

# DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL PATCH OF TIMOLOL MALEATE

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## ABSTRACT

**Introduction:** The oral transmucosal Timolol maleate delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver which enhance the bioavailability as well decreases the adverse effect. **Objective:** The present investigation highlights the formulation and evaluation of mucoadhesive buccal patch of Timolol maleate because Timolol maleate has biphasic solubility hence relatively permeated through buccal mucosa, which is well supplied with both vascular and lymphatic drainage. **Material and Method:** The mucoadhesive buccal patches of Timolol maleate were prepared by solvent casting technique using polymers like Hydroxypropylmethyl cellulose-15cps and Polyvinyl pyrrolidone. The formulated films were evaluated for their physicochemical parameters like surface pH, percentage moisture absorption, swelling percentage, thickness, folding endurance and drug content. *In vitro* permeation and *in vitro* release studies were performed with pH 6.8 phosphate buffer solution. **Result and Discussion:** The patches exhibited controlled release for more than 12 h. The *in vitro* release data were fit to different equations and kinetic models to explain release profiles. The kinetic models used were zero order, first order Higuchi's and Peppas's. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation CK2 (3 % HPMC and 1 % PVP). **Conclusion:** Good results were obtained both in physico chemical characteristics and *in vitro* studies in formulation CK2. Hence the formulations of Timolol maleate bioadhesive buccal patch is a promising one as the controlled drug delivery with improved bioavailability.

**Keywords:** Buccal patches, Timolol maleate, Mucosa, Solvent casting technique

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## INTRODUCTION

The buccal region offers an attractive route for systemic drug delivery for extended periods of time. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Over the last two decades mucoadhesion has become a topic of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (with in gastro intestinal tract) or systemic delivery, by retaining a formulation in intimate contact with absorption site (in the buccal cavity). Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time. <sup>[1]</sup> The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver. <sup>[2]</sup> These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. Buccal patch may be preferred over adhesive tablet in terms of flexibility and comfort. In addition they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, the buccal films are able to protect the wound surface, thus

reducing pain and treating oral diseases more effectively. <sup>[3]</sup> Timolol is a  $\beta$ -adrenergic blocker used in the treatment of hypertension, and it is also used in the management of glaucoma, angina pectoris, myocardial infarction and in the prophylaxis of migraine. On oral administration, it undergoes first pass metabolism and also causes gastric problems such as sclerosing peritonitis, retroperitoneal fibrosis, nausea, vomiting, diarrhea, constipation and abdominal cramping. <sup>[4]</sup> Timolol maleate has a molecular weight of 432.5 with biphasic solubility, <sup>[5]</sup> soluble in both aqueous solvents and also in lipids. Thus, it was considered as a potential drug for buccal drug delivery. Various attempts have been made to develop the formulation of mucoadhesive buccal films of Timolol maleate for improving and enhancing bioavailability in a controlled release fashion. It may also be possible to avoid the first pass effect and presystemic elimination in the gastro intestinal tract and liver.

The present investigation highlights the formulation and evaluation of mucoadhesive buccal patches of Timolol maleate. The mucoadhesive buccal patches of Timolol maleate were prepared by

solvent casting technique using polymers of Hydroxy propyl methyl cellulose-15 cps and Poly vinyl pyrrolidone.

## MATERIALS AND METHODS

### Materials

Timolol maleate was a gift sample from Ven Petrochem Mumbai, India. Hydroxy propyl methyl cellulose (15cps) was gifted from Macleod Mumbai, India. Poly vinyl pyrrolidone was procured from Central Drug House of India, New Delhi, India. Methanol, Dichloromethane (RFCL limited, New Delhi, India). All other reagents used were of analytical grade. The films were prepared by Solvent Casting Method

### Fabrication of Timolol Maleate Buccal Patch

The films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate. [6, 7, 8] Composition of a single circular cast film of various formulations is given in the Table 1. The calculated quantities of polymers Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC) and Poly Vinyl Pyrrolidone (PVP) were dispersed in 10ml of mixture of methanol and dichloromethane in ratio 1:1. An accurately weighed 160 mg Timolol maleate was incorporated in polymeric solutions after levigation with propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then this were casted on a glass surface employing 'O' shape ring having 4.2 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried films were separated and the backing membrane used was aluminum foil. Then the formulations were stored in desiccators.

