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Formulation and Evaluation of Buccal Tablet Rabeprazole Sodium Tablet

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ABSTRACT

Buccal mucosa is an attractive route for systemic delivery of drugs and it is relatively permeable with a rich blood supply. Rabeprazole Sodium is a Proton Pump Inhibitor (PPI). It is mostly prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. Rabeprazole Sodium having highest acid inhibiting effect among other PPI and H2-antagonist. However, Drug having very short half-life (1.5 hr) and low bioavailability (52%). 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. In this present 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. One is to attach firmly to the buccal mucosa and 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 polymers present which are polyacrylic acid derivative such as polycarbophil and other polymer like sodium alginate, Chitosan, HPC, HEC, Sodium CMC, Polyox, HPMC etc. In the Present work, Gantrenz and HPMC selected for the adhesive dosage form. Gantrenz MS 955 is Polyacrylic acid derivative and having both anion and cation.

Keywords: *Rabeprazole Sodium Tablet, Buccal mucosa, Gantrenz, HPMC, Zollinger-Ellison syndrome.*

INTRODUCTION

The oral mucosa is divided into two main regions, the outer most vestibules and the oral cavity. The vestibule is attached on the outside by the lips and cheeks and other on the inside is attached by the upper and lower dental arches. The oral cavity is located within the dental arches framed on the upper side by the hard and soft palates and on the bottom by the tongue and floor of the mouth [1]. The oral mucosa consists of an outermost layer which is made by stratified squamous epithelium, below which situated a basement membrane and below the this, lamina propria and submucosa [2,3].

Peptic ulcer disease embraces both gastric and duodenal ulcers and has been a significant threat to the world's population over the past two centuries, with a high morbidity and substantial mortality [4]. Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence. Development of ulcer disease and death from it's been related to the birth of urbanization and was interpreted as a birth-cohort event with the height of disease in those born during the late 19th century [5,6]. Our understanding of the disease changed greatly with the

invention of *Campylobacter pyloridis* (renamed *Helicobacter pylori* in 1989 thanks to a revised taxonomic classification) in 1982 by Warren and Marshall [7-9]. This discovery switched the notion from an acid-driven disease to a communicable disease, opening a large area for intensive research that resulted within the reconciliation of previously suggested mechanisms of pathogenesis. The autumn of the acid dogma in peptic ulceration disease, which had found its undisputed acceptance during and after the introduction of histamine H2-receptor antagonists, led to this therapeutic principle [10-11]. Maintenance acid suppressive therapy for peptic ulcer, which followed decades of dominance of surgical interventions (subtotal gastric resections, several varieties of vagotomy), was replaced with a short-term antibiotic regimen targeting eradication of *H pylori* infection *H. pylori* eradication as cure of ulcer received its full recognition when the honour for Medicine and Physiology was awarded to Warren and Marshall in 2005. This recognition has not, however, closed the chapter on peptic ulcers [12-15]. The management of ulcer disease and its complications remains a clinical challenge. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin are an increasingly important explanation for ulcers and their complications even in H pylori-negative patients. Other rare causes of ulcer disease within the absence of H pylori, NSAIDs, and aspirin also exist [16-20].

MATERIAL

Table.1. List of Materials used in Experiment and Obtained

Sr. No.	Material	Obtained from
1	Rabeprazole sodium	Alembic Ltd.
2	Magnesium oxide	GISIPS Dehradun.
3	Magnesium carbonate	GISIPS Dehradun.
4	Sodium carbonate	GISIPS Dehradun Ltd.
5	Gantrez MS 955	ISP Limited
6	Microcrystalline cellulose	GISIPS Dehradun.
7	Talc	GISIPS Dehradun
8	Magnesium stearate	GISIPS Dehradun
9	Lactose	Rusan Pharma ltd Dehradun

METHODOLOGY

1. Preformulation Study

It is the primary step in rational development of dosage types of drug substance. Preformulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with Excipients. The general objective of preformulation testing is to get information useful to the formulator in developing stable and bio-available dosage forms which will be mass-produced.

1.1 Organoleptic Properties

This includes recording of color, odor and taste of the new drug using descriptive terminology. Record of color of early batches is incredibly useful in establishing appropriate specifications for later production. Drugs generally have a characteristic odors..

1.2 Solubility Study

Solid drugs administered orally are often administered for systemic activity

and must dissolve in fluids before their absorption. Hence rate of dissolution of medication can influence rate and extent of their absorption. Solubility study was performed at 37˚C.

1.3 Angle of Repose

The angle of repose of powder blend was resolute by the funnel method. The accurately weight powder blend were taken within the funnel. The peak of the funnel was adjusted in such the simplest way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the subsequent equation (Table 2).

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Table.2. Relation between Angle of Repose and Type of Flow

Angle of Repose	Types of Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

1.4 Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) was resolute. A quantity of two gm of powder blend from each formula, previously shaken to interrupt any agglomerates formed, was introduced in to 10 ml measuring cylinder. at the moment the initial volume was noted and also the cylinder was allowed to represent its own weight on to a tough surface from the peak of two.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the subsequent equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

1.5 Compressibility Index

Compressibility Index of powder blend determined by Carr's compressibility index. It's an easy test to gauge the LBD and TBD of a powder and therefore the rate at which it packed down (Table 3). The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Table. 3. Effect of Carr's Index and Housner's Ratio on Flow Property

Carr's Index	Flow character	Hausner's ratio
≤ 10	Excellent	1.00–1.11
11-15	Good	1.12–1.18
16-20	Fair	1.19–1.25
21-25	Passable	1.26–1.34
26-31	Poor	1.35–1.45
32-37	Very poor	1.46–1.59
38	Very, very poor	>1.60

1.6 Hausner's Ratio

It is calculated from bulk density and tap density.

Hausner's ratio = Tapped density/Bulk density

Values less than 1.25 indicate good flow (20% Carr index.) and also the value greater than 1.25 indicates poor flow (33% Carr index.). If it's between 1.25-1.5 added glidant normally to enhance flows

1.7 Total Porosity

Total porosity was determined by measuring the volume occupied by a selected Weight of a powder (Vbulk) and therefore the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V)

Porosity (%) =Vbulk-V/Vbulk x 100

1.8 pH Stability Profile

The pH stability profile of Rabeprazole sodium was studied at 25˚C and therefore the percentage of original drug remaining after 24 hours of period of time was resolute. Stock solution (1mg/ml) of rabeprazole sodium was prepared in several standard pH (1 to 8) solutions. The solutions were stored for twenty-four hrs and after 24 hrs % conc. of Rabeprazole sodium was firm by UV spectroscopy method.

2. Spectral Analysis of Rabeprazole Sodium

Determination of UV spectrum of Rabeprazole Sodium

The standard solution of concentration 10 µg/ml of Rabeprazole sodium was prepared in Phosphate buffer pH 6.8. The absorbance of those was measured at entire range of UV for the determination of λ max using UV/Visible spectro-photometer. The standard solution of concentration 0, 5, 10, 15, 20, 25 µg/ml of Rabeprazole sodium were prepared in Phosphate buffer pH 6.8. The absorbance of those prepared solutions was measured at 283 nm using UV/Visible spectrophotometer.

