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Full Length Original Research Paper

Formulation and Characterization of Prochlorperazine films for Buccal Delivery

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Abstract:
The buccal region offers an attractive site of administration of drugs for systemic use. A buccal drug delivery system was developed for Prochlorperazine, a dopamine D_2 receptor antagonist with antiemetic property using HPMC (15 and 47 cps), ethyl cellulose, and PVP. The prepared patches were characterized by means of film thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, percentage moisture loss, tensile strength, percentage elongation, surface pH, *Invitro* studies, *exvivo* mucoadhesion studies and *Invivo* absorption studies to determine the amount of drug release from selected films. *In vitro* release studies of drug-loaded patches in phosphate buffer solution (pH, 6.6) exhibited drug release in the range of 35.64 to 72.33% in 30 min. *In vivo* studies on rabbits showed 80.40% of drug absorption from the patches containing HPMC and PVP as a polymer. Good correlation among *in vitro* release and *in vivo* studies was observed. Short-term stability study on the films revealed no significant changes in drug content and release studies after 4 weeks. The findings suggest that the present prochlorperazine maleate containing buccal film could be potentially useful to control the emesis induced by anti-cancer agents or opioid analgesics in patients who limit the oral intake.

Keywords: Buccal Films, prochlorperazine maleate, Dopamine receptor, emesis

Introduction

It has been reported that approximately 70% of patients with advanced cancer complain of pain and about half of them have severe symptom that require medication with strong opioid analgesics.[1,2] Opioid compounds have a potent and effective analgesic action but have several adverse reactions, including constipation and nausea / vomiting.[3,4] Nausea and vomiting is known to be elicited in 30–50% of strong opioid analgesic users. Dopamine D_2 receptor antagonists such as prochlorperazine are effective in suppressing opioid analgesic-induced nausea and vomiting. Therefore, the prophylactic medication with dopamine D_2 receptor antagonists is recommended for prevention of nausea and vomiting associated with strong opioid analgesics. Moreover, D_2 receptor antagonists are often used for ameliorating chemotherapy-induced nausea and vomiting in patients who experienced uncontrolled emesis regardless of the conventional premedication regimen such as the combination of 5-HT3 receptor antagonists and dexamethasone.[5,6,7,8] However, the emetic symptoms those appear in such uncontrolled patients often results in dysphagia or difficulty in oral intake.

Retention of an administered antiemetic oral dose and its subsequent absorption during therapy is critically affected by recurrent emesis, a process coordinated by vomiting centre in the lateral reticular formation of the medulla receiving inputs from the chemoreceptor trigger zone and other neural sites. Retention of oral dose is prerequisite for absorption to prevent emesis.[9] The problem of non-retention of administered antiemetic can be overcome by using oral-transmucosal route in

patients with dysphagia or aphagia. [10] The buccal route and buccal dosage forms have the advantage of allowing excellent accessibility, reasonable patient acceptance and compliance avoids first pass metabolism and involves relatively robust mucosa and utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration. Hence, for the patients who limit the oral intake, Prochlorperazine maleate containing buccal film were developed which can be a potential dosage form to control emesis induced by Anti-cancer agents.

Materials and Methods

Prochlorperazine Maleate was received from Nicholas Piramal, Mumbai, India as a gift sample. HPMC, Ethyl cellulose, PVP were purchased from SD fine-chemicals limited, Mumbai. Glycerin, Tween 80 were purchased from Loba chemie, Mumbai. All other reagents and chemicals used were of analytical grade.

Preparation of Buccal Mucoadhesive Films

The solvent casting method was followed in this study for preparation of films. Buccoadhesive films were prepared using polymer HPMC (15cps and 47cps) along with the drug PCZ and a suitable solvent. Weighed quantity of HPMC was taken in boiling tube. To this ethanol was added and vortexed. Sufficient care was taken to prevent the formation of lumps. Further ethanol was added to the above polymer solution and dispersion was vortexed followed by the addition of three drops of glycerin. The boiling tube was set-aside for 6 hours to allow the polymer to swell. Prochlorperazine maleate was dissolved in ethanol and in one drop of tween 80 separately. This drug solution was added to the polymer solution and mixed well. It was set-aside for some time to exclude any entrapped air and finally the drug-polymer solution was poured into the glass moulds. Drying of these patches for 8 hrs was carried out in oven placed over a flat surface.

The patches formed were removed carefully, placed in vacuum oven and vacuum was applied to remove traces of solvent if any. They were stored in desiccators till the evaluation tests were performed. The composition of the patches is given in table 01.

Formulated patches were then subjected to the weight and thickness uniformity, swelling studies, percentage moisture loss, surface pH, folding endurance and tensile strength, content uniformity test and in-vitro release studies.

Weight Uniformity

For evaluation of films, 1 sq.cm. each of every formulation were taken and weighed individually on a digital balance .The average weights were calculated.

Thickness:

The thickness of the film was measured using digital vernier calliper with a least count of 0.01 mm at different spots of the films. The thickness was measured at ten different spots of the film and average was taken. [11]

Determination of swelling index

A 10 ml aliquot of phosphate buffer pH 6.6 was poured over the glass assembly containing the optimized buccoadhesive film. The glass assembly was stored at room temperature. After 5, 10, 20, 30, 45and 60 minutes, the films were removed and the excess water on their surface was carefully removed using filter paper. Swelling index of the buccoadhesive at respective time points was calculated employing an equation below.

