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Formulation and Evaluation of Mucoadhesive Buccal Tablet of Repaglinide

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ABSTRACT

The aim of present investigation was formulation and evaluation of mucoadhesive buccal tablet of Repaglinide to study the effect of different polymers on release profile of drug for prolonged release. In this study mucoadhesive buccal tablet were prepared by direct compression method. Various rheological characteristics of the powder bed like bulk density, compressibility index, and angle of repose were evaluated and studied. Mucoadhesive buccal tablets were compressed on a 8 station mini press using 10 mm flat faced punches and were all assessed for weight variation, hardness, thickness, percent swelling index, mucoadhesive strength and in vitro release of the drug by using USP TDT 08L dissolution testing apparatus method II using a paddle at 50 rpm. Data was optimized by using 3^2 full factorial design by using software named as design expert and with the help of kinetic study. The stability studies showed that there is no decrease in the drug content of all formulations for the period of 2 months.

Keywords: Buccal tablet, Repaglinide, HPMC K100M, Xanthan gum.

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INTRODUCTION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere biological surface for an extended period of time. Among the various routes of drug delivery the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosas are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities) offer distinct advantages over peroral administration for systemic effect. These advantages include possible bypass of first-pass effects and avoidance of presystemic elimination within the GI tract.

The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and trans-mucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, where as the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.

Mucoadhesive drug delivery systems

Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass in activation of drug.

MATERIALS &METHODS

Materials

Repaglinide was provided as sample from Swapnroop Laboratories Aurangabad. HPMC K100M, Chitosan, dextrose, mannitol, ethyl cellulose.

Ingredient used in formulation

Table1: Ingredient used in formulation.

Sr. No	Name of ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Repaglinide	10	10	10	10	10	10	10	10	10
2	HPMC K 100 M	15	15	15	20	20	20	25	25	25
3	Chitosan	15	20	25	15	20	25	15	20	25
5	Dextrose	35	35	35	35	35	35	35	35	35
6	Mannitol	25	20	15	20	15	10	15	10	5
7	Ethyl cellulose	100	100	100	100	100	100	100	100	100

Preformulation studies

Preformulation studies on the obtained sample of drug for identification and compatibility studies were performed

Characterization of the Drug

Organoleptic properties

The sample of Repaglinide was studied for organoleptic properties such as colour, odour and appearance.

Melting point

The melting points of Repaglinide were determined by melting point apparatus. Observed value was compared with the reported value.

Drug excipient compatibility study

Drug excipient compatibility was performed by liquid Fourier Transform infrared. It was performed by mixing drug with excipient in equal proportion and then IR spectrum was noted for mixture using NaCl cell. Small amount of the mixture was placed on the sample cell, the cell was then filtered in sample holder, spectra were scanned over a frequency range 4000-400cm-1 with FTIR instrument and the spectral analysis were done.

Preparation of Mucoadhesive buccal tablet (By Direct compression method)

1. Weighing of ingredients
2. Milling of drug and Excipients
3. Mixing of drug and Excipients
4. Tablet compression

EVALUATION OF MUCOADHESIVE BUCCAL TABLETS

Hardness test

Hardness test was conducted for three tablets from each batch and average values were calculated.

Weight variation test

Weight variation test was performed for ten tablets from each batch using an electronic balance and average values were calculated.

Table 2: Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

Thickness

The thicknesses of buccal tablets were determined using digital micrometer (Digital Caliper, Aerospace, India). Ten individual tablets from each batch were used and the average thickness was calculated.

Friability test

Friability of twenty randomly selected tablets from each formulation were determined by using the Roche type friabilator.

In vitro drug release for Repaglinide tablet

The drug release profile was studied using USP dissolution testing apparatus method II using a paddle at 50 rpm 900ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of 37 ±0.5°C was maintained. 5ml aliquots at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12 h respectively were pipette out and the same volume was replaced with pH 6.8 phosphate buffer. Absorbance was measured at λmax282nm and from which percentage of Repaglinide was calculated using calibration curve.