2.1 Compatibility Studies

Drug-Polymer-Excipients Compatibility Studies

This can be 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 final analysis correction was made using dried salt then the spectra of the dried mixture of drug, formulation mixture and restrainer were recorded on FTIR.

5.4. Formulation of Buccal Tablets

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 get bilayered tablets with final hardness.

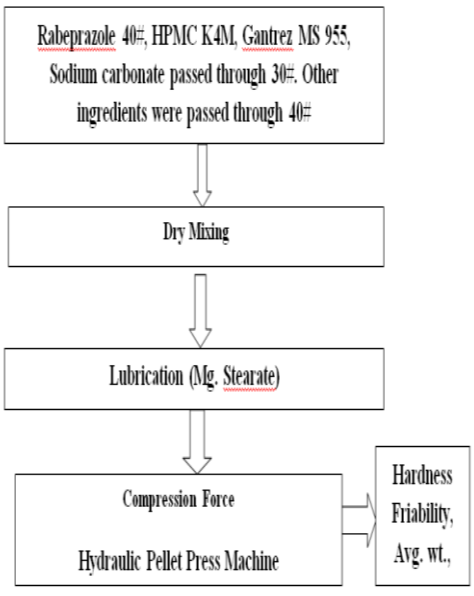

Fig. 1. Flow Chart

3.0 Preliminary Batches
Optimization of Stabilizer

Table. 4. Optimization of Stabilizer

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Rabeprazole sodium	20	20	20	20	20	20
Magnesium Oxide (MgO)	60	100	-	-	-	-
Magnesium Carbonate($MgCO_3$)	-	-	60	100	-	-
Sodium Carbonate (Na_2CO_3)	-	-	-	-	60	100
Gantrenz MS-955	15	15	15	15	15	15
Hydroxypropylmethylcellulose (HPMC K4M)	8	8	8	8	8	8
Microcrystalline cellulose (MCC)	30	30	30	30	30	30
Mg. stearate	1%	1%	1%	1%	1%	1%
Talc	2%	2%	2%	2%	2%	2%
Lactose	10	10	10	10	10	10
Ethyl cellulose	65	65	65	65	65	65
Total weight	215	255	215	255	215	255

(All Weight in mg)

Preliminary Batches for Dissolution Profile (5 hr Release)

Table. 5. Preliminary Batches

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Rabeprazole sodium	20	20	20	20	20	20
Sodium Carbonate (Na_2CO_3)	120	120	140	140	140	140
Gantrez MS-955	15	20	20	25	30	35
Hydroxypropylmethylcellulose (HPMC K4M)	8	8	8	8	8	8
Microcrystalline cellulose (MCC)	30	30	30	30	30	30
Mg. stearate	1%	1%	1%	1%	1%	1%
Talc	2%	2%	2%	2%	2%	2%
Lactose	10	10	10	10	10	10
Ethyl cellulose	65	65	65	65	65	65
Total weight	275	280	300	305	310	315

4. Evaluation

4.1 Weight variation

To study weight variation twenty tablets of the formulation were weighed employing a Sartorius balance and also the test was performed in line with the official method.

4.2 Thickness and Friability

Thickness of every formulation was measured using vernier calipers. Five tablets from each batch were used and average values were calculated.

4.3 **Hardness**

The hardness of 5 tablets was firm using the hardness tester and also the average values were calculated.

5**. Content Uniformity**

Five tablets from each formulation were crushed and mixed separately. From the mixture 20 mg of Rabeprazole sodium equivalent of mixture was extracted in 100 ml of Phosphate buffer (pH 6.8) and also the solution was filter through 0.45µm

membrane. The absorbance was measured at 283 nm after suitable dilution employing a Shimadzu UV-1700 UV/Vis double beam spectrophotometer. This procedure was repeated thrice to induce accuracy within the result.

6. Disintegration

The USP 28 <710> method was wont to evaluate disintegration of buccal tablet. Place one tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at 37±2˚C because the immersion fluid. After 4 hrs, lift the basket from fluid and observe the tablets.

7. *In-vitro* dissolution study:

The US Pharmacopoeia (USP) XXIII rotating paddle method was accustomed study the drug release from the tablets.

Dissolution medium :500ml of phosphate buffer (pH 6.8).
Temperature : 37°C ± 0.5°C
Rotation speed : 50 rpm.

The backing layer of buccal tablet was attached to the vessel with instant adhesive (cyanoacrylate adhesive). 5 ml sample was withdrawn at predetermined time intervals and replaced with fresh medium. The samples was filtered through Whatman paper 0.45µ and analyzed after appropriate dilution by UV spectrophotometry at 283 nm.

8. *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 therefore the compartments clamped together. The donor compartment was stuffed with 1 ml of Phosphate buffer (pH 6.8). The receptor compartment (22 ml capacity) was full of phosphate buffer (pH 6.8) and also the hydrodynamics within 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 employing a UV spectrophotometer. The cumulative amount of permeated drug was plotted versus time, and also 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 that the diffusional area.

9. Formulation and Optimization of Buccoadhesive Tablets by Using 32 Full Factorial Designs

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it's going to difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables don't seem to be considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design additionally to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variety and their interactions. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The number of experiments required for these studies is dependent on the number of independent variables

selected. The response (Yi) is measured for each trial.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where Y is that the variable quantity,
b0 is that the arithmetic mean response of the nine runs and
bi is that the estimated coefficient for the factor Xi.

The main effects (X1 and X2) represent the common results of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed. A 32 randomized full factorial design was utilized within the present study.

During this design two factors were evaluated, each at three levels, and experimental trials were dispensed in the slightest degree nine possible combinations. The look layout and coded value of independent factor is shown below. The factors were selected supported preliminary study. The concentration of Gantrez MS 955 (X1) and concentration of HPMC K4M (X2) were selected as independent variables. The bioadhesive strength (Y1) and T50% (Y2) were selected as dependent variables.

Statistical validity of the polynomials was established on the premise of ANOVA provision within the Microsoft software. Level of significance was considered at $p < 0.05$.

The best-fitting mathematical model was selected supported the comparison of several statistical parameters, including the coefficient of variation (CV), the multiple regression coefficient (R2), the adjusted multivariate analysis coefficient (adjusted R2), and also the predicted residual sum of squares (PRESS), provided by the software. PRESS indicates how well the model fits the info, and for the chosen model, it should be small relative to the opposite models into account. The 3-D response surface Bottom of Form graphs and the 2-D contour plots were also generated by the Sigmastat software. Subsequently, the desirability approach was used to generate the optimum settings for the formulations.

Formulation Codes		**Independent variable**	
		X_1	**X_2**
F13		-1	-1
F14		-1	0
F15		-1	+1
F16		0	-1
F17		0	0
F18		0	+1
F19		+1	-1
F20		+1	0
F21		+1	+1
Independent Variable	**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

10. Drug Release Kinetics

To study the mechanism of Rabeprazole release from the matrix tablets, the release data were fitted to the following equations:

1) Zero-order equation

$Q_t=Q_0+k_0t$

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k0 is the zero-order release rate.