### Surface pH of films

Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petridish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. [9] The mean of three reading was recorded.

### Percentage moisture absorption (PMA)

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. . Agar (5% w/v) was dissolved in hot water, transferred into Petri plates and allowed to solidify. [10] Six patches from each formulation series were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37 °C for one hour over the agar surface. The initial and final weights were recorded and percentage moisture absorption was calculated by using the formula. [11]

$$\% \text{Moisture absorption} = (\text{Final weight} - \text{Initial weight}) / \text{initial weight} \times 100$$

### Swelling Percentage (% S)

A drug loaded films were placed in a thoroughly cleaned petridish and a graph paper was placed beneath the petridish, to measure the increase in area due to swelling of the film. 50 ml of pH 6.8 phosphate buffer was poured into the petridish. An increase in the weight of the patch was noted for 60 min and the weight was calculated. The swelling percentage was calculated by using the following formula. [12, 13]

$$\% S = (\text{Wet weight} - \text{dry weight}) / \text{dry weight} \times 100$$

### Folding endurance

Folding endurance of the film was determined by repeatedly folding one patch at the same place till it broke or folded manually, which was considered satisfactory to reveal good film properties. [14] The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three films.

### Drug content uniformity

A film cut into three pieces of equal diameter was taken in separate 100 ml of pH 6.8 phosphate buffers and continuously stirred for 2 h. The solutions were filtered, suitably diluted and analyzed at 294 nm in a UV Spectrometer. The average of drug content of three films was taken as final reading.

### Mucoadhesive strength

A modified balance method was used for determining the *ex-vivo* mucoadhesive strength. Fresh goat buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The fresh goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 6.8, and held on the left side of the balance. The glass vial with rubber stopper was placed and tightly fitted in the center of glass beaker containing phosphate buffer (pH 6.8, 37-C ± 1°C) just touching the mucosal surface. The patch was stuck to the lower side of the rubber stopper of the glass vial with adhesive. The left and right pans were balanced by adding a 5-g weight on the right hand pan. When the 5-g weight was removed from the right-hand pan, the left-hand pan along with the patch was bowered over the mucosa. The balance was kept in this position for 5 minutes. Water (equivalent to weight) was added slowly at 100 drops/min to the right-hand pan until the patch detached from the mucosal surface. The weight (gram force) required to detach the patch from the mucosal surface gave the measure of mucoadhesive strength. The experiments were performed in triplicate and average values with standard deviation (SD) were reported. [15]

**Tensile Strength and Percentage elongation**

Tensile strength of films was determined using an apparatus fabricated in laboratory. A small film strip (2cm<sup>2</sup>) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly.<sup>[7]</sup>

**Tensile strength =break force /Cross section area of patch**

Percentage elongation determined by noting the distance travelled by pointer before break of the film on the graph paper.<sup>[16]</sup>

**% Elongation = [(increase in length/original length) x 100]/ Original cross section area of patch**

**In Vitro Release Study**

A buccal strip of 1 cm<sup>2</sup> (containing 10 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 45° in a 150 ml beaker containing 100 ml of pH 6.8 buffer preheated to 37°C. The beaker was kept in 37°C 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

**In-vitro permeation studies**

In this study, goat buccal mucosa was used as a barrier membrane. The buccal pouch of freshly sacrificed animal was procured from local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides. It was then washed in isotonic phosphate buffer (pH6.8) and used immediately. The *ex vivo* permeation studies of mucoadhesive buccal films of timolol maleate through an excised layer of goat buccal mucosa were carried out using the Franz diffusion cell. A 1 x 1 cm film of each formulation under study was placed in intimate contact with the excised goat buccal mucosa and the topside was covered with aluminum foil as a backing membrane. A bead was placed in the receptor compartment filled with 15 ml of pH phosphate buffer. The cell contents were stirred with a magnetic stirrer and temperature of 37±1° was maintained throughout the experiment. The samples were withdrawn at every hour, filtered, diluted suitably and then analyzed using UV- spectrophotometer at 294 nm.