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$$Swelling\ index = \frac{T_t - T_0}{T_0} \times 100$$

Where, T_t is the thickness of the film at time't' and T_0 is the initial thickness of the film. [12]

Similarly, a graph paper was placed beneath the glass assembly, to measure the increase in the area. Ten ml of phosphate buffer solution, pH 6.6, was poured into the glass assembly. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the increase in area was calculated.

Surface pH

The films used for determination of swelling index were used for determination of their surface pH using universal pH paper. The mean of three readings was recorded. [13]

Folding Endurance

Folding endurance of the films was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good film properties. 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 on five films. [14]

Drug Content Uniformity

Three film units 1 sq.cm. each of every formulation were taken in separate 100 ml volumetric flasks, and 100 ml of phosphate buffer pH 6.6 was added, continuously stirred for 1h. Similarly, a blank was carried out using a drug free patch. The solutions were filtered and absorbance was measured in UV-spectrophotometer at 277nm. [15, 16]

Percentage Moisture Loss

Percentage moisture loss is carried to check the integrity of films at dry condition. Percentage moisture loss was determined by keeping the patches in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out, re-weighed and the percentage moisture loss was calculated using the following formula,

Percentage Moisture Loss = ((Initial weight – Final weight)/ Initial weight) x 100

Viscosity

The Viscosity of the ethanolic solutions containing both polymer and plasticizer was determined. A Brookfield viscometer (LVDV-E model) attached to the helipath spindle number 18 was used. The viscosity was measured at 60 rpm at room temperature. The recorded values are the mean of three determinations. [16]

Determination of Mechanical Properties

Tensile strength and percentage elongation of the films were determined with universal strength testing machine. The sensitivity of the machine was 1gm. It consists of two load cell grips. The lower one was fixed while the upper one was movable. The test film of specific size was fixed between these cell grips and force was gradually applied till the film was broken. The tensile strength of the films was taken directly from the dial reading. The percentage elongation of the films was calculated by applying the following equation, [13]

Percentage elongation = (Increase in length/ Original length) x 100

In Vitro Release Studies

The release of PCZ from the prepared bioadhesive patches into phosphate buffer pH 6.6 at 37 ± 0.5 °C was performed using a special modified Levy method. [17] Each bioadhesive film was adhered to the side wall of a vessel (100 ml beaker) using cyanoacrylate. [18] Adequate sink conditions were provided by placing 50 ml of phosphate buffer pH

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6.6 in each vessel. Each covered vessel was fitted with a magnetic stirrer rotating at a rate of approximately 150 rpm. After time intervals each of 5, 15, 30, 60, 90, 120, 180, 240 and 300 minutes., 3 ml sample was withdrawn, filtered through a millipore filter of 0.45 µm pore size and assayed spectrophotometrically at λmax 277 nm. Immediately after each sample withdrawal, a similar volume of phosphate buffer pH 6.6 was added to the release medium to maintain the volume in the vessel constant. The absorbance of the polymeric additives was negligible and did not interfere with λmax of the drug. The release data were kinetically analyzed using different kinetic models to determine the mechanism of drug release from the different mucoadhesive systems.

Ex Vivo Mucoadhesion Time

The residence time for the formulation, that is, the time taken for the film to detach or erode completely from the mucosa was measured ex vivo, by application of the film on freshly excised porcine buccal mucosa. The porcine mucosa was cut to an appropriate size of a 3 cm x 3 cm patch and fixed on the internal side of a beaker with cyanoacrylate glue. The film was first wetted with 50 mL of phosphate buffer and attached to the porcine buccal tissue by applying light pressure with a finger tip for 20 seconds. The beaker was filled with 200 ml phosphate buffer and kept at 37° C on a magnetic stirrer. After 2 minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and during the test, the time taken for the film to completely erode or detach from the mucosa was observed as the ex vivo mucoadhesion time.

In Vivo Absorption Studies:

In vivo absorption studies were conducted for the selected formulation patch V based on its invitro and exvivo performance using rabbits. Three male rabbits weighing 2.0 to 4.0 kg were selected for the invivo release study of the PCZ. The animals were fasted for overnight with *adlibitum*.[12] The rabbits were anesthetized with combination of phenobarbital sodium IP and ketamine hydrochloride (30 mg/kg) by *i.p.* route. The selected patch of size 1 x 1 sq.cm were cut and fixed on a cellophane paper which acts as a backing layer so that the drug release was made unidirectional and thread was tied to it, so that the patches can be easily removed from the buccal cavity. After 10 min of the anaesthetic injection, the patches were placed (separately) in the buccal cavity one at a time. The patches were taken out at 10, 20, and 30 min (Patch V). The patches were dissolved in 10 ml of phosphate buffer solution, pH 6.6. The drug present in the patch represents drug remain unabsorbed which was analysed by measuring its absorbance at 277 nm using phosphate buffer solution, pH 6.6 as blank. The process was repeated three times to validate the results.

Ageing

Optimized medicated selected patches were subjected to stability testing. Patches were placed in a glass beaker lined with aluminium foil and maintained at 40 ± 2 °C and 75 ± 5% RH for 1 month as per ICH guidelines. Apart from this the patches were also exposed to room conditions for 4 weeks. Changes in the appearance and drug content of the stored patches were investigated after storage. [19]

Results and Discussion:

Physical Characteristics of Patches

The patches were translucent, having good strength, and visually smooth surface. The drug and polymer distribution was uniform.