Table 3: In vitro drug release studies details

Apparatus used	USP Type II dissolution test apparatus
Dissolution medium	Phosphate buffer pH 6.8
Dissolution medium volume	900 ml
Temperature	37± 0.5°c
Speed of basket	50 rpm
Sampling intervals	1 Hrs
Sample withdraw	5 ml
Absorbance measured	282 nm

In vitro mucoadhesive strength

In vitro mucoadhesive strength of tablet was measured with goat Oral mucosa, using a modified physical balance. On one side of the balance, a rubber closure tied with thread was attached and on other side empty polythene bag was attached. Goat oral mucosa was obtained from a local slaughter house and stored in a phosphate buffer pH 6.8 upon collection. The experiments were performed within 3 h of collection of oral mucosa which has been separated from sheep stomach. The goat stomach mucosa was fixed to the opening of the glass vial with thread and then placed in a beaker, well packed. Phosphate buffer pH 6.8 was added into the beaker up to the upper surface of the buccal mucosa to maintained oral mucosal viability during the experiment. The tablet was sticked to the rubber closure with cyanoacrylate glue, then the beaker was raised slowly until contact between goat oral mucosa and tablet was established. A preload of 5 gm was placed on the clamp for 5 min (preload time) to establish adhesion bonding between tablet and goat oral mucosa. The preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp and water was then added in the polythene bag by pipette in drop-wise manner, at a constant rate. The weight of water required to detach tablet from stomach mucosa was noted as in vitro mucoadhesive strength, and these experiments were repeated with fresh mucosa in an identical manner. The modified physical balance for *in vitro* mucoadhesive strength determination consisting of polythene bag (on one side) and rubber closure for attachment of tablet (on other side).

Swelling Study

Buccal tablet are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8 for 8 hrs at regular interval of time (1, 2, 4, 6 and 8 hr) and The tablet are removed from the petri dishes and excess surface water is removed using filter paper. The tablet are weighed (W2) and swelling index (SI) is calculated as follows

$$SI = (W2-W1)/W1$$

Drug content uniformity

Ten tablets were accurately weighed and powder crushed in a glass pestle mortar. An accurately weighed amount equivalent to 5 mg of pure drug was taken, and the assay was performed UV spectrophotometer.

Optimization by 3^2 factorial designs:

Optimization is the key parameter in the development of any product factorial designs used to evaluate two or more factors simultaneously interactions can be determined in the factorial design. A study in which two factors and three levels are involved is called as 3^2 factorial design. For the present work 3^2 factorial design selected and 2 factors were evaluated at three possible levels by formulating all possible 9 formulation combination which are shown in table 3.

Formulation code assigned to the batches

$X_{1=}$ HPMC K100M

$X_{2=}$ Xanthan gum

Table 4: design summary.

Factor	Name	Unit	Type	Min.	Max.	-1 actual	+1 actual	Mean	Std. Dev.
A	HPMC K100M	%	Numeric	15	25	-1.00	1.00	40	12.18
B	Xanthan Gum	%	Numeric	15	25	-1.00	1.00	40	12.18

HPMC K100M and Chitosan are independent variable used in the formulation. They are mucoadhesive polymer to increase the residence time of formulation in oral cavity and also show their effect on mucoadhesive strength, swelling index, in vitro drug release.

Independent variable

X1= HPMC K100M

X2= Xanthan gum

Dependent variable

Y1= Drug release

Y2= Swelling index

Y3= Mucoadhesive strength

***In- Vitro* Drug Release Kinetic Study**

Zero Order Kinetics

A Zero order release would be predicted by the following equation,

$$Qt-Q0=K^0t$$

Where

Qt =Amount of drug release dissolved in time 't'

Co=Initial amount of drug concentration in solution.

K^0t=Zero order rate constant.