2) First-order equation

$\ln Q_t=\ln Q_0+k_1t$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first-order release rate constant.

3) Higuchi s equation

$Q= kH\ t^{½}$

Here, Q is the amount of drug release at time t, and kH is the Higuchi diffusion rate constant

4) Koresmeyer's equation

$Mt= M\infty\ Kt^n$

Where, Mt is the amount of drug released at time t, $M\infty$ is the amount of drug released after infinite time, Kt is a kinetic constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent indicative of the drug release mechanism.

A modified balance method was used for determining the *Ex Vivo* mucoadhesive strength. Fresh sheep buccal mucosa was obtained from an area slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with water then with phosphate & buffer (pH 6.8) at 37°C.

The sheep buccal mucosa was take away 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 therefore the plank was assembled with a touch crown block. After hydrating the sheep mucosa with water, the tablet was brought in-tuned with the mucosa by applying little force for minute. After initial contact, the tablet was encircled by a thread which fastened a light-weight 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 also the minimum detachment force was calculated accordingly. The experiments were performed in triplicate and average values with variance were reported. This detachment force gave the mucoadhesive strength of the buccal tablet in grams (Figure 2).

10. Bioadhesive Strength

Bioadhesive strength was calculated by the following equation:

Actual wt for detachment: ……gm
Force of detachment (dynes) = Actual wt for detachment (gm) × g
Where g= acceleration due to the gravity (980 cm/ sec^2)
Force for detachment per unit area (dyne/cm^2) = Force of detachment (dynes)/ πr^2

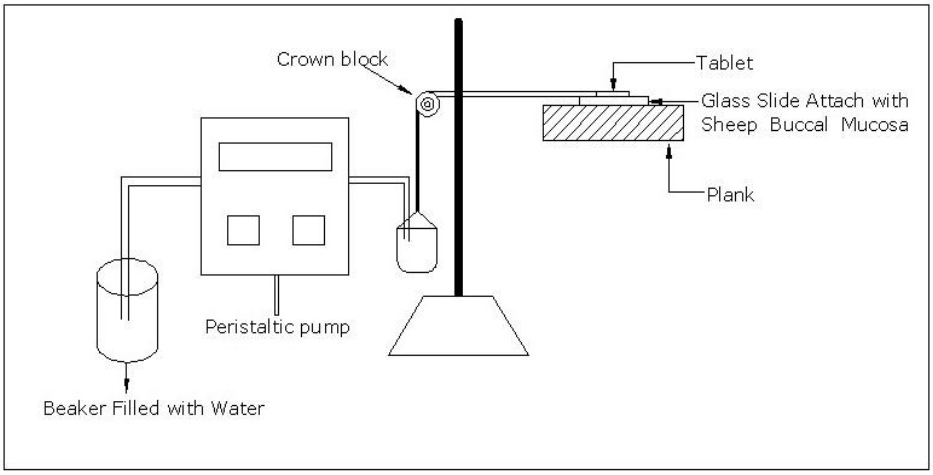

Fig. 2. Set up for Measuring Bioadhesive Strength

12. Stability Study

The purpose of stability study is to produce evidence on the quality of a drug substance or drug product which varies with time under the influence of a spread of environmental factors like temperature, humidity and light-weight. Formulations were selected for stability on the idea 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. 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 varied physicochemical parameters i.e. content uniformity, thickness, weight variation, bioadhesive strength, dissolution study and in-vitro diffusion study.

RESULT AND DISCUSSION

1. Preformulation

1.1 Solubility

Table. 6. Solubility determination

Solvent	Solubility(mg/ml)	Observation
Distilled water	0.36	Practically soluble
Phosphate buffer pH 6.8	0.49	Practically soluble

1.2 Calibration Curve

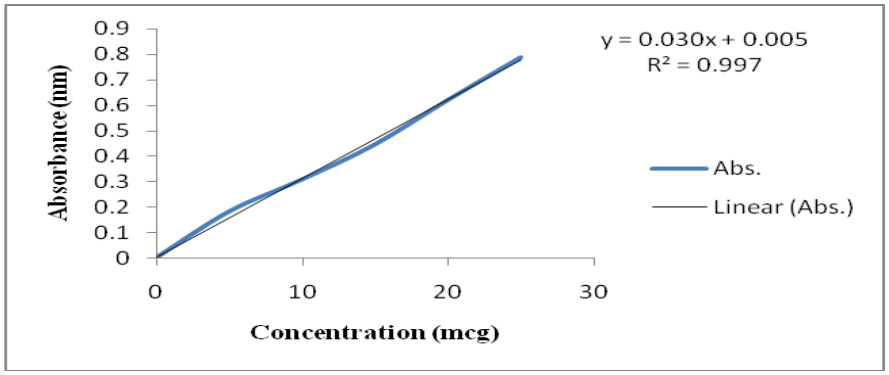

Fig. 3. Calibration curve of Rabeprazole Sodium in Phosphate Buffer (pH 6.8) at 284 nm Wavelength

Table. 7. Standard calibration curve of Rabeprazole Sodium in Phosphate Buffer (pH 6.8)

Concentration	Absorbance			Mean± SD
	1	2	3	
0	0	0	0	0
5	0.182	0.180	0.182	0.182
10	0.308	0.305	0.306	0.307±0.001
15	0.446	0.443	0.445	0.445±0.001
20	0.621	0.620	0.618	0.619±0.002
25	0.789	0.785	0.786	0.787±0.002
Y= 0.030x + 0.005 R^2= 0.9				