Thickness, Weight uniformity, Surface pH, and Folding endurance of films:

All the drug-loaded films had almost uniform thickness ranging from 0.2018 to 0.2272 mm and the films weight ranged from 14.6833 to 22.8500 mg. The surface pH of all prochlorperazine maleate patches was within ± 0.3 units of the neutral pH and hence no mucosal irritation is expected. Ultimately patient compliance is achieved. Films did not show any cracks even after folding for more than 300 times. Folding endurance did not vary when the comparison was made between plain films and drug-loaded films. The results are given in the Table 02.

Swelling studies

This study determines the extent of water uptake or the degree of hydration by the hydrophilic polymers used in the fabrication of the films. Most of the mucoadhesive polymers undergo some degree of swelling after hydration, which is necessary to initiate intimate contact of the film with the mucosal surface. Weight and area increase due to swelling of 6 patches were studied. The entire data are shown in the Figure 1 and in Figure 2 respectively. The Study shows patch V and I containing HPMC (15 cps) have more pronounced swelling. Swelling in terms of weight, Patch IV shows least swelling, possibly due to the presence of ethyl cellulose in formulation. Swelling in terms of area was found more pronounced in patch V and VI which contain HPMC and PVP. These results can be contributed by the concept that due to swelling there is increase in weight. Similarly, Patch IV showed least increase in area due to swelling due to the ethyl cellulose.

Mechanical Properties of Films:

Tensile strength was determined and is depicted in the Figure 3 which indicates that the tensile strengths of drug loaded patches were higher than blank patches. This is justified because prochlorperazine maleate is slightly soluble and is strengthened by the bonding of polymer chains. The tensile strengths of drug loaded patches are in the order of IV >II >III >I >VI > V. This indicates HPMC chains produce effective cross-linking with ethyl cellulose. Among all the patches studied, patch IV showed highest tensile strength and patch V showed lowest tensile strength. This may be contributed due the hydrogen bonding between drug and polymer. While the order of percentage elongation for the blank and drug loaded films in the Figure 4 follows the order as IV > III > II > I >VI > V and also shows that the percentage elongation of drug loaded patches were higher than blank patches. prochlorperazine is slightly soluble and strengthened the bonding of polymer chains which may be attributed due to hydrogen bonding between drug and polymer. HPMC chains produce effective cross-linking. Among all the patches studied patch IV showed higher percentage elongation and patch V showed lower percentage elongation.

Percentage moisture loss:

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. The capacity of the film to give away water is an important intrinsic parameter of the polymeric system in consideration to the release of drug. The data presented in Table 02 reveals that

percentage moisture loss is least in patches III and IV as these contain water insoluble polymer ethyl cellulose. However, patches I and II exhibited highest loss due to presence of water soluble polymer HPMC. In patches III and IV the loss decreased compared to patches I and II because of the replacement of a part of HPMC by PVP.

Content uniformity of prochlorperazine maleate patches:

The results of amount of drug present in patches are expressed as AM ± SD and reported in the Table 02. The results indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 80.26 to 88.72. All the formulations showed more than 80% of the drug loading indicating much of the drug is not lost.

Viscosity:

Viscosity of polymer solutions was determined in LVDV-E Brookfield viscometer. Solutions of polymers were prepared same as those used for the preparation of films (working concentrations). The viscosities of the solutions are as shown in Table 03. Viscosity of film IV was high when compared to others. It could be because of ethyl cellulose using as co-polymer where as viscosity is least in film I probably due to dispersion of polymer in ethanol. However there is a need to explore the relation between viscosity and other properties of films.

***In Vitro* Release Studies**

Figure 5 shows the cumulative drug release profiles of PCZ films containing various ratios of polymer HPMC and PVP. *Invitro* release studies of prochlorperazine maleate patches were carried out in phosphate buffer solution, pH 6.6. It is apparent from the graph that the release of prochlorperazine maleate decreased when the viscosity of HPMC is increased. Ethylcellulose retarded the release rate of drug from HPMC patches (patches III and IV) while the PVP in the films increased the drug release rate from HPMC films. This result of drug release can be correlated with the percent moisture loss. Percent moisture loss is an indication of the capacity of polymer to retain moisture content. More the moisture retention in the patches more could be the tendency of drug release. It was found viscosity of the polymer also has its influence on the drug release rate. If the viscosity of the polymeric solution is more, then drug release rate will also be more.

Kinetics of Drug Release (Zero and First Order) and Release Mechanisms

Data of in vitro drug-release were fit into different equations and kinetic models to explain the release kinetics of prochlorperazine maleate from these patches. The Table 04 indicates that the regression values are higher with zero order and therefore the release kinetics of prochlorperazine maleate followed zero order from all the patches.

To understand the release mechanisms of prochlorperazine maleate, the data of *in vitro* drug release were fit into Higuchi's model and Hixon-Crowell cube root law model. The data of *in vitro* drug release from the patch V are fit into the models specified. The equations generated for all the patches are shown in the Table 04. Application of Hixon – Crowell cube root law, the equation $(M_0^{1/3} - M^{1/3}) = kt$,provides information about the release mechanism, namely dissolution rate limited. Application of Higuchi's equation ($M = K\ t^{1/2}$) provides information about the release mechanism, namely diffusion rate limited.