When the data were plotted as cumulative % drug release versus time, if the plot is linear then data obeys zero order kinetics with slope equal to K0. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First Order Kinetics:

A first order release would be predicted by the following equation

$$\text{Log } Qt=\text{Log } Q0-Klt/2.303$$

Where,

Qt=Amount of drug released in time 't'

Co=Initial amount of drug concentration in solution.

Klt=first order rate constant

When data were plotted as log cumulative% drug remaining versus time yields a straight line indicating that the release

follows first order kinetics. The constant K can be obtained multiplying slope values.

Higuchi's Model:

Drug release from the matrix device by diffusion has been described by Higuchi's diffusion equation

Ft=Q=VD5/T(2C-5Cs)Cst

Where,

Q=Amount of drug release dissolved in time't'.

Co=diffusion coefficient of drug in the release matrix.

Cs=Solubility of drug in the matrix.

5=porosity of matrix

t=Tortuosity

T=Time (h)

The equation may be simplified then the equation becomes,

Ft=Q=KhX t1/2

Where,

Kh=Higuchi dissolution constant

When data were plotted according to this equation, i.e. cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

PeppasKorsmeyer Equation

In 1983 korsmeyeret. al developed a simple, semiempirical model,when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t)

At/Ao=Kt/n

Where,

K=Constant

n=Release

t=Time

At and Ao=Absolute cumulative amount of drug released at times.

This is used when the release mechanism is not well known or when more than one type of a release phenomenon could be involved.

RESULT AND DISCUSSION

Preformulation study

Identification and Characterization of the Drug

Organoleptic Properties

The organoleptic properties of Repaglinide such as colour, appearance, odour was observed visually

Table 5: Identification tests of Repaglinide

Parameter	Reported value	Observed value
Appearance	Crystalline	Crystalline
Colour	White	White
Odour	Odourless	Odourless

Melting Point

The melting point was determined by melting point apparatus and the melting point was found to be

Table 6: Melting point of Repaglinide

Parameter	Standard	Observed
Melting Point	130-131^0 C	128-132^0 C

Solubility

Solubility of Repaglinide was checked in various solvents

Table 7: Determination of drug solubility in various solvents

Sr. No.	Solvent	Descriptive term
1	Methanol	Soluble
2	Water	Insoluble

DRUG EXCIPIENTS COMPATABILITY STUDY

Infra red spectrum

The FTIR spectrum of pure Repaglinide showed peaks in wave numbers (cm-1) which corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Repaglinide is shown in figure 1.

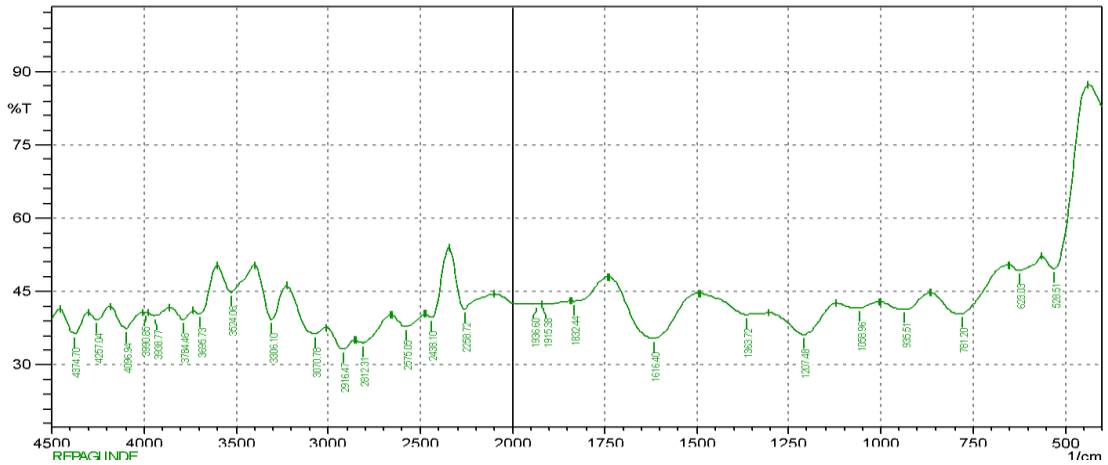

Figure 1: FT-IR Spectrum of Repaglinide.