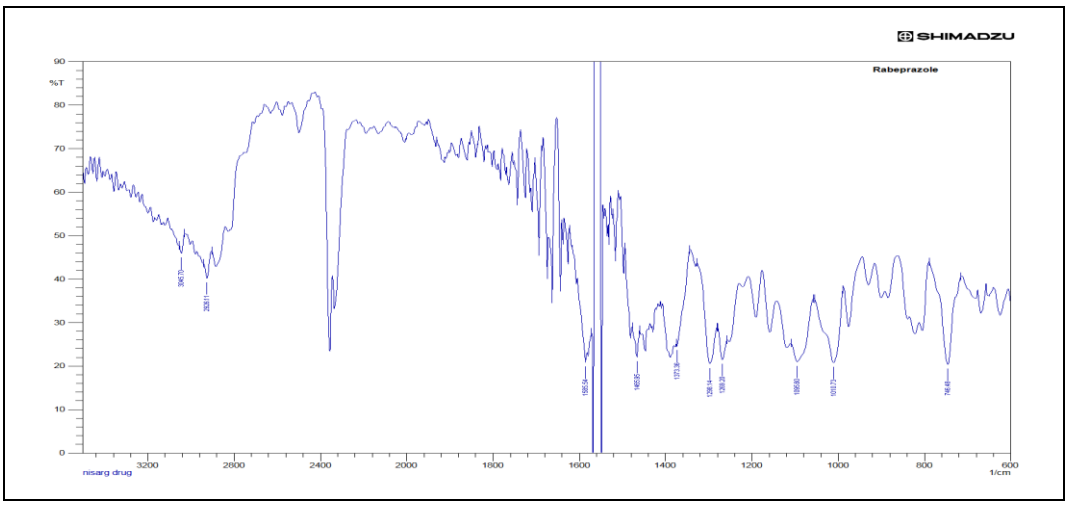

Fig. 4. FTIR of Rabeprazole Sodium

1.3 Compatibility Study

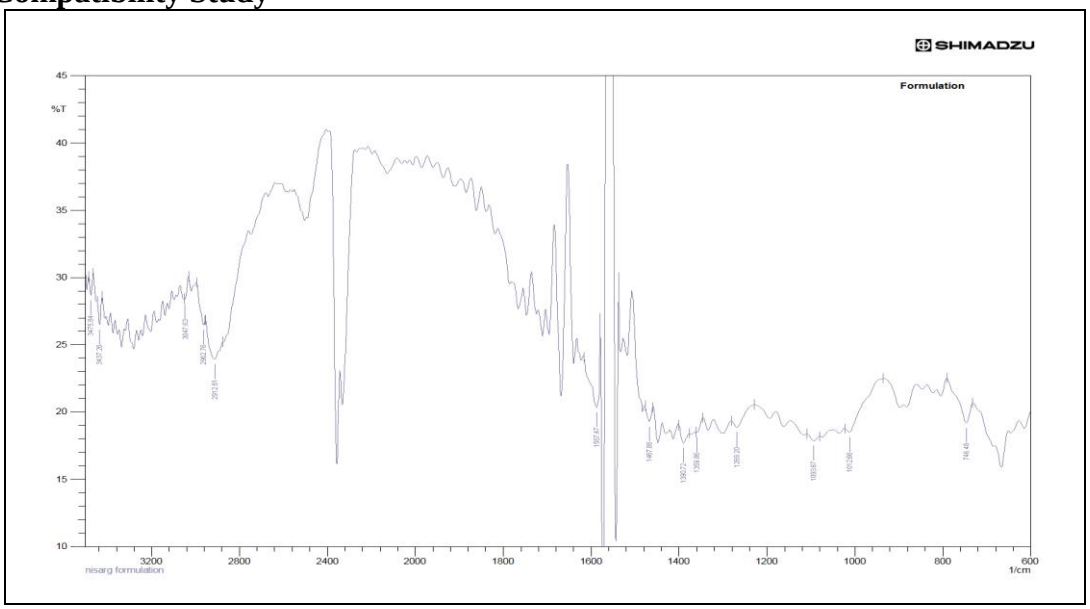

Fig.5. FTIR of Formulation

Table. 8. Characteristic peaks of Rabeprazole Sodium in FTIR Spectrum

Frequency (cm^{-1})	Description
3047	Aromatic C-H stretching
2926	Aliphatic C-H stretching
1584	Aromatic C-C, C-N
1465, 1369	Aliphatic C-H bending
1299, 1011	C-O stretching
1269	C-N stretching
1094	S-O stretching
747	Aromatic C-H bending

Drug-excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between rabeprazole sodium and the polymers used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

Table 9. Result of Flow property study of Rabeprazole Sodium

Drug	Angle of Repose(º)	Loose Bulk Density (gm/cc)	Tapped Bulk Density (gm/cc)	Carr's Index (%)	Hausner's Ratio
Rabeprazole Sodium	30.13°	0.466	0.564	27.48	1.37

2. Result of Flow Property Study

2.1 Preliminary Batches

2.1.1 Optimization of Stabilizer

Table. 10. Micromeritics properties of powder blends of different batches

Powder blend	Angle of Repose (^{0})	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's ratio	Drug Content (%)
F1	20	0.424	0.515	17.66	1.21	97.56
F2	18	0.432	0.519	16.76	1.2	98.32
F3	21	0.421	0.504	16.46	1.19	99.00
F4	23	0.391	0.514	23.92	1.31	98.21
F5	26	0.386	0.526	26.61	1.36	98.0
F6	30	0.396	0.538	26.39	1.35	98.10
F7	24	0.420	0.518	18.91	1.23	97.75
F8	29	0.418	0.521	19.76	1.24	98.64

F9	22	0.386	0.526	26.61	1.36	99.01
F10	26	0.432	0.510	16.0	1.18	98.30
F11	25	0.456	0.540	15.55	1.18	97.56
F12	21	0.386	0.525	26.47	1.36	99.01

Table. 11. Evaluation of Tablets

Formulation code	Average wt of tablets (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	213.0±0.04	1.90±0.07	4.0±0.01	0.43±0.04
F2	255.5±2.11	1.82±0.15	4.2±0.0	0.40±0.06
F3	214.0±2.83	1.90±0.01	3.9±0.13	0.44±0.02
F4	254.6±1.42	2.10±0.08	4.0±0.02	0.42±0.02
F5	213.5±0.706	2.05±0.067	3.9±0.15	0.54±0.03
F6	254.6±0.01	2.10±0.07	4.1±0.14	0.42±0.02
F7	273.0±0.02	2.20±0.02	3.8±0.0	0.39±0.04
F8	277.9±0.707	2.24±0.014	3.9±0.14	0.48±0.02
F9	299.1±2.82	2.34±0.01	3.9±0.12	0.48±0.01
F10	304.6±1.4	2.28±0.05	4.1±0.1	0.54±0.02
F11	309.2±1.5	2.36±0.05	3.9±0.13	0.58±0.02
F12	312.3±0.707	2.38±0.05	4.1±0.1	0.55±0.01