**Drug Release Kinetics**

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs. time, first order (Equation 2) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs. square root of time.<sup>[17]</sup>

$$C = K^0 t \quad (1)$$

Where K<sup>0</sup> is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K<sup>0</sup> and intercept the origin of the axes.

$$\text{Log } C = \text{Log } C^0 - kt/2.303 \quad (2)$$

where C<sup>0</sup> is the initial concentration of drug, k is the first order constant, and t is the time.

$$Q = Kt^{1/2} \quad (3)$$

where K is the constant reflecting the design variables of the system and t is the time in hours.<sup>[18]</sup> Hence, drug release rate is proportional to the reciprocal of the square root of time.

**Mechanism of Drug Release**

Drug release were plotted in Korsmeyer et al's equation (Equation 5) as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.<sup>[19]</sup>

$$Mt/M_\infty = Ktn \quad (4)$$

Where Mt/M<sub>∞</sub> is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/ polymer system, and n is an exponent that characterizes the mechanism of release of tracers. If the exponent n =0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n< 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

**RESULTS AND DISCUSSION**

The prepared Timolol maleate muco adhesive buccal patches were evaluated or characterized based upon their physico chemical and mechanical characteristics like surface pH, PMA, swelling percentage, thickness, folding endurance, drug content, tensile strength and mucoadhesive strength as presented in Table 2.

Considering the fact that acidic or alkaline pH may affect or cause the irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films were determined by using suitable means. All the prepared formulations of Timolol maleate buccal patch were in the pH range within the range of salivary pH (6.5 to 6.8). The observed surface pH of the formulation A ,B C , AK1, AK2, BK1, BK2, CK1 and CK2 was

6.56±0.15, 6.66±0.15, 6.68±0.11, 6.65±0.17, 6.63±0.11, 6.67±0.12, 6.69±0.14, 6.72±0.13, and 6.7 ±0.13 respectively. It was found that there was no significant difference of surface pH in all the formulation.

The swelling percentage of the formulated buccal films was observed in pH 6.8 phosphate buffer. Order of swelling index was CK2> BK2> CK1> AK2> BK1> C> AK1 >A>B as presented in Figure 1. Maximum swelling index of patch made by HPMC alone was 78.24± 1.37 and minimum was 69.6± 0.55. Maximum swelling index of patch made by HPMC and PVP was 168±4.42 and minimum was 72.51±0.96, it was shown that HPMC and PVP both have swelling property, as content of HPMC increases, swelling percentage also increases. Addition of PVP increases swelling percentage as can be seen in Figure 1. Ideal buccal film, apart from good bioadhesive strength, should be flexible, elastic and strong enough to withstand breakage due to stress caused during its residence in the mouth. The tensile strength (TS) and elongation at break (E/B) shows the strength and elasticity of the film. A soft and weak polymer is characterized by a low TS and E/B; a hard and brittle polymer is defined by a moderate TS, and low E/B; a soft and tough polymer is characterized by a moderate TS and a high E/B; whereas a hard and tough polymer is characterized by high TS and E/B.<sup>[16]</sup> It is suggested that an ideal buccal film should have a relatively high TS and E/B.<sup>[20]</sup> The results of the mechanical properties are presented in Table 2. TS increased with the increase in polymeric content but E/B values decreased with the increase in HPMC polymer content but E/B increased with addition of PVP. Order of tensile strength was CK2 >BK2 >CK1 >AK2 >BK1 >C >AK1 >B >A as seen in Figure 2. This shows that addition of PVP increases tensile strength. Maximum TS was exhibited by CK2 patch (5.1±1.23 kg.mm<sup>-2</sup>) and minimum was exhibited by A (1.26 ±0.24kg.mm<sup>-2</sup>). Order of E/B is A> AK1 >B >AK2 >BK2 >BK1 >CK2 >CK1 >C Maximum E/B was seen with AK2 and the least was observed with C. Tensile strength values indicate that there is no statistically significant difference (p < 0.05) between the next immediate formulations. But statistically significant difference was observed in elongation at break values between the next immediate formulations as shown in Figure 2.