Fourier transform infra-red spectroscopy (FTIR)

Infra-red spectra of drug and polymers showed matching peck with the drug spectra. The data obtained from the IR spectra showed no evidence of the interaction between the drug and the polymer studies. All the major characteristics pecks of the drug were present in the drug polymer combination spectra which indicate compatibility of drug with the polymers.

Drug + HPMC K100M

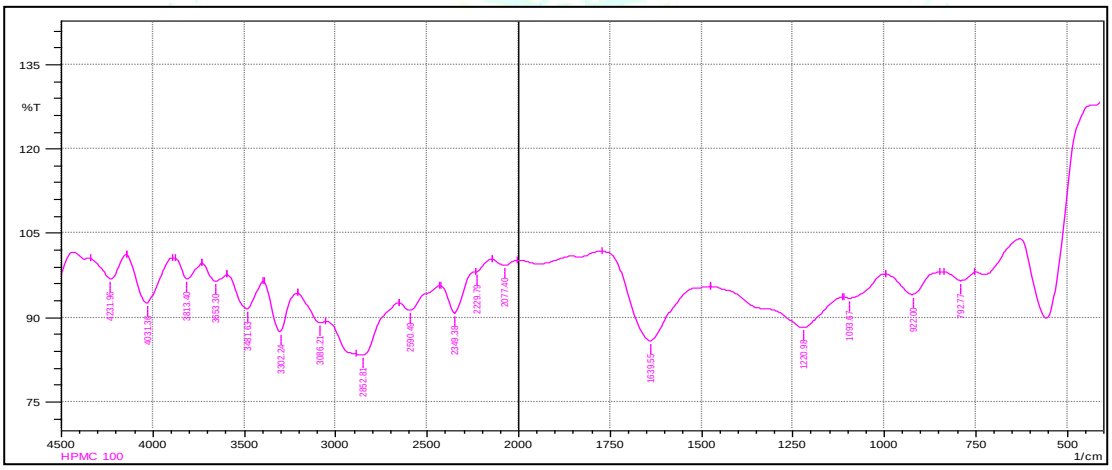

Figure 2: FTIR Spectrum of Drug + HPMC K100M

Drug + Chitosan

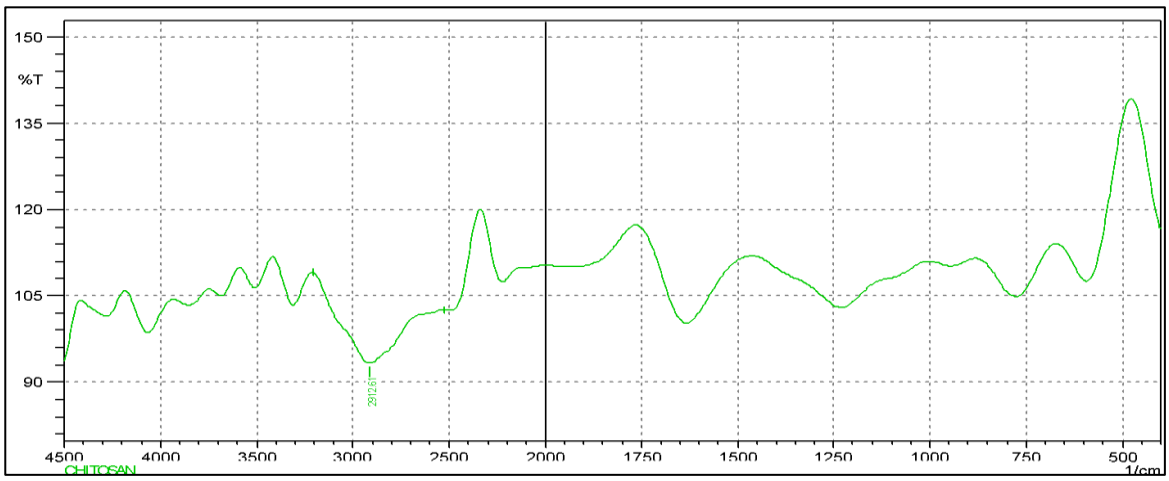

Figure 3: FTIR Spectrum of Drug + Chitosan Mixture

Differential Scanning Calorimetry

Thermal analysis of drug was carried out using DSC. The Differential Scanning Calorimetry curve of repaglinide profiles a sharp exothermic peak at 134^0 C corresponding to its melting, and indicating its crystalline nature and purity of sample. The DSC thermogram is shown in **Figure 4.**