Perusal to Table 04 indicates that R^2 values are higher for Higuchi's model compared to Hixon – Crowell for all the patches. Hence prochlorperazine maleate release from the all the

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patches followed diffusion rate controlled mechanism.

In vivo Absorption of PCZ in Rabbit Buccal Mucosa from Patches

Patch V was selected for the *in vivo* studies out of six formulations on the basis of *in vitro* release rate. The *in vivo* absorption studies were conducted on rabbits for the patches V. The method used for this purpose was the measurement of disappearance of the drug from the patches. Data was recorded and each recording was an average of three determinations. About 84.59% of PCZ was absorbed from patch V within 30 min which is shown in Figure 6.

Kinetics of Absorption of PCZ through Rabbit Buccal Mucosa

The absorption data for PCZ were processed into graphs in Figure 7 to understand the linear relationship i.e., kinetic principles. The data were processed for regression analysis and equation. A perusal to the graph indicates that the buccal absorption of PCZ from rabbit buccal mucosa followed first order from patch V.

In Vitro In Vivo Correlation: *In vitro* release vs. *in vivo* rabbit buccal absorption of PCZ from patch V

The concept of *in vitro - in vivo* correlation has been extensively used by pharmaceutical scientists. *In vitro* release studies and their correlation with *in vivo* studies will be helpful to predict therapeutic efficiency of the dosage form. So correlation between *in vitro* release behavior of a drug and it's *in vivo* absorption in rabbits must be demonstrated experimentally to reproduce therapeutic response.

The relevant data were taken from the *in vitro* release and *in vivo* buccal absorption for the patch V. The data obtained were recorded and were regressed using MS-Excel statistical program. A perusal to the Figure 8 indicated good correlation (R^2 = 0.996) for patchV.

Ageing

Optimized medicated patches were subjected to short term stability testing. Patches were placed in a glass beaker lined with aluminium foil and maintained at 40 $\pm$ 2 °C and 75 $\pm$ 5% RH for 1 month as per ICH guidelines. Apart from this, the patches were also exposed to room conditions for 1 month. The patches were observed for their appearance and texture. These properties did not change during the period of the study. The appearance and texture was retained. Changes in the drug content of the stored patches were investigated during storage. The data presented were the mean of three determinations. Percentage drug present in the patches was determined spectrophotometrically and represented in the Figure 9 and Figure 10. Percentage decrease in drug content in all the patches was also calculated and represented in the Figure11 and 12 . Perusal to the Figures it is indicated that the drug loss is less though the patches were stored for one month. Further there is a need of accelerated stability testing of these dosage forms to determine their shelf life. Buccal mucoadhesive patches containing PCZ showed satisfactory characteristics without being drastically influenced by ageing.

Conclusion:

This study demonstrated that prochlorperazine maleate could be successfully delivered in buccal films. These films met various criteria revealing excellent stability and dissolution profile. The films exhibited satisfactory characteristics regarding to integrity, flexibility, dispersion of drug, and other quality control parameters. The release

kinetics indicated zero order release from all the patches. R^2 values are higher for Higuchi's model compared to Hixon – Crowell model for all the patches. Hence prochlorperazine release from the patches followed diffusion rate controlled. The *in vivo* buccal absorption kinetics in rabbits indicated that about 80.40% of the drug was absorbed in 30 min from the patch V. The absorption kinetics was studied by regression analysis (R^2 =0.999). The absorption of prochlorperazine followed first order.

The results can be extrapolated to the human beings as the structure and permeability of buccal membrane of rabbits is similar to that of human beings. Hence the development of bioadhesive buccal formulations for prochlorperazine may be a promising one as the dose of prochlorperazine may be decreased and hence side effects may be reduced. This study could be further extended to explore the different possibilities of developing the dosage forms and enhancing the bioavailabilty of prochlorperazine maleate for the treatment of chemotherapy induced nausea and vomiting.

Table 1: Composition of different mucoadhesive formulations containing prochlorperazine maleate

Contents**	Formulation					
	I	II	III	IV	V	VI
Prochlorperazine maleate	150	150	150	150	150	150
HPMC, 15cps	250	*	200	*	200	*
HPMC, 47cps	*	250	*	200	*	200
Ethyl cellulose	*	*	50	50	*	*
PVP	*	*	*	*	50	50
Ethanol	8	8	8	8	8	8

**All the ingredients are in mg except ethanol which was taken in ml
HPMC = Hydroxypropyl methylcellulose; PVP = Poly vinyl pyrrolidone

Table 2: Physical Characterization of buccoadhesive formulations of PCZ

Patch Code	Average thickness (mm) AM ± SD	Weight Uniformity (mg) AM ± SD	Moisture loss (%) AM ± SD	% Drug present	Folding Endurance
I	0.2018 ± 0.0026	14.6833 ± 0.2926	9.6679 ± 0.5014	84.86 ± 0.3415	> 300
II	0.1951 ± 0.0040	16.2330 ± 0.3076	8.6637 ± 0.6774	80.26 ± 0.3918	>300
III	0.2125 ± 0.0053	20.5000 ± 1.3236	5.9883 ± 0.6583	88.72 ± 4.3960	>300
IV	0.2272 ± 0.0074	22.8500 ± 1.4167	4.1316 ± 0.7270	86.46 ± 1.8892	>300
V	0.1753 ± 0.0055	19.4000 ± 1.3115	8.8509 ± 1.1528	87.87 ± 1.6641	>300
VI	0.1858 ± 0.0089	22.8500 ± 1.1725	7.9639 ± 0.5712	81.93 ± 2.2332	>300

