Research Article

Formulation and Process Optimization of Buccoadhesive Tablet of Rabeprazole

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ABSTRACT

The aim of the study was to prepare and evaluate bucco-adhesive tablets of rabeprazole sodium that avoid gastric degradation and first pass metabolism, thereby increasing the drug bioavailability and onset of action. The drug, rabeprazole sodium, belongs to a class of antisecretory compounds. In the present work, different ratios of Gantrez MS 955 along with HPMC K4M were studied to give bioadhesive strength. To stabilize the drug in human saliva different stabilizers were studied, of which sodium carbonate was found the best. A 3^2 full factorial design was applied to investigate the combined effect of Gantrez MS 955 concentration (X_1) and HPMC K4M concentration (X_2). Results of the multiple regression analysis revealed that the independent variables significantly affected the dependent variables (bioadhesive strength (Y_1) and t_{50} (Y_2)). On the basis of multiple linear regression analysis and contour plot evaluation, it was found that the effect of Gantrez is comparatively more pronounced than that of HPMC K4M on bioadhesion. The formulation F19 fulfilled all the criteria set from the desirability search. From the *in vitro* diffusion study flux was calculated for the optimized batch. Study of the effect of tablet diameter and the environmental factors on the bioadhesion of the tablet was done. To study the environmental factor on bioadhesion, prehydration time and contact time were considered. Result found that increase in prehydration time decrease in bioadhesive strength and increase in contact time increased bioadhesive strength. Thus a stable buccoadhesive formulation optimized for formulation ingredients and process parameters was prepared successfully.

Keywords: Rabeprazole sodium, buccal tablets, Gantrenz MS 955, HPMC K4M.

INTRODUCTION

Buccal mucosa is an attractive route for systemic delivery of drugs as it is relatively permeable with a rich blood supply. Moreover, it has high robustness and accessibility. A drug can be easily applied and localized at the application site, and can also be removed from there if necessary[1-3]. The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract. Buccal delivery for the transmucosal absorption of drugs into the systemic circulation offers a number of advantages over oral delivery, especially for those drugs that have poor oral bioavailability and/or those drugs that suffer from extensive first-pass metabolism in the liver. Conceivably, buccal delivery systems provide ease of administration and thereby increase patient compliance[4-9].

Rabeprazole Sodium is a Proton Pump Inhibitor (PPI). It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. Rabeprazole sodium having the highest acid inhibiting effect among other PPI and H2- antagonist. However, Drug having very short half-life (1.5 hr) and low bioavailability (52%). Antisecretory therapy with a rapid onset of action and sustained antisecretory effect may help to address some of the unmet needs, especially in the management of gastro-oesophageal reflux disease, nonvariceal upper gastrointestinal bleeding and non-steroidal anti-inflammatory drug-related gastrointestinal

complication. Further, in the marketed formulation various dosage form (granules, tablets and pellets are available) which is enteric coated due to degradation in the gastric and therefore onset of action delayed. The objective of present study is to design buccoadhesive bilayered tablets which will release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first pass metabolism for improvement in bioavailability, to reduce dosing frequency and to improve patient compliance[10-13].

In this study, an attempt has been made to develop a Rabeprazole sodium buccal adhesive tablet to avoid the gastric degradation and first pass metabolism. Two prime considerations in the design of a buccal adhesive tablet is- One to attach firmly to the buccal mucosa and the other (in case of rabeprazole) is the stability of Rabeprazole sodium in human saliva, since it is very unstable in acidic and neutral media.

There are various bioadhesive polymer present which are polyacrylic acid derivative such as polycarbophil and other polymer like sodium alginate, chitosan, HPC, HEC, sodium CMC, polyox, HPMC etc. Gantrenz MS 955 is polyacrylic acid derivative and having both anion and cation components[7,9,10.] In the Present work, Gantrenz and HPMC were selected for the adhesive dosage form.

EXPERIMENTAL

Materials

Rabeprazole sodium was obtained as gift sample from Alembic Ltd., Vadodra, India. Gantrez MS 955 was obtained from ISP India Ltd., India. Magnesium oxide, Magnesium carbonate, Sodium carbonate, Microcrystalline cellulose (MCC), Lactose, Talc, Magnesium stearate were purchased from S.D. Fine Chemicals Ltd., Mumbai, India. All ingredients were analytical grade.