**The value denote Mean ± SD*

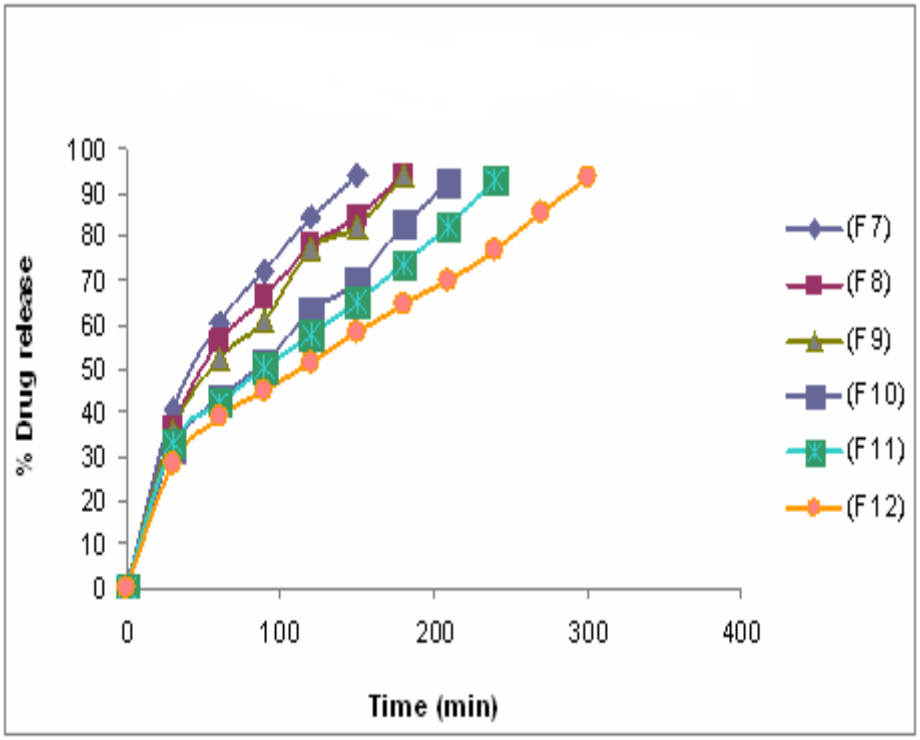

Fig.6. In Vitro Dissolution Profile of Preliminary Batches

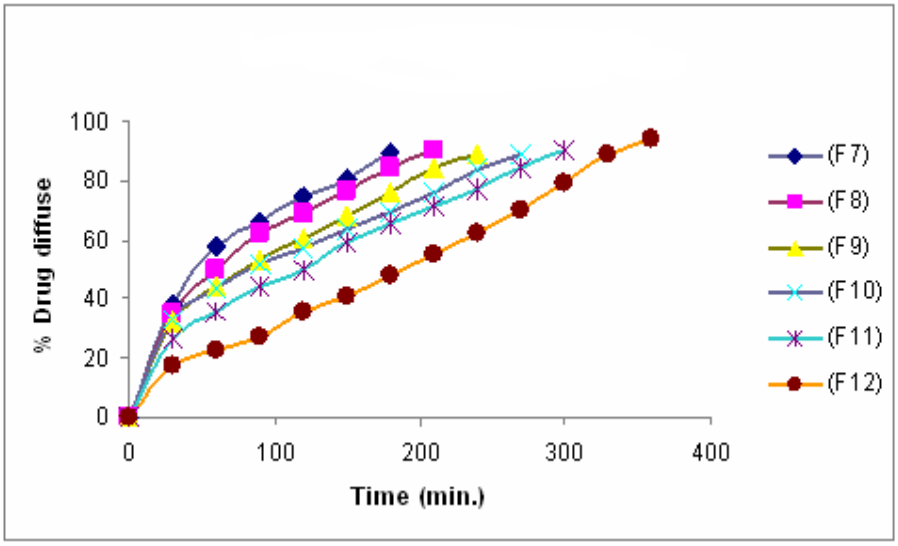

Fig. 7. In Vitro diffusion profile of preliminary batches using cellophane membrane

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. One is to attach firmly to the buccal mucosa and other in case of rabeprazole is the stability of Rabeprazole sodium in human saliva, since it is very unstable in acidic and neutral media. 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. The rabeprazole (20mg) tablets prepared with Gantrez or HPMC K4M did not collapse. However, turn 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 pressing 20mg of rabeprazole, 15mg of gantrez and different amount of alkali materials such as magnesium oxide, magnesium carbonate and sodium carbonate. In the formulation of oral enteric coated PPI granules and tablets, these alkali materials have been used as stabilizer of PPI. They prevented the decomposing of rabeprazole in acidic gastric fluid which penetrated into the enteric coating walls, since they provided the alkali environment for PPI. 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 shows that both batch F1 which contain 60 mg MgO and batch F2 which contain 100 mg magnesium oxide turns violet to black after 70 to 140 min. and drug content after was 83% to 86%. In case of batch F3 and F4 which contain $MgCO_3$, 60 and 100 mg respectively, tablet turns violet or black after 50 to 120 min. and drug content was 84.32% to 88.30%. In case of batch F5 and F6 which contain Na_2CO_3, which contain 60 and

100mg respectively, tablet turns violet or black after 110min. to 225 min. and drug content was 85.89% to 92%.
Sodium carbonate was selected as stabiliser 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 30-40mg, HPMC 8-16 mg and sodium carbonate 140 mg was considered.

3. Formulation and Optimization of Buccoadhesive Tablets by using 3^2 Full Factorial Designs

Table. 12. Micromeritic properties of powder blends of different batches

Formulation codes	Independent variable		Dependent variable	
	X_1	X_2	Y_1	Y_2
F13	-1	-1	12	91.72
F14	-1	0	12.61	101.68
F15	-1	+1	12.91	111.7
F16	0	-1	12.78	89.89
F17	0	0	13.23	95.9
F18	0	+1	13.61	106.08
F19	+1	-1	15.21	85.18
F20	+1	0	15.54	92.32
F21	+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 65mg Ethyl Cellulose as backing layer. Total weight (320 mg

3.1 Powder Blend Property

Table 13. Micromeritic Properties of Powder Blends of Different Batches

Powder blend	Angle of Repose (^{0})	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's ratio	Drug Content (%)
F13	19	0.486	0.593	18.04	1.18	98.56
F14	17	0.432	0.519	16.76	1.2	98.12
F15	24	0.421	0.504	16.46	1.19	97.00
F16	20	0.391	0.514	23.92	1.31	98.32
F17	25	0.490	0.568	13.73	1.13	99.0
F18	22	0.482	0.588	16.81	1.17	97.10
F19	20	0.420	0.518	18.91	1.23	97.15

F20	18	0.418	0.521	19.76	1.24	98.14
F21	19	0.497	0.591	15.90	1.16	99.11

Table 14. Evaluations of Tablets

Formulation code	Average wt of tablets(mg)	Thickness(mm)	Hardness (kg/cm^2)	Friability (%)
F13	315±0.32	2.2±0.12	4.0±0.23	0.40
F15	321±0.78	2.2±0.1	3.8±0.31	0.46
F16	317±0.65	2.3±0.06	4.0±0.43	0.44
F17	314±0.23	2.2±0.1	3.8±0.17	0.50
F18	318±0.65	2.1±0.09	4.2±0.32	0.42
F19	320±0.94	2.2±0.13	4.0±0.48	0.38
F20	318±0.68	2.1±0.09	4.0±0.23	0.36
F21	316±0.24	2.3±0.15	3.8±0.45	0.44

**The value denote the Mean ±SD (n=3)*

The micromeritic properties of the powder blend of the formulation were checked, wherein the angle of repose was found to be around 17 to 25°, which shows good flowing property of the blend. The loose bulk density and the tapped bulk density were found to be between 0.396-0.468 gm/cc. The Carr's index was observed to be 16.13 % and 23.92 % and hausner's ratio was found to be between 1.16-1.24. The drug content was in the range of 97.10 – 99.11 %, which passes the official requirement. This ensured the uniformity of the drug content in the tablets. Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. Hardness of the prepared tablets was observed within the range of 3.8 to 4.2 kg/cm^2. Thicknesses of all the tablets were found in the range of 2.1 to 2.3 mm.