Swelling studies of the patches:

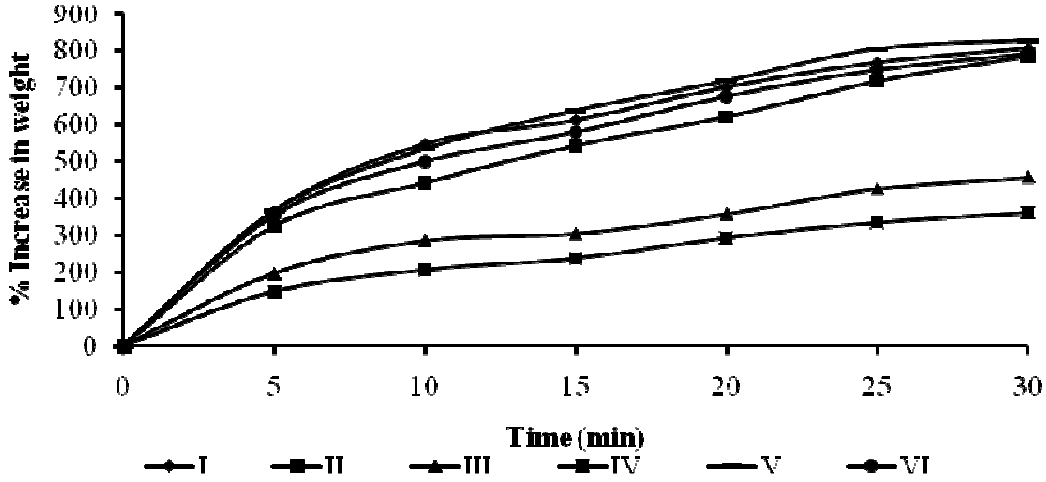

Figure 1: Swelling studies of prochlorperazine maleate films - Change in weight in phosphate buffer pH 6.6.

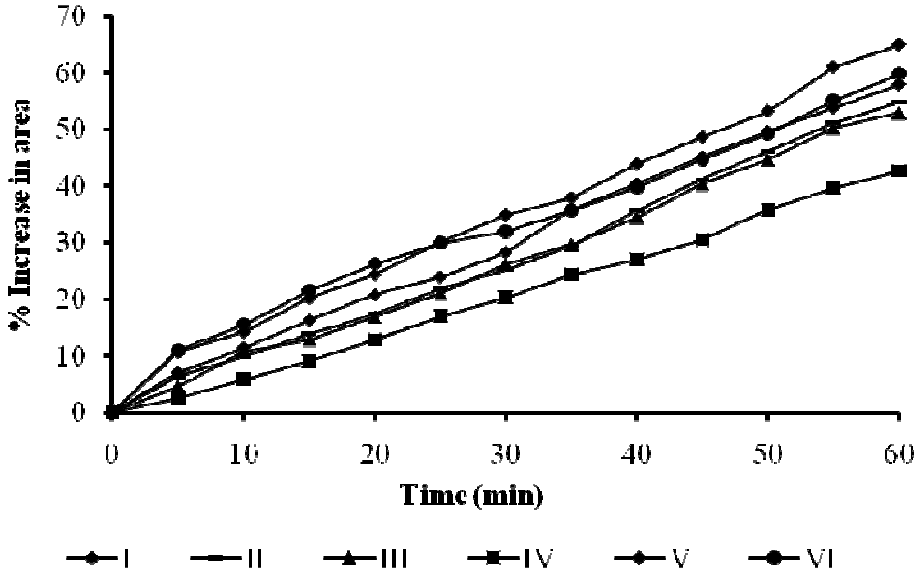

Figure 2: Swelling studies of prochlorperazine maleate patches - Change in area in phosphate buffer in pH 6.6

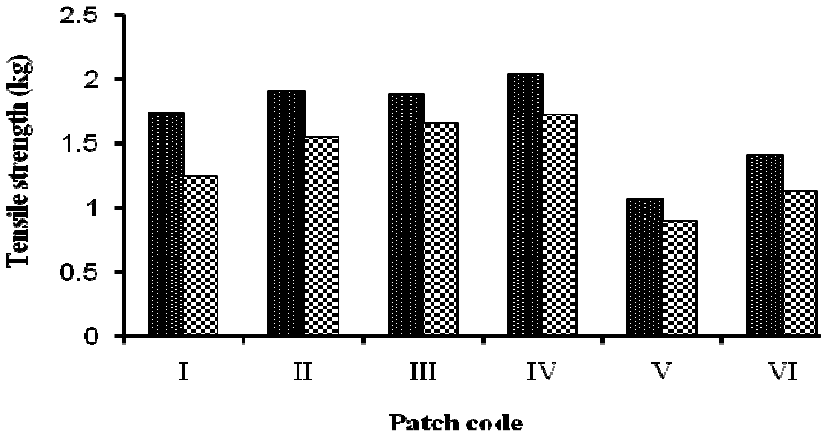

Figure 3: Tensile strength of patches determined for the blank (dotted) and drug loaded patches (black filled).