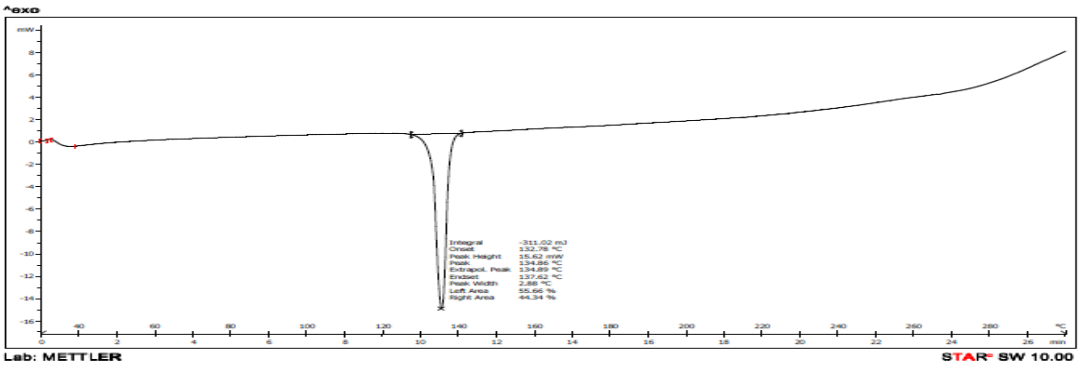

Figure 4: DSC Thermogram of Repaglinide

PRE-COMPRESSION PARAMETERS

Table 8: Pre compression parameters for Mucoadhesive buccal tablet

Formulation code	Angle of repose (^{0}) Mean ±S.D*	Bulk density(g/ml) Mean ±S.D*	Tapped density (g/ml) Mean ±S.D*	Carr's index (%) Mean ±S.D*	Hausner's ratio Mean ±S.D*
F_1	33.97±1.71	0.39±0.015	0.45±0.015	13.33±1.45	1.15±0.020
F_2	34.59±0.79	0.38±0.010	0.43±0.010	11.62±1.45	1.10±0.013
F_3	33.40± 0.86	0.36±0.005	0.41±0.010	12.19±0.94	1.13±0.011
F_4	30.46 ±0.83	0.37±0.006	0.41±0.016	09.75±1.63	1.10±0.008
F_5	30.71±0.68	0.37±0.011	0.42±0.016	11.24±1.67	1.12±0.012
F_6	32.82±1.05	0.38±0.008	0.42±0.008	09.52±1.28	1.10±0.016
F_7	29.74±1.03	0.37±0.009	0.42±0.008	11.90±0.86	1.13±0.021
F_8	31.47±0.98	0.37±0.010	0.43±0.009	13.95±1.50	1.16±0.020
F_9	31.76 ±1.22	0.38±0.013	0.44±0.010	13.63±0.99	1.15±0.015