The film thickness was observed by using digital vernier caliper and was found to be in the range of 0.183±0.02mm to 0.31±0.35mm as presented in Table 2. As concentrations of polymer HPMC increases, the viscosity of casting solution also increases which is responsible for increase in thickness. The folding endurance was found to be highest for formulation CK2 (328±26.45) and the lowest for formulation A (186±7.211). It was found that the folding endurance was increased with the addition of PVP with HPMC and increase in the percentage of HPMC (B 254±10.55, A 186±7.211). The observed results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 98±1 to 100±0.057. In case of Patch A, the percent recovery was relatively low which may be due to less percentage of HPMC.

*In vitro* bioadhesion measurements are routinely performed for mucoadhesive dosage forms and, most commonly used technique for evaluation of buccal patches is the measurement of adhesive strength. Work of adhesion, is a measure of work that must be

done to remove a patch or film from the tissue. Peak detachment force is the maximum applied force at which the patch detaches from tissue. Order of mucoadhesive strength was CK2> CK1> C> BK2> BK1> AK2> B> AK1> A which shows that mucoadhesive strength increases with amount of bioadhesive polymer HPMC.

*In vitro* drug release studies were performed for all the prepared formulation by using phosphate buffer pH 6.8 as dissolution medium and measuring drug concentration by UV spectrophotometrically at 294 nm. The studies were performed up to 12 h. Distinguishable difference was observed in the release of Timolol maleate containing HPMC and PVP. The graph was plotted by taking Cumulative percentage release Vs Time and the graphs were shown in the Figure 3. The cumulative percentage drug release was observed in the formulation C, AK2, BK2 and CK2 after 12 hour was found to be 98.76%, 94.78%, 92.27% and 92.02% respectively. The cumulative percentage drug release was observed in the formulation AK2 and BK2 after 12 hour was found to be 94.78 % and 92.27 % respectively. The observed results were indicate that use of HPMC alone show maximum release characteristics in the formulation C due to hydration and excessive swelling percentage of polymer. But addition of PVP may retard the release of drugs may be due to increase in bioadhesion property of polymer. Formulations CK2 retards the release rate and was selected as optimized formulation as it has maximum tensile strength and mucoadhesive strength.

The zero-order rate (Equation 1) describes the systems where the drug release rate is independent of its concentration. Figure 3 shows the cumulative amount of drug release vs time for zero-order kinetics. The first order (Equation 2), which describes the release from systems where the release rate is concentration dependent, is illustrated by Figure 4, which shows the log cumulative percent drug remaining vs. time. Higuchi's model (Equation 3) describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. Figure 5 illustrates the Higuchi square root kinetics, showing the cumulative percent drug release vs. the square root of time. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R<sup>2</sup>) was determined as given in Table 3.

It was found that the *in vitro* drug release of Timolol maleate buccoadhesive patch was best explained by zero order as in Figure 3 and peppas model as in Figure 6, as the plots showed the good linearity. The correlation coefficient values (R<sup>2</sup>) indicate the kinetic of drug release was of zero order and the mechanism of drug release was by peppas plot indicates the super case II transport evidenced with diffusion exponent values (n) as seen in Table 3.

## CONCLUSION

The Timolol maleate buccal films were prepared by the method of solvent casting technique, using polymers Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC) and Poly Vinyl Pyrrolidone (PVP). They dispersed in ethanol and dichloromethane and 50 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The prepared Timolol maleate buccal

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patches were evaluated or characterized based upon their physico chemical and mechanical characteristics like surface pH, PMA, swelling percentage, thickness, folding endurance, drug content, tensile strength and mucoadhesive strength. The release rate of Timolol maleate from buccal patch was significantly affected by the type and changes in the polymer mixing ratios. Lower release rates were observed by mixing the amount of PVP in HPMC containing formulations buccal patch. Tensile strength as well as mucoadhesive strength is increased with addition of PVP in HPMC formulation of patch. Good results were obtained both in physico chemical characteristics and *in vitro* studies in formulation CK2. Hence the formulations of Timolol maleate bioadhesive buccal patch is a promising one as the controlled drug delivery, improve bioavailability.