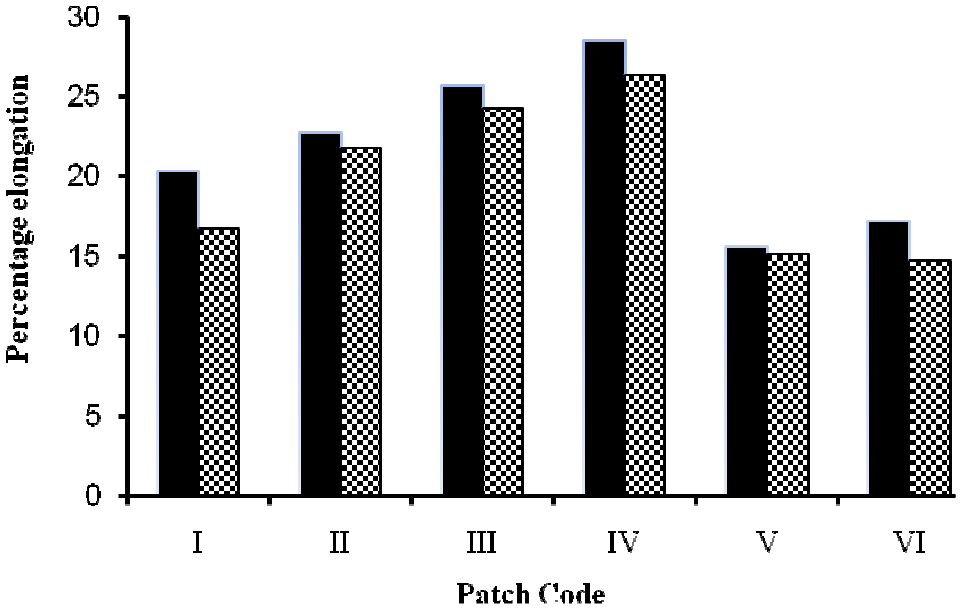

Figure 4: Percentage elongation of patches determined for the blank (dotted) and drug loaded patches (black filled)

Table 3: Viscosity of polymers determined by Brookfield viscometer

Patch Code	Polymer (mg)		*Viscosity (cps) AM + SD
I	HPMC (15 cps)	250	12.30 ± 0.4966
II	HPMC (47 cps)	250	18.07 ± 0.8213
III	HPMC (15 cps) Ethyl cellulose	200 50	23.19 ± 1.3285
IV	HPMC (47 cps) Ethyl cellulose	200 50	32.16 ± 2.2722
V	HPMC (47 cps) Poly vinyl pyrrolidone	200 50	13.26 ± 0.9514
VI	HPMC (15 cps) Poly vinyl pyrrolidone	200 50	20.91 ± 1.6786

*Each reading is an average of three determinations

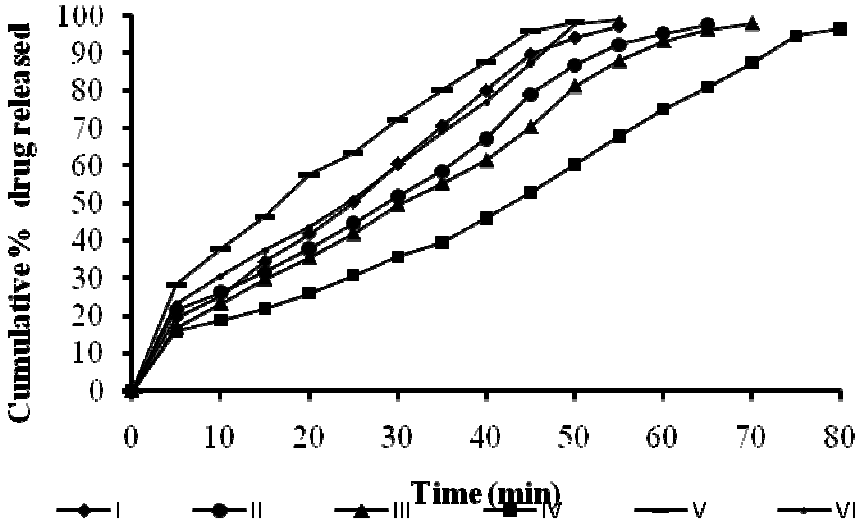

Figure 5: *In vitro* cumulative release of prochlorperazine maleate from patches I to VI

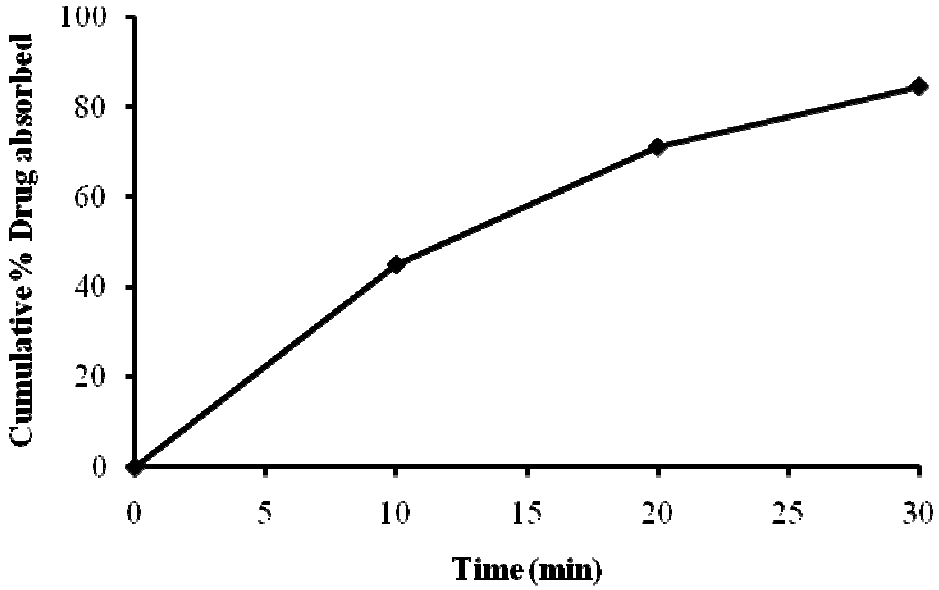

Figure 6: *In vivo* absorption of PCZ in rabbit buccal mucosa from patch V.