10.4 Evaluation of *In-vitro* Dissolution

Regression Statistics		
Multiple R	0.999	
R Square	0.999	
Adjusted R square	0.998	
Standard error	0.055	
Observations	9	
Coefficients		
b_0	39.435	0.0002
b_1	-1.94	0.0004
b_2	0.310833	0.026
b_{11}	0.0326	0.0002
b_{22}	-0.00406	0.196
b_{12}	-0.00325	0.100
Equation		
$Y_1 = 39.435 - 1.94 (X_1) + 0.310 (X_2) - 0.000325(X_1X_2) + 0.0326 (X_{11}) - 0.10092 (X_{22})$		

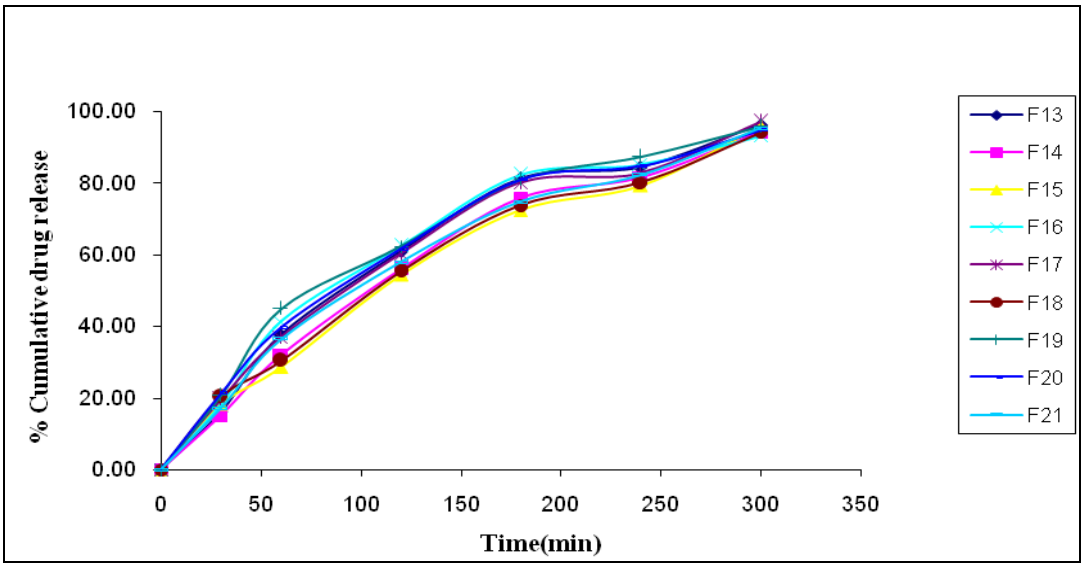

Fig. 8. In vitro Dissolution Study of Factorial Design

4. *In vitro* Bioadhesive Strength

Table 15. *In Vitro* Bioadhesive Strength

Formulation	Actual weight (gm)	Force for detachment (dyne)	Force detachment per unit area(dyne/cm^2)
F13	1.38	1356	12.06±0.08
F14	1.45	1425	12.61±0.09
F15	1.48	1459.34	12.91±0.04
F16	1.47	1444.65	12.78±0.18
F17	1.52	1495.51	13.23±0.28
F18	1.56	1538.47	13.61±0.19
F19	1.75	1719.33	15.21±0.19
F20	1.79	1756.64	15.54±0.24
F21	1.82	1792.81	15.86±0.14

*The value denoted Mean ± SD. (n=3)

4.1 *In Vitro* Bioadhesive Strength

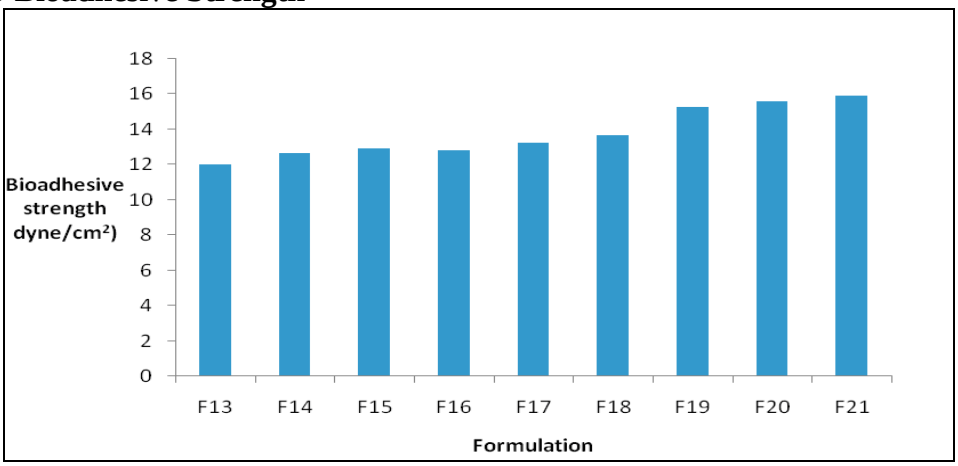

Fig.9. Evaluation of Bioadhesive Strength for Factorial Design

4.2 Effect of Variable on Bioadhesion

Table its the values of various response parameters of the nine optimization batches. The constant and regression coefficients for Y1 (bioadhesion force) 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=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 force, Y_1. The high 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. 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 mucoadhesive force 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.

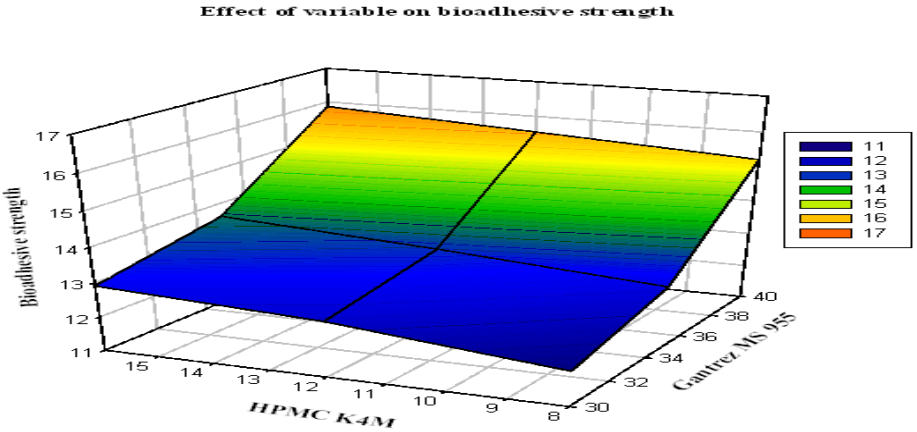

Fig. 10. Contour Graph for Y_1 (3-D)