### ACKNOWLEDGEMENT

We wish to thank Ven PetroChem India, for providing gift sample of Timolol maleate. We are also grateful to the Management of Raj Kumar Goel Institute of Technology, Ghaziabad for providing facility to complete this project.

### CONFLICT OF INTEREST

Authors do not have any conflict of interest.

**Table 1: Composition of Timolol Maleate Buccal Patches**

Ingredients	A	B	C	AK1	AK2	BK1	BK2	CK1	CK2
Timolol Maleate(mg)	192	192	192	192	192	192	192	192	192
HPMC	2%	2.5%	3%	2%	2.5%	2%	2.5%	3%	3%
PVP	--	--	--	0.5%	1%	0.5%	1%	0.5%	1%
Propylene Glycol (5% w/w of dry weight of polymer)	50	50	50	50	50	50	50	50	50

**Table 2- Different Evaluation Parameter**

Batch	T <sub>±SD</sub> (in mm)	PMA <sub>±SD</sub>	S.P. <sub>±SD</sub>	T.S. (kg/mm <sup>2</sup> )	E % (mm <sup>2</sup> )	F.E.	M.S. <sub>±S.D.</sub>	% Drug content <sub>± S.D.</sub>
A	0.183 <sub>±0.02</sub>	Deformed	69.90 <sub>±0.85</sub>	1.26 <sub>±0.24</sub>	2.4	186	6	98 <sub>±1</sub>
B	0.194 <sub>±0.019</sub>	Deformed	69.6 <sub>±0.55</sub>	2.30 <sub>±0.46</sub>	1.74	254	6.4	99.92 <sub>±0.11</sub>
C	0.0236 <sub>±0.025</sub>	20.72 <sub>±1.76</sub>	78.24 <sub>±1.37</sub>	3.4 <sub>±0.67</sub>	1.2	296	7.2	99 <sub>±0.5</sub>
AK1	0.187 <sub>±0.02</sub>	15.37 <sub>±1.20</sub>	72.51 <sub>±0.96</sub>	2.45 <sub>±0.64</sub>	1.9	242	6.2	97.5 <sub>±1.2</sub>
AK2	0.205 <sub>±0.008</sub>	16.45 <sub>±1.21</sub>	131.23 <sub>±3.35</sub>	4.2 <sub>±1.1</sub>	1.48	285	6.7	99 <sub>±0.55</sub>
BK1	0.224 <sub>±0.023</sub>	18.72 <sub>±1.57</sub>	98.94 <sub>±2.25</sub>	3.68 <sub>±0.87</sub>	1.32	282	6.9	99 <sub>±0.8</sub>
BK2	0.245 <sub>±0.026</sub>	28.2 <sub>±5.2</sub>	152.74 <sub>±3.48</sub>	4.78 <sub>±1.14</sub>	1.37	300	7.05	99.5 <sub>±0.24</sub>
CK1	0.28 <sub>±0.031</sub>	35.25 <sub>±5.5</sub>	139.76 <sub>±2.28</sub>	4.4 <sub>±1.5</sub>	1.28	>300	7.5	100
CK2	0.31 <sub>±0.35</sub>	39.78 <sub>±6.2</sub>	168 <sub>±4.42</sub>	5.1 <sub>±1.23</sub>	1.29	>300	8.2	100

SD= Standard Deviation (n=3), PMA= Percent Moisture Absorption, M.S. = Mucoadhesive Strength, T.S= Tensile Strength, S.P. = Swelling Percentage, F.E. = Folding Endurance, T= Thickness, E= Elongation.