Formulation of Buccal Tablets

Bilayered tablets of a backing layer and adhesive drug reservoir layer were prepared by covering one side of single layer tablet with a layer of Ethyl cellulose. Ethyl cellulose was selected as hydrophobic polymer has very low water permeability, thus providing an impermeable backing layer that can prevent drug loss in oral cavity. Drug-containing layer of the tablets was prepared by direct compression of drug blended with HPMC, Gantrez MS and other excipients using 12 mm flat faced punches at a lower hardness. Then the backing layer was compressed, consisting of Ethyl cellulose on the drug-containing layer to obtain bilayered tablets with final hardness. Selection of the stabilizers like Magnesium oxide, Magnesium carbonate, Sodium carbonate was also done followed by concentration optimization (Table 1).

Experimental Design

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and bi is the estimated coefficient for the factor *X*i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate non-linearity.

A 3^2 factorial design study was undertaken to assess the effect on formulation with regards bioadhesive strength (Y_1) and T50% (Y_2). The concentration of Gantrez MS 955 (X_1) and concentration of HPMC K4M (X_2) were selected as independent variables. The low, medium and high values were decided based on other tests of polymers as studied in preliminary batches. The design matrix for the experiment is shown in Table 1.

Characterization of buccal tablets

Compatibility Studies

Drug-polymer - excipient compatibility studies:

This was confirmed by carrying out by Infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulation were recorded by dispersion of drug and mixture of formulation in suitable solvent (KBr) using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR.

In-Vitro dissolution study

Release studies were carried out using 500 ml of freshly prepared phosphate buffer (pH 6.8) maintained at 37 ± 0.5ºC,as the medium and rotating the paddles at 50 rpm. [United States Pharmacopoeia (USP) XXIII] The backing layer of buccal tablet was attached to the vessel with instant adhesive (cyanoacrylate adhesive). At each sampling interval, 5 ml of the sample was withdrawn and replaced by an equal volume of fresh medium. The samples were filtered through a 0.45 µ membrane filter and diluted as required. The absorbance of the sampled solution was measured at the maximum wavelength of 283 nm using Shimadzu 1700 UV spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from the standard curve. The drug in phosphate buffer (pH 6.8) followed Beer–Lambert's law in the range of 10– 35µg/ml with correlation co-efficient of 0.997.

In-Vitro diffusion study

The *in vitro* buccal drug permeation study of rabeprazole sodium through the sheep buccal mucosa was performed using Frank's diffusion cell at 37°C ±0.2°C, mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the membrane and the compartments clamped together. The donor compartment was filled with 1 ml of Phosphate buffer (pH 6.8). The receptor compartment (22 ml capacity) was filled with phosphate buffer (pH 6.8) and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. 1 ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 283 nm using a UV spectrophotometer. The cumulative amount of permeated drug was plotted versus time, and the steady state flux (Jss) was calculated using the formula:

$$Jss = \Delta M/(A.\Delta t)$$

where ΔM is the amount of drug transported across the membrane during the time Δt and A is the diffusional area.

Bioadhesive strength

A modified balance method was used for determining the ex vivo mucoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter[15].The mucosal membrane was separated by removing underlying fat and loose tissues.The membrane was washed with distilled water and then with phosphate buffer (pH 6.8) at 37°C. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer (pH 6.8). A piece of buccal mucosa was tied to the glass , which was fixed on plank and the plank was assembled with a little crown block. After hydrating the sheep mucosa with distilled water, the tablet was brought in contact with the mucosa by applying little force for minute. After initial contact, the tablet was encircled by a thread which fastened a light plastic beaker through the crown block. Then, water was dropped into the beaker at a speed of 2ml/min using peristaltic pump until the tablet and sheep mucosa were pulled apart by the gravity of water. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The experiments were performed in triplicate and average values with standard deviation were reported. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

Statistical analysis

Tests for significant differences between means were performed by Student's t-test or one-way ANOVA. Differences were considered significant at $P < 0.05$.

Kinetics of drug release

The dissolution profile of all the batches was fitted to various models such as zero-order, first-order, Higuchi[16], Hixon-Crowell[17], Korsmeyer and Peppas[18-20], and Weibull models[21,22] to ascertain the kinetic modeling of drug release. The least value of sum of square of residuals (SSR) and Fishers ratio (F) were used to select the most appropriate kinetic model[23].