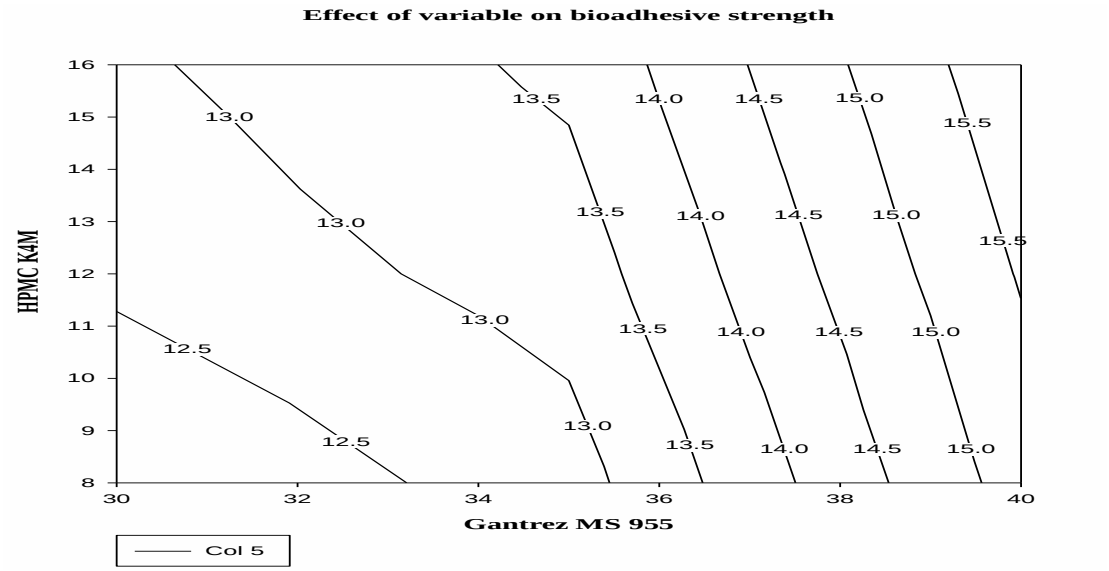

Fig. 11. Contour Graph for Y_1 (Bioadhesive Strength)

5. Time-Dependent Mucoadhesion Study

Table 16. Effect of time on bioadhesive strength

Time(min.)	Detachment force(dyne/cm^2)
0	0
5	12.54
15	15.25
25	17.86
40	20.65
65	20.8
80	21.2
120	21.43
300	22.32

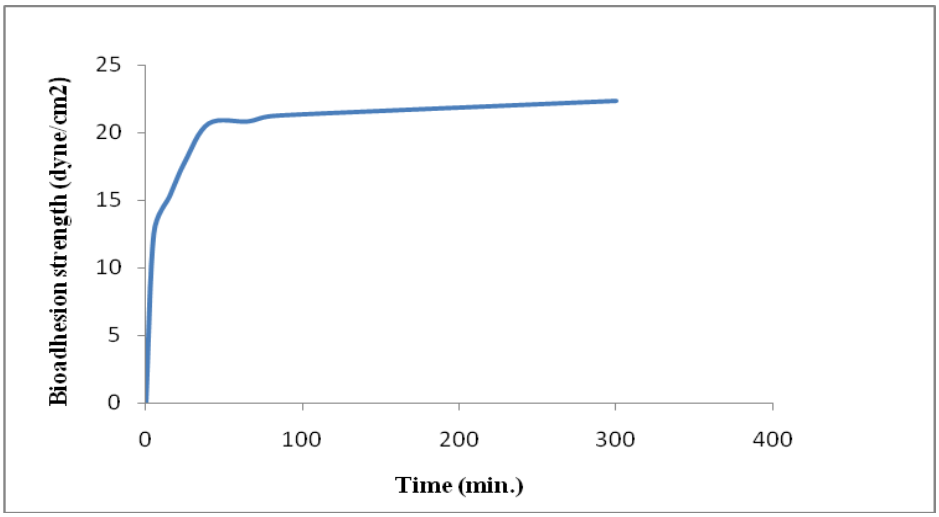

Fig. 12. Force of Detachment from Excised Sheep Buccal Mucosa for Directly Compressed Buccal Tablet for Batch F17

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 12. It can be noted that the values of the force of detachment increased with time for batch 17.

Additionally, batch 17 has 5 hr of in vitro residence time with sufficient amount of detachment force.

5.1 Effect of Variable on release Y_2 (50% Drug Release)

Regression Statistics		
Multiple R	0.9982	
R Square	0.9965	
Adjusted R square	0.9907	
Standard error	0.7909	
Observations	9	
Coefficients		
Coefficient	**Coefficient value**	**P-value**
b_0	58.68	0.133
b_1	0.957	0.588
b_2	4.26	0.029
b_{11}	-0.01	0.662
b_{22}	0.044	0.291
b_{12}	-0.09	0.017
Equation		
$\mathbf{Y_2=58.68+ 0.957(X_1) +4.26(X_2) – 0.09(X_1X_2)- 0.01 (X_{11})+0.044 (X_{22})}$		

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. 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.

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

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.

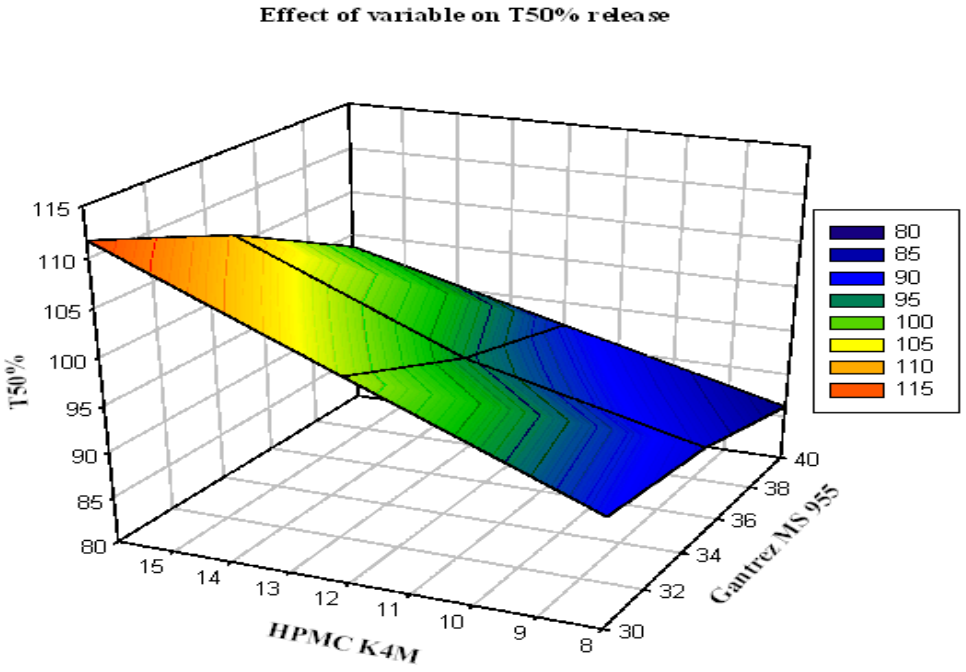

Fig. 13. Contour graph for Y_2 (3-D)