***n=6**

POST COMPRESSION PARAMETERS

Table 9: Post compression parameters for Mucoadhesive buccal tablet

Formulation code	Hardness (Kg/cm2)*	Thickness (mm)*	Friability (%)*	Weight variation (mg)*	pH*
F_1	5.9±0.11	3.21±0.011	0.89±0.023	248±1.04	6.8±0.09
F_2	5.8±0.12	3.25±0.010	0.82±0.014	252±1.41	6.6±0.11
F_3	5.6±0.10	3.22±0.008	0.40±0.017	247±1.47	6.7±0.08
F_4	5.5±0.12	3.20±0.014	0.40±0.034	253±1.04	6.6±0.10
F_5	5.8±0.10	3.25±0.011	0.60±0.029	250±1.94	6.8±0.11
F_6	6.0 ±0.11	3.20±0.011	0.40±0.021	248±1.47	6.7±0.14
F_7	6.0±0.14	3.24±0.021	0.56±0.026	250±1.72	6.8±0.12
F_8	5.7±0.14	3.21±0.011	0.44±0.014	247±1.41	6.8±0.10
F_9	5.9±0.13	3.19±0.011	0.40±0.026	246±1.60	6.7±0.08

Drug content

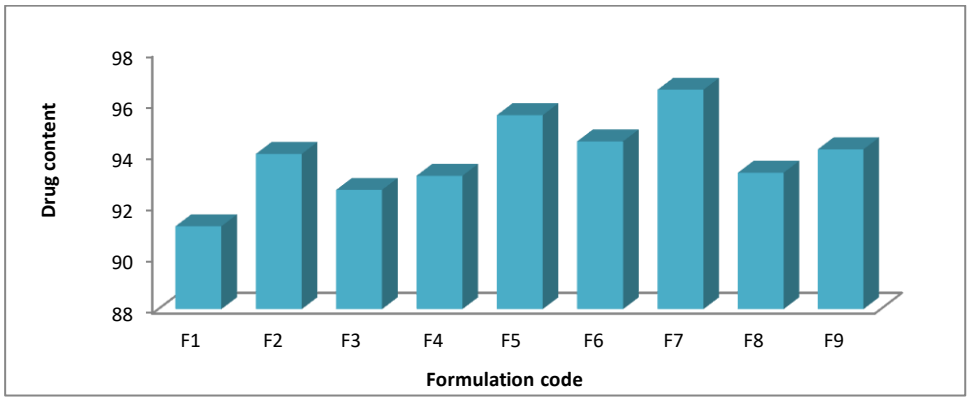

Figure 5: Graphical presentation of drug content

Swelling study

The swelling index of Repaglinide buccal tablet for 8 hrs. The water uptake nature of the polymer is one of the important properties that affect the onset of swelling. Swelling index increases with increases concentration of the HPMC K100M and xanthan gum. The formulation **F_7** possessing highest swelling index.