Table 3-Release kinetics

Batch	Zero Order		First Order		Higuchi		Korsmeyer-Peppas		
	R <sup>2</sup>	K <sub>0</sub> (h <sup>-1</sup> )	R <sup>2</sup>	K <sub>1</sub> (h <sup>-1</sup> )	R <sup>2</sup>	K <sub>H</sub> (h <sup>-1/2</sup> )	R <sup>2</sup>	n	K <sub>KP</sub> (h <sup>-n</sup> )
C	0.98	8.23	0.79	0.004	0.87	4.2	0.97	1.07	0.06
AK2	0.98	7.89	0.88	0.002	0.88	4.04	0.97	1.12	0.06
BK2	0.97	7.69	0.86	0.002	0.86	3.87	0.98	1.16	0.05
CK2	0.97	7.50	0.86	0.002	0.86	3.76	0.99	1.24	0.04

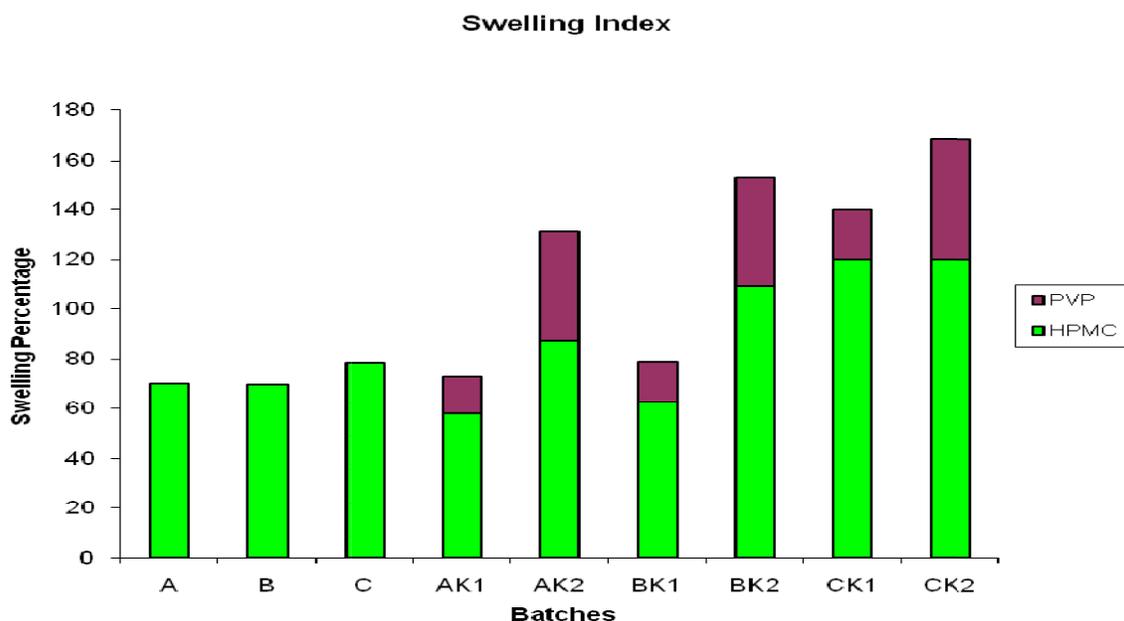


Figure 1: Swelling index of batches A, B, C, AK1, AK2, BK1, BK2, CK1 and CK2.