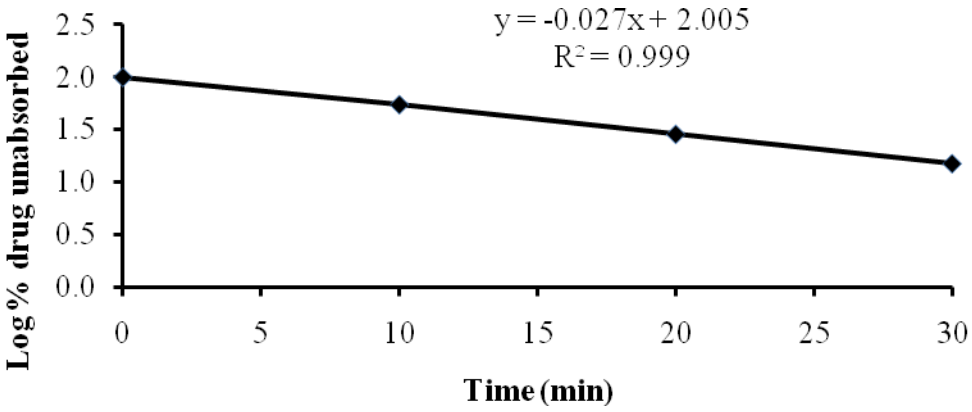

Figure 7: *In vivo* First order absorption of PCZ in rabbit buccal mucosa from patch V.

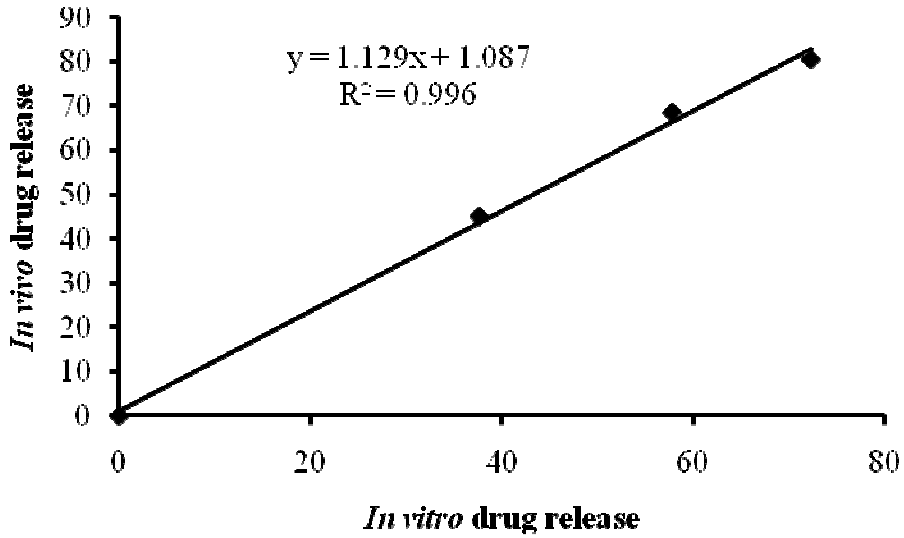

Figure 8: *In vitro* release Vs *in vivo* rabbit buccal absorption of PCZ from patch V

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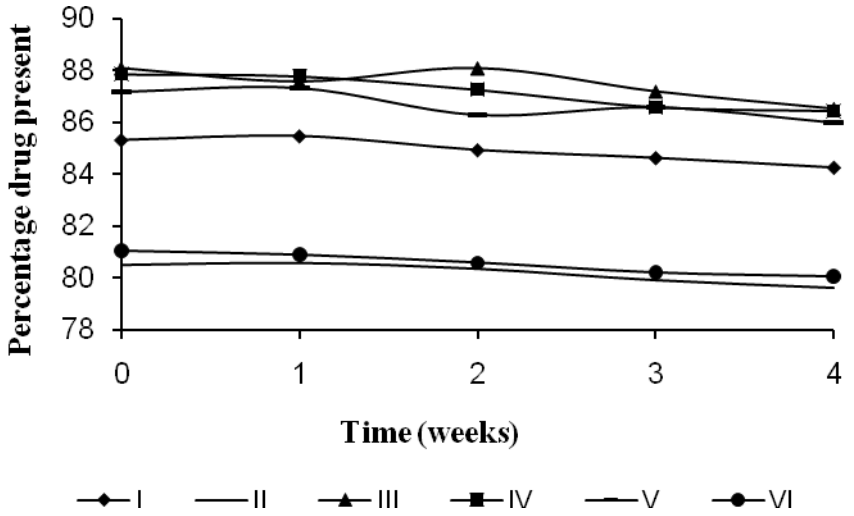

Figure 9: Percentage drug present in PCZ patches (I to VI) after one month storage under controlled conditions.