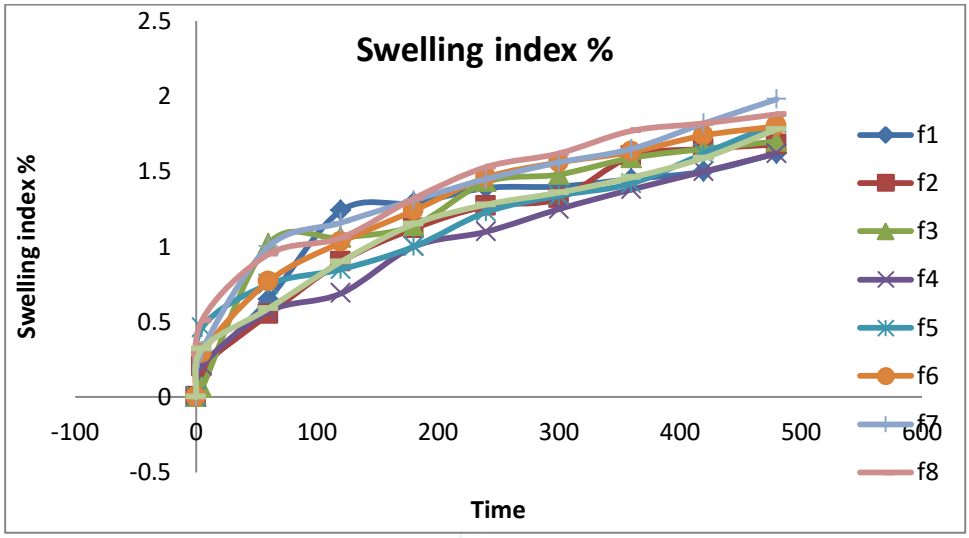

Figure 6: Graphical Presentation of swelling index

Mucoadhesive strength

The highest bioadhesion strength was possessed by the formulation containing HPMC K 100 M and Xanthan gum. Increases in the concentration of HPMC K100 M and Xanthan gum increases bioadhesion strength of the formulation.

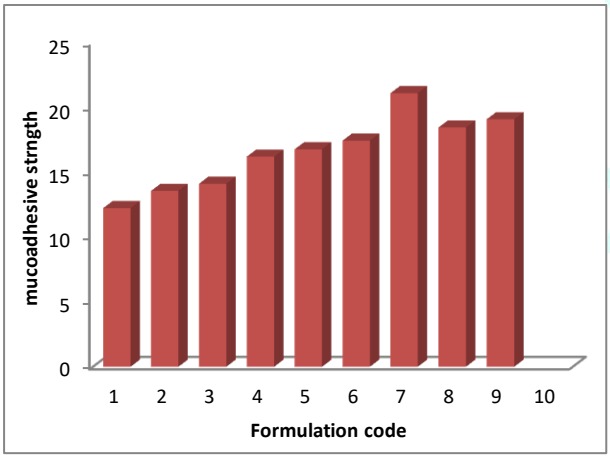

Figure 7: Graphical presentation of Mucoadhesive strength

In-vitro dissolution study

In -Vitro drug Release Studies of Repaglinide buccal tablets were determined using USP type II apparatus. The drug release was found to vary according to the ratio of mucoadhesive polymers. The formulation **F_7** showed the optimum drug release 96.21% at the end of 12 hrs containing HPMC K100M and xanthan gum.