Stability study

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Formulations were selected for stability on the basis of the in vitro drug release profile. The formulations were subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines i.e. room temperature, 25ºC/ 60% RH in alu/alu foil for 1 months in thermo stated ovens. The samples (n=3) were taken out at 0, 30 days. Tablets were evaluated for the different physicochemical parameters i.e. content uniformity, thickness, weight variation, bioadhesive strength, dissolution study and in-vitro diffusion study.

RESULTS AND DISCUSSION

Formulation of rabeprazole buccal tablets

Rabeprazole buccal tablets were prepared using various polymers and other excipients. The stability of rabeprazole tablets in phosphate buffer (pH 6.8) was evaluated by their appearance characteristic, such as color and shape, and rabeprazole content. The neutral phosphate buffer which penetrates into the rabeprazole tablets decomposed the drug in them, since it is unstable in neutral media. Furthermore, it gradually changed their color from white to violet or black due to the decomposition of rabeprazole. In the worst case, it caused the collapse of tablets followed by completely decomposing the rabeprazole in the tablets. Rabeprazole (20mg) tablets prepared with Gantrez or HPMC K4M did not collapse. However, it turned black and had only 75% to 83% of initial rabeprazole content at 5 hr. These result suggested that the rabeprazole tablets with only bioadhesive polymer could not stabilize the drug in phosphate buffer. To stabilize the rabeprazole tablets in phosphate buffer (pH 6.8), rabeprazole tablets were prepared by compressing rabeprazole, gantrez and different amount of alkali materials such as magnesium oxide, magnesium carbonate and sodium carbonate. In the formulation of rabeprazole tablet, these alkali materials were used as stabilizers of rabeprazole, since rabeprazole degrade in the gastric and neutral environment.

Result showed that batches of MgO in selected concentration turned violet to black after 70 to 140 min. and the drug content was 83% to 86%. In case of batches containing $MgCO_3$, tablets turned violet or black after 50 to 120 min. and the drug content was 84.32% to 88.30%. while in case of batches containing Na_2CO_3, tablet turned violet or black after 110min. to 225 min. and drug content was 85.89% to 92%. Thus szodium carbonate was selected as stabilizer and its concentration was optimized. Sodium carbonate with 140 mg was found optimum. To evaluate the release profile for 5 hr, different concentration of Gantrez was selected. Finally, for factorial design Gantrez 30-40 mg, HPMC 8-16 mg and sodium carbonate 140 mg were considered.

Experimental study and statistical report

A total of nine batches were prepared using 3^2 Full Factorial Design taking the polymers Gantrez and HPMC K4M in different concentrations as the variables to

assess the effect on formulation with regards to bioadhesion strength and

T50%. The fitted equations (full models) relating the responses (i.e. bioadhesion strength and T50%) to the transformed factor are shown in below. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The high values of correlation coefficient for the dependent variables indicate a good fit. The equations may be used to obtain estimates of the response since small error of variance was noticed in the replicates.

Effect of variable on bioadhesion

The constant and regression coefficients for Y_1 (bioadhesion strength) are as follows:

$$Y_1 = 39.435 - 1.94 (X_1) + 0.310 (X_2) - 0.000325(X_1X_2) + 0.0326 (X_{11}) - 0.10092 (X_{22}) \ldots\ldots (1)$$

The polynomial model was found to be significant with an *F* value of 1044.725 (p=0.000293). The value of correlation coefficient was found to be 0.9994, indicating a good fit. Equation 1 reveals that both the factors (X_1 and X_2) affect bioadhesion strength. The p value of X_1X_2 suggests that the interaction between X_1 and X_2 is not significant. The combined effect of factors X_1 and X_2 can further be elucidated with the help of response surface and contour plots, which demonstrate that Y_1 varies in a linear fashion with the amount of both the polymers (figure 1). However, the steeper ascent in the response surface with Gantrez (X_1) than with HPMC K4M (X_2) is clearly discernible from both the plots, indicating that the effect of Gantrez is comparatively more pronounced than that of HPMC K4M. From this discussion, one can conclude that the bioadhesion may be changed by appropriate selection of the levels of X_1 and X_2.