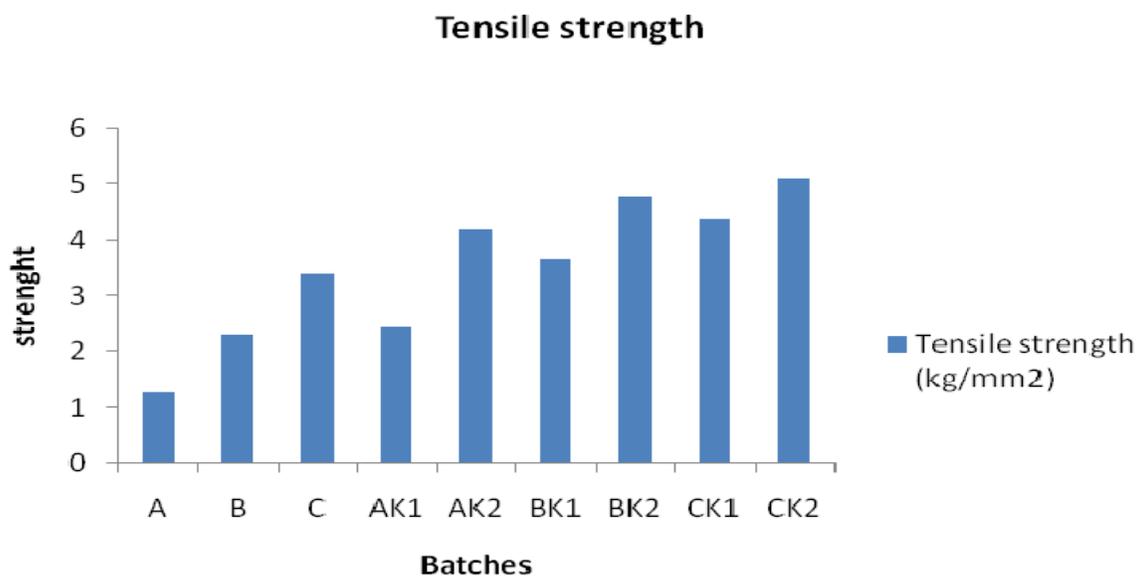


Figure 2: Tensile Strength of batches A, B, C, AK1, AK2, BK1, BK2, CK1 and CK2.

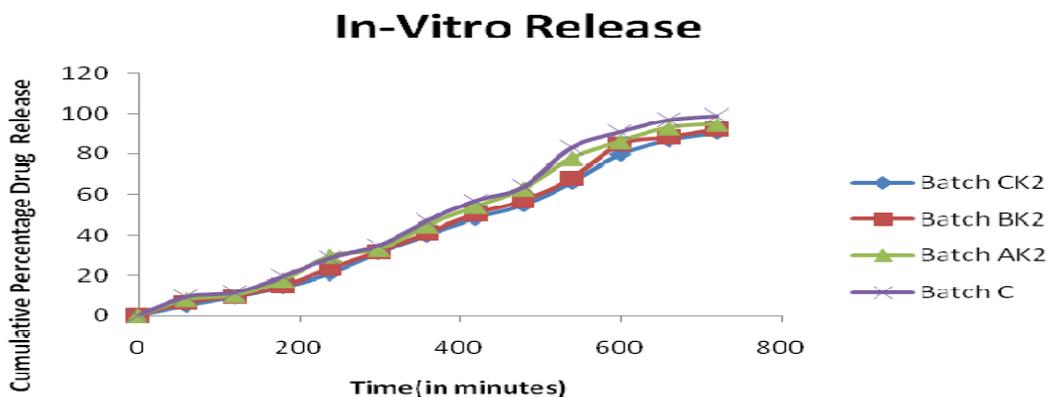


Figure 3: Zero order plot of in vitro drug release profile of batches C, AK2, BK2 and CK2 between Percent Cumulative drug releases vs. Time