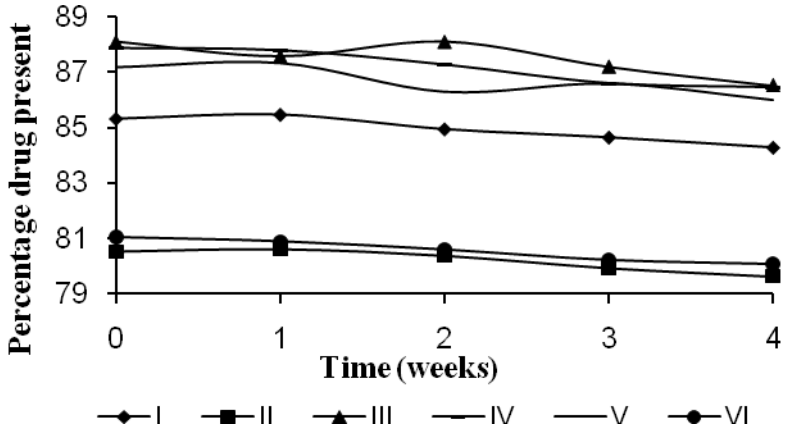

Figure 10: Percentage drug present in PCZ patches (I to VI) after one month storage under room conditions.

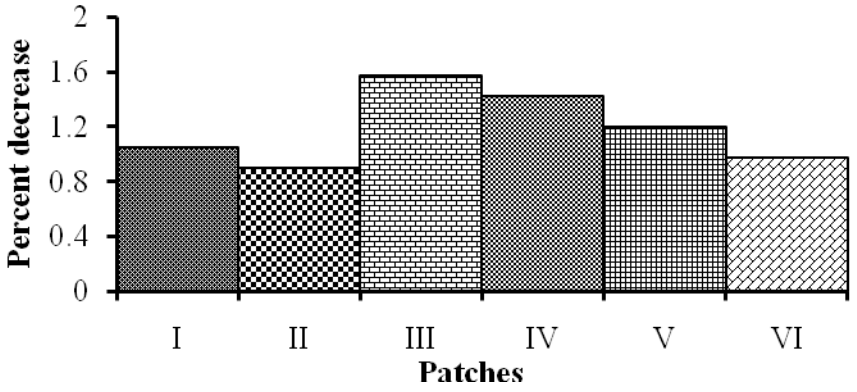

Figure 11: Percentage drug decrease in PCZ patches after one month storage under controlled conditions.

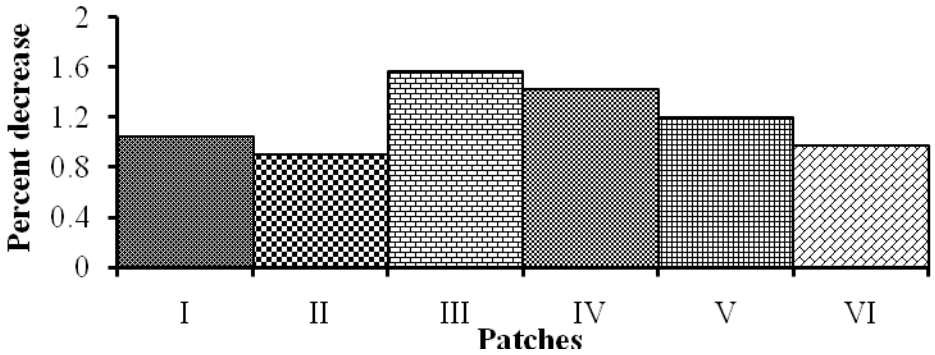

Figure 12: Percentage drug decrease in PCZ patches after one month storage under room conditions.

Table 4: Kinetic Analysis of the release data of different prochlorperazine maleate mucoadhesive films.

Patch Code	*In vitro* release in Phosphate buffer pH 6.6 Regression equations			
	Zero order	First order	Hixon-Crowell model	Higuchi's model
I	y = -1.759x + 93.19 R^2 = 0.988	Log y = -0.025x + 2.180 R^2 = 0.887	y = 0.011x - 0.042 R^2 = 0.959	y = 14.17x - 12.89 R^2 = 0.949
II	y = -1.468x + 91.30 R^2 = 0.982	Log y = -0.022x + 2.184 R^2 = 0.882	y = 0.009x - 0.049 R^2 = 0.943	y = 13.04x - 12.02 R^2 = 0.947
III	y = -1.392x + 92.77 R^2 = 0.988	Log y = -0.021x + 2.208 R^2 = 0.87	y = 0.009x - 0.049 R^2 = 0.949	y = 12.88x - 14.30 R^2 = 0.949
IV	y = -1.176x + 97.08 R^2 = 0.988	Log y = -0.015x + 2.178 R^2 = 0.823	y = 0.007x - 0.053 R^2 = 0.913	y = 11.75x - 8.206 R^2 = 0.988
V	y = -1.804x + 84.44 R^2 = 0.957	Log y =-0.030x + 2.148 R^2 = 0.881	**y =** 0.013x - 0.01 R^2 = 0.966	y = 14.26x - 4.469 R^2 = 0.990
VI	y = -1.708x + 90.69 R^2 = 0.984	Log y = -0.030x + 2.254 R^2 = 0.776	y = 0.012x - 0.048 R^2 = 0.905	y = 13.81x - 10.07 R^2 = 0.953

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