The nature of difference in bioadhesive strength between Gantrez and HPMC formulations could plausibly be attributed to formation of hydrogen bonds between the Gantrez and proton accepting groups, which do not happen in case of HPMC because it does not contain proton-donating carboxyl groups. Glass transition temperature (Tg) and polymer mobility have been considered to be important criteria for mucoadhesion by de Vries et al. (1988), indicating the lower the Tg, the higher would be the polymer mobility, which would produce higher levels of mucoadhesion. A potential reason for an increase in mucoadhesive bond strength with increasing Gantrez content may be due to enhanced water uptake by the gum which resulted in tablet swelling and mobilization of flexible polyacrylic acid chains. The mechanism of bioadhesion may potentially result from chain interpenetration and physical entanglement of Gantrez with the mucus layer. In our studies it was evident that Gantrez, might exhibits high relaxation properties due to low Tg, demonstrated relatively higher adhesive forces in formulation than HPMC, which possesses higher Tg and, consequently, a higher polymer mobility.

Effect of variable on release Y_2 (50% drug release)

The quadratic model for T50% (Y_2) was found to be non-significant with an F value of 172.66. In this case, factors X_2 as well as the interaction factor X_1X_2 were found to be significant. The variables had a significant effect on T50%. A relationship was obtained between the fraction of HPMC K4M and T50%, and it was observed that as the fraction of HPMC K4M increased, the value of T50% increased, at all the three levels of Gantrez (figure 2). On increasing the amount of Gantrez, decrease the T50%. It may be due to the water soluble nature of the Gantrez and thereby it forms voids in matrix. It may be the dissolution based release mechanism for Gantrez. And for HPMC K4M, It may be the diffusion based release mechanism.

$Y_2 = 58.68 + 0.957(X_1) + 4.26(X_2) - 0.09(X_1X_2) - 0.01(X_{11}) + 0.044(X_{22})$…….**(2)**

T50% drug release is important criteria to achieve the effective concentration of rabeprazole sodium (Acid inhibition is dose-dependent effect). With this consideration, time required to release T50% should be less.

Selection of optimized batch

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent (response) variables Y_1 and Y_2 and the optimized formula was arrived at by keeping the bioadhesion force greater than 13 dyne/cm^2 and T50% was kept between 80 and 90 min. The formulation batch F19 fulfilled all the criteria set from the desirability search. To gainsay the reliability of the response surface model, a new optimized formulation (as per formulation F19) was prepared according to the predicted model and evaluated for the responses. The results in table 2 illustrate a good relationship between the experimental and predicted values, which confirms the practicability and validity of the model. The predicted error for all the response variables was below 6% indicating that the RSM optimization technique was appropriate for optimizing the Rabeprazole sodium bioadhesive buccal tablets.

***In vitro* diffusion (permeation) study of optimized Batch**

To determine the diffusion study, formulation 7 was selected because it required less time to release 50% of drug and having enough bioadhesive strength. From the graph (figure 3) it was observed that drug has sufficient amount of permeation i.e agreement with the 90% of BCS guideline. The flux of this optimized batch was 8.28 µg.cm2^{-1}min^{-1}and lag time was 298.1. This may be due to the higher hydration of polymer. Increase in the concentration of Gantrez leads to increase the diffusion of Rabeprazole sodium through the buccal mucosa.

Bioadhesion strength of the optimised batch

A profile showing the values of the force of detachment of the buccal tablets following their application to excised sheep buccal mucosa is shown in figure 4. It can be noted that the values of the force of detachment increased with time for batch. Additionally, this batch has 5 hr of *in vitro* residence time with sufficient amount of detachment force.

Kinetics of Drug Release

The dissolution profile of the optimized batch was fitted to various models such as zero-order, first-order, Higuchi, Hixon-Crowell, Korsmeyer and Peppas, and Weibull models to ascertain the kinetic modeling of drug release. As observed from study the drug release mechanisms of the matrix tablets were evaluated by using the Korsmeyer-Peppas semi-empirical model. The calculated exponent (n) indicated that all the formulations followed non-Fickian transport mechanism, that is, drug release from the matrix based on dissolution and diffusion. It might be the Gantrez showing release based on dissolution due to void formation in the matrix. At the same time HPMC K4M might be showing release based on diffusion mechanism.