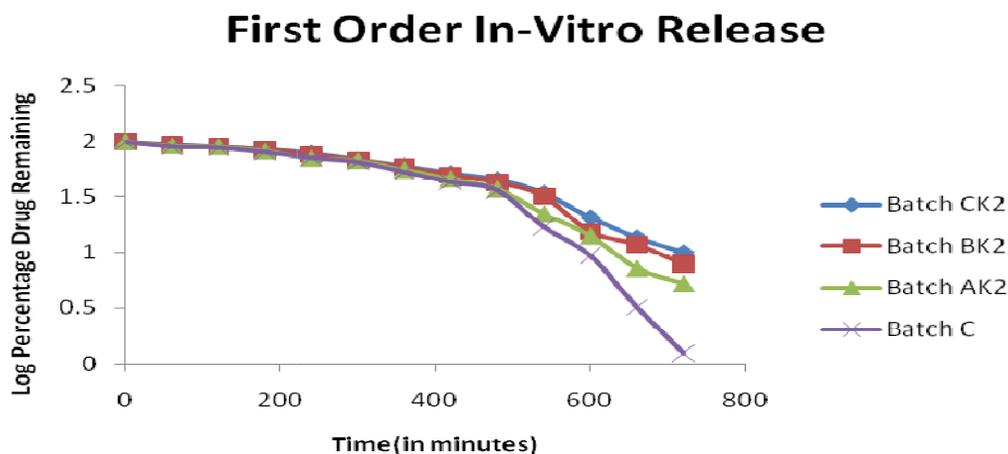


Figure 4: First Order kinetics of in vitro drug release profile of batches C, AK2, BK2 and CK2 between log % drug remaining vs. Time

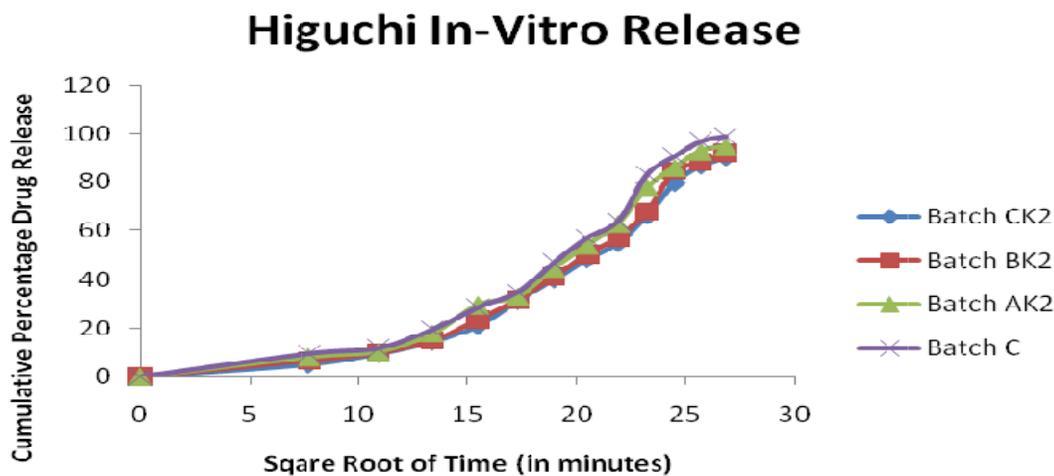


Figure 5: Higuchi plot of in vitro drug release profile of batch C, AK2, BK2 and CK2 between cumulative % drug releases vs. root square of time

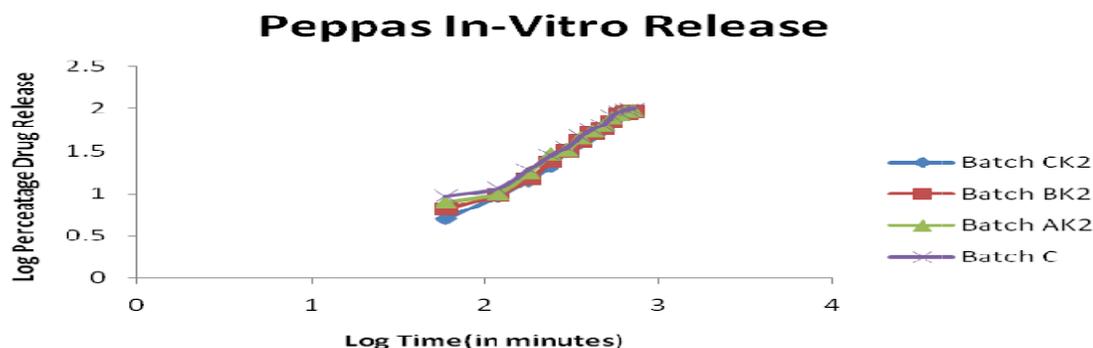


Figure 6: Kinetics of in vitro drug release profile of batches C, AK2, BK2 and CK2 between log % cumulative drug releases vs. log time.

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