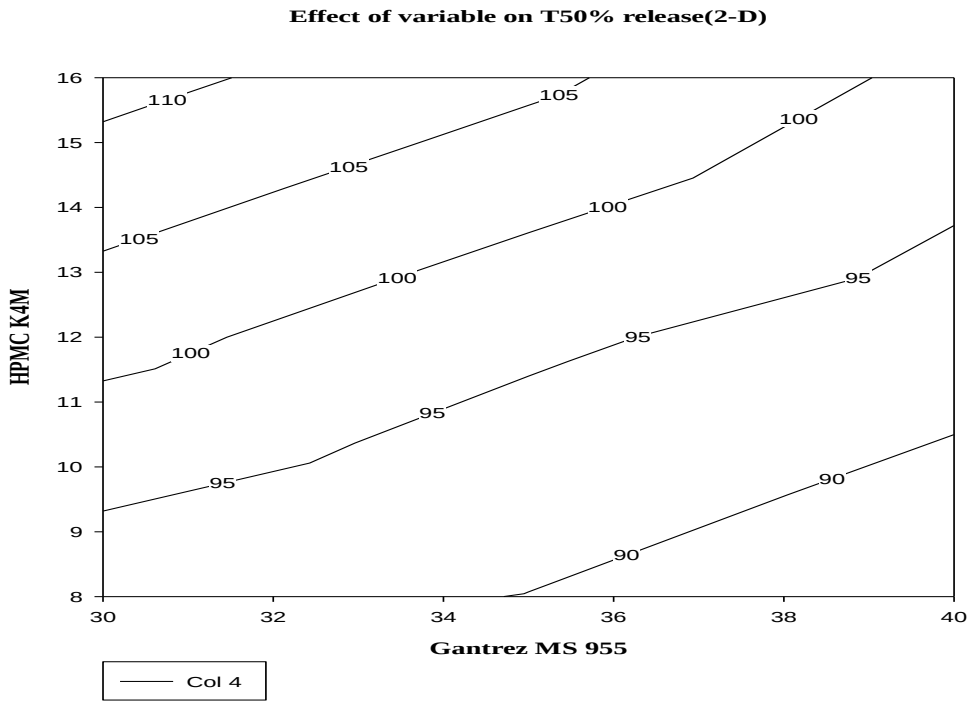

Fig. 14.Contour graph for Y_2 (T50%)

5.2 For the 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 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.

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%.

5.3 Drug Release Kinetic Studies from Buccal Tablet of Rabeprazole Sodium

Formulation	**Zero order (R^2)**	**First order (R^2)**	**Higuchi (R^2)**	**Hixon crowel (R^2)**	**Peppas**		
					R^2	**n**	**k**
F13	0.9605	0.8901	0.9887	0.9605	0.9834	0.7221	0.0173
F14	0.9764	0.9205	0.9953	0.9764	0.9939	0.7309	0.0156
F15	0.9845	0.9359	0.9960	0.9845	0.9960	0.7439	0.0142
F16	0.9442	0.8669	0.9802	0.9442	0.9719	0.7007	0.0196
F17	0.9647	0.8965	0.9901	0.9647	0.9852	0.7218	0.0172
F18	0.9797	0.9268	0.9960	0.9797	0.9951	0.7339	0.0151
F19	0.9486	0.8652	0.9486	0.9486	0.9699	0.7044	0.0196
F20	0.9551	0.8800	0.9551	0.9551	0.9782	0.7085	0.0186
F21	0.9756	0.9068	0.9756	0.9756	0.9889	0.7110	0.0176

As observed from the table, the values regression correlation coefficient for all the formulations was near to 0.99 in case of zero order drug release so drug release from tablet followed zero order drug release.

Drug release mechanisms of the matrix tablets were evaluated by using the Korsmeyer-Peppas semi-empirical model.

In this model, the value of n identifies the release mechanism of drug. For matrix type tablet, $0.45 \leq n$ corresponds to a Fickians diffusion mechanism, $0.45 < n \leq 0.89$ to Non-Fickians transport, and $n = 0.89$ to Case ll (relaxational) transport and $n > 0.89$ to Super Case ll transport.

The calculated exponent (n) indicates 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 form in the matrix. And HPMC K4M might be showing release based on diffusion mechanism.

5.4 *In vitro* Diffusion (Permeation) Study of Optimized Batch

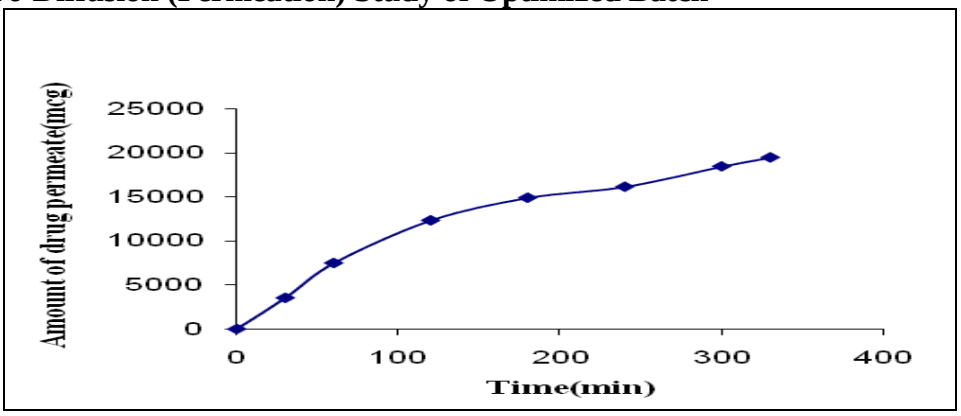

Fig. 15. In vitro diffusion (permeation) study of optimized batch using sheep buccal mucosa

To determine the diffusion study, Formulation 19 was selected because it required less time to release 50% of drug and having enough bioadhesive strength. As described in the chapter 5, diffusion was carried out. From the figure 15. it was observed that drug has sufficient amount of permeation *i.e.* agreement with the 90% of BCS guideline. As given in the method, flux was calculated. For batch F19, flux was 8.28 $\mu g.cm2^{-1}min^{-1}$and lag time was 298.1. This may be due to the higher hydration of polymer. Depending upon ratio of Gantrez, which also effect the diffusion of drug. Increase in the concentration of Gantrez leads to increase the diffusion of Rabeprazole sodium through the buccal mucosa.

Stability Study

Table. 17. Stability Study Parameter of Optimized F19 Up To 30 Days.

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	15.21	15.00	15.14

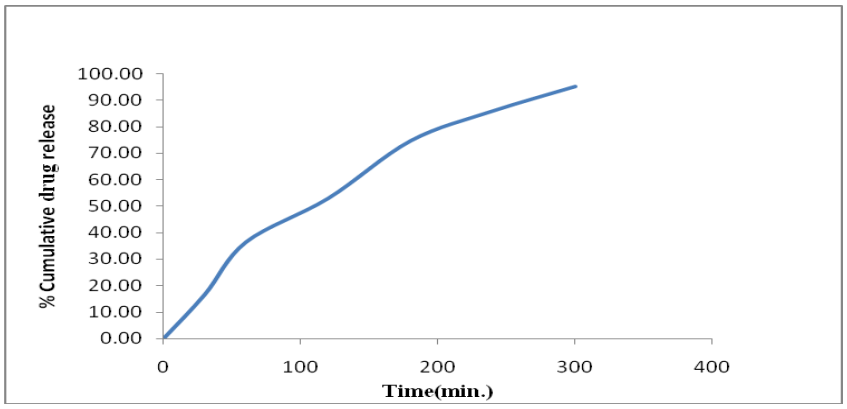

Fig. 16. In vitro dissolution of F19 batch after 30 days

After the 30 days stability of Formulation F19, values of all parameter like % drug content, bioadhesive strength, and were almost similar to the initial values. The result also showed there is no change in the tablet shape, color. The drug dissolution and diffusion profile was just a copycat of the initial profile. 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 bucco adhesive 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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