Stability study

After 30 days of stability of the optimized batch, values of all parameter like % drug content, bioadhesive strength, and were almost similar to the initial values as seen in table 3. The result also showed there is no change in the tablet shape, color. The drug dissolution and diffusion profile was just the same of the initial profile (figure 5). There was not any significant change in any value, so formulation is stable. This

study is agreement with the ICH guideline Q1A (R2), i.e. no significant change (5%).

CONCLUSION

The study suggests that the hydrophilic bioadhesive tablets of Rabeprazole sodium can be designed using HPMC and Gantrez. The matrices demonstrated adequate bioadhesion with buccal mucosa. Moreover, *in vitro* bioadhesive strength versus time measurements demonstrated that the polymer possessed excellent mucoadhesive properties allowing for the convenient application and removal of the tablets from the buccal mucosa. The mechanism of bioadhesion may potentially result from chain interpenetration and physical entanglement of Gantrez with the mucus layer. The rate of release of the drug substance as well as the bioadhesive bond strength of the formulation can be modulated by varying the amount of Gantrez included in the tablet. The mucoadhesive buccal tablets evaluated in the present study were easy to formulate, inexpensive, provide easy application and convenient removal from the mucosal surface, and did not irreversibly damage the underlying tissue. Therefore, such tablet formulations containing a polyacrylic acid bioadhesive polymer, Gantrez, may represent an improved buccal delivery system for a variety of water-soluble, low molecular weight drug substances The Rabeprazole sodium containing buccoadhesive tablets could provide an alternative to the conventional dosage form for the treatment of GERD and other peptic ulcer disease with faster onset of action.

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Table I: Rabeprozole sodium buccal Tablet Batches using 3^2 Full Factorial Design Layout

Formulation codes	Independent variable		Dependent variable	
	X_1	X_2	Y_1	Y_2
F1	-1	-1	12.00	91.72
F2	-1	0	12.61	101.68
F3	-1	+1	12.91	111.7
F4	0	-1	12.78	89.89
F5	0	0	13.23	95.9
F6	0	+1	13.61	106.08
F7	+1	-1	15.21	85.18
F8	+1	0	15.54	92.32
F9	+1	+1	15.86	98.55

Translation of coded levels in actual units

Independent Variables	Real Value		
	Low (-1)	Medium (0)	High (+1)
Gantrez MS 955 (X_1)	30 mg	35 mg	40 mg
HPMC K4M (X_2)	8 mg	12 mg	16 mg

Note: All Formulations contain 20 mg of drug, 140 mg of sodium carbonate, 25 to 30% MCC and 65 mg Ethyl Cellulose as backing layer. Total weight: 320 mg.

Table II: The Predicted and Observed Response Variables of the Optimal Buccal Bioadhesive Tablets

	Y_1(Bioadhesive strength)	Y_2 (T50%)
Predicted	15.18	86.37
Observed	14.45	88.05
Predicted error (%)	4.8	1.90

Predicted error (%) = (observed value − predicted value)/predicted value × 100%.

Table III: Stability study data of the optimized batch

Parameters	Time (days)		
	0 days	30 days	
	25±2°C 60 ± 5%RH	25±2°C 60 ± 5%RH	40±2°C 75 ± 5%RH
% drug content (%)	97.15	96.56	96.43
Bioadhesive strength (dyne/cm^2)	15.21	15.00	15.14

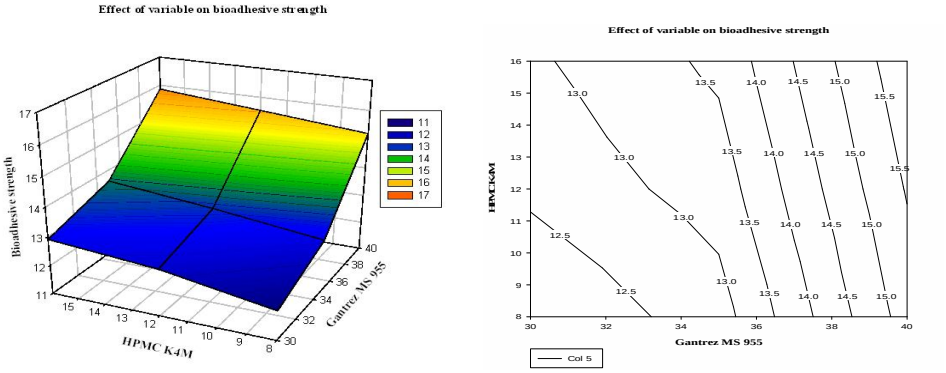

Fig.1: Contour graph for Y_1 (bioadhesive strength)

