Figure 3: *In Vitro* drug release profile of buccal patches containing HPMC with PVP

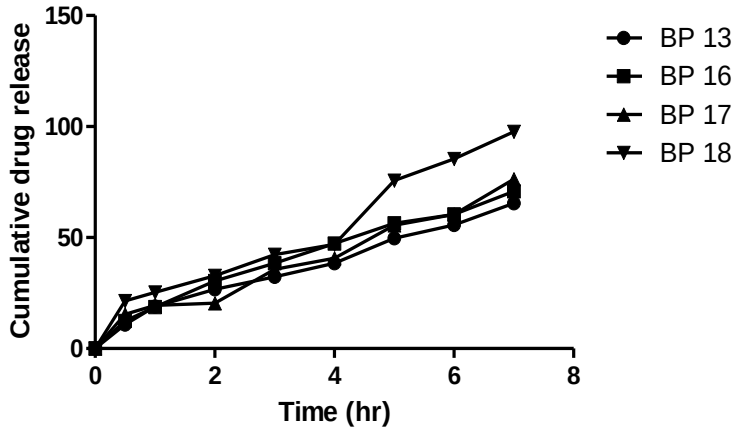


Figure 4: *In Vitro* drug release profile of buccal patches containing CP 934 with PVP

Drug release kinetics:

Bioadhesive buccal patches containing SCMC, HPMC and Carbopol showed a zero order drug release (table 22). For all patches n value of power law is between 0.5 -1 indicated anomalous release. usion F4 shows the best kinetics release rate and dissolution release rate 98.54%.Buccal patch as one of the promising tool for delivery of timolol in order to avoid swallowing problem, improved patient compliance and bioavailability

Table 8: Drug release kinetics of bioadhesive buccal patches

Formulation	Zero order	First order	Higuchi Model	Krossmeyer peppas model	n value
BP 2	0.9382	0.8908	0.8588	0.8960	0.8614
BP 4	0.9219	0.8520	0.8508	0.8928	0.7398
BP 5	0.9123	0.8329	0.8454	0.8908	0.7095
BP 6	0.9335	0.8319	0.8673	0.9152	0.7406
BP 9	0.9790	0.9503	0.9169	0.9756	0.9976
BP 10	0.9840	0.9613	0.9367	0.9776	0.9511

BP 11	0.9903	0.9657	0.9447	0.9843	0.9728
BP 12	0.9827	0.9625	0.9430	0.9785	0.9988
BP 13	0.9919	0.9724	0.9705	0.9741	0.6321
BP 16	0.9898	0.9872	0.9812	0.9978	0.6650
BP 17	0.9733	0.9121	0.9146	0.9025	0.6947

CONCLUSION:

In conclusion F4 shows the best kinetics release rate and dissolution release rate 98.54%.Buccal patch as one of the promising tool for delivery of timolol in order to avoid swallowing problem, improved patient compliance and bioavailability.

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