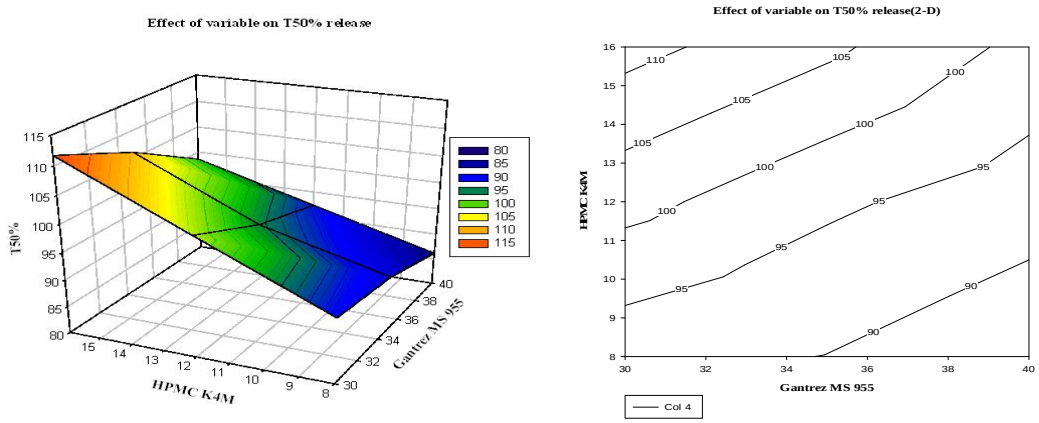

Fig. 2 : Contour graph for Y_2 (50% drug release)

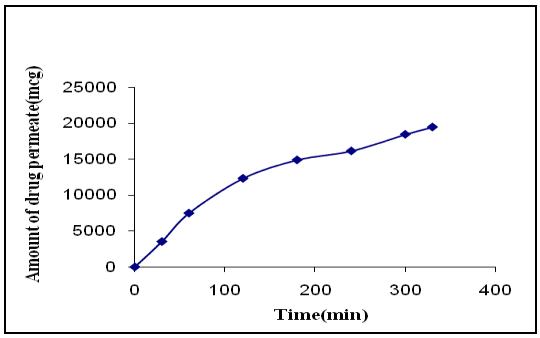

Fig. 3: *In vitro* diffusion (permeation) study of optimized batch using sheep buccal mucosa

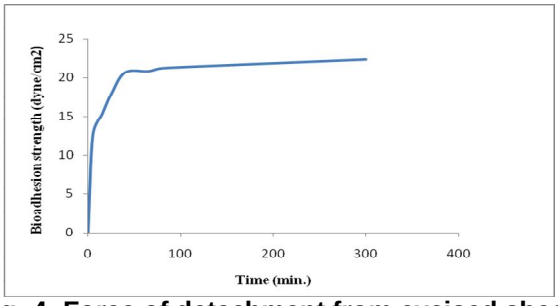

Fig. 4: Force of detachment from excised sheep buccal mucosa for directly compressed buccal tablet for optimized batch

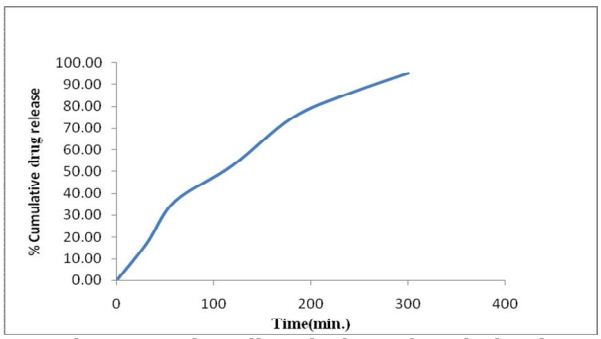

Fig. 5: *In vitro* dissolution of optimized batch after 30 days

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