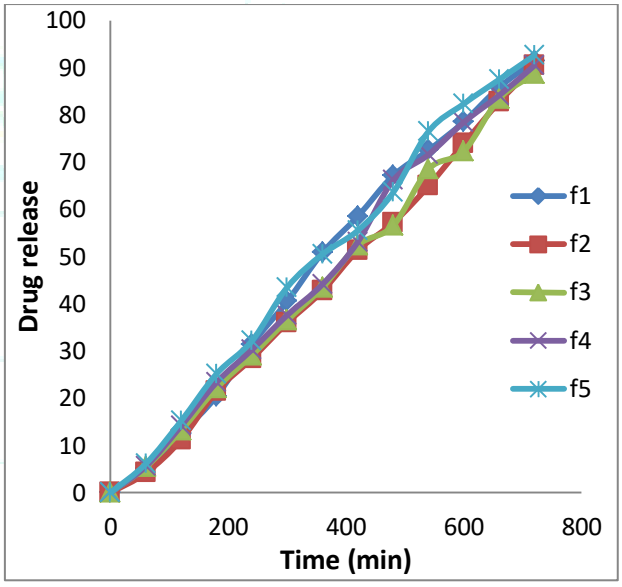

Figure 8: Graphical presentation of In-vitro drug release

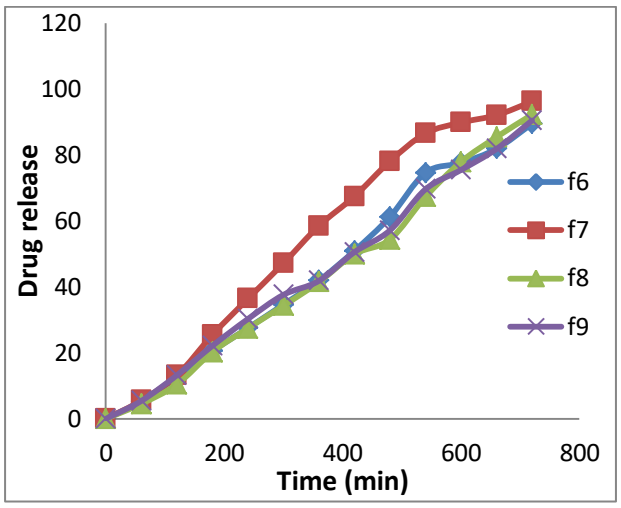

Figure 9: Graphical presentation of In-vitro drug release

Optimization

A 3^2 full factorial design was selected and 2 factors were evaluated at 2 levels, respectively. The percentage of HPMC K100M (X1) and Xanthan Gum (X2) were selected as independent variables and dependent variables drug release, swelling index, mucoadhesive strength. The data obtain were treated using design expert software and analyzed statistically using analysis of variance (ANOVA).

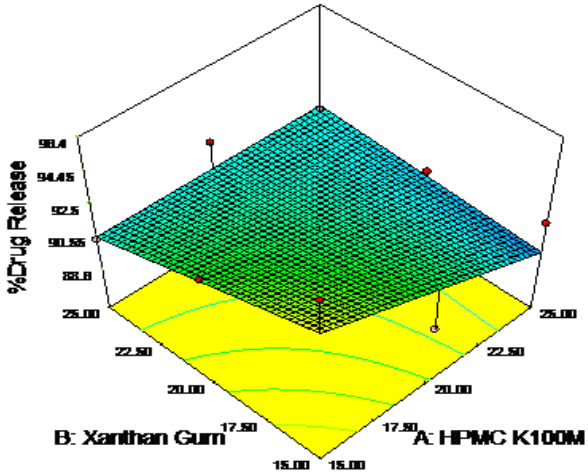

Figure 10: surface response plot showing effect of HPMC K100M and Xanthan Gum on drug release

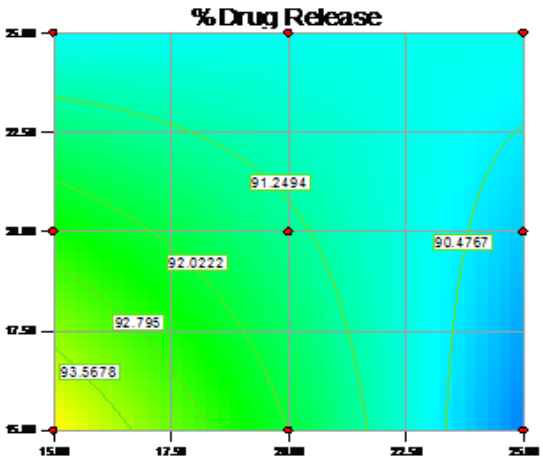

Figure 11: Counter plot showing effect of HPMC K100M and Xanthan Gum on drug release

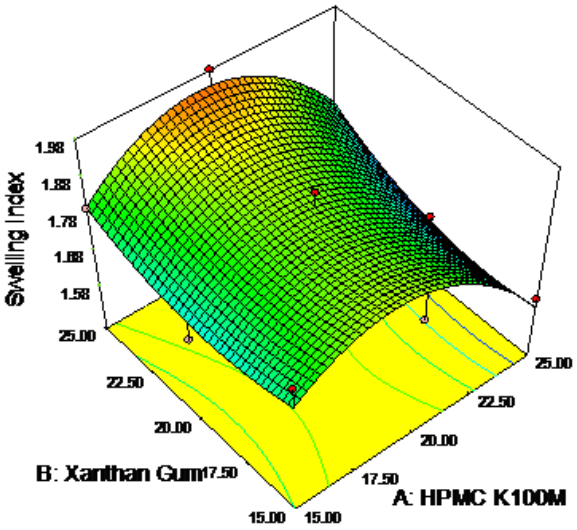

Figure 12: surface response plot showing effect of HPMC K100M and Xanthan Gum on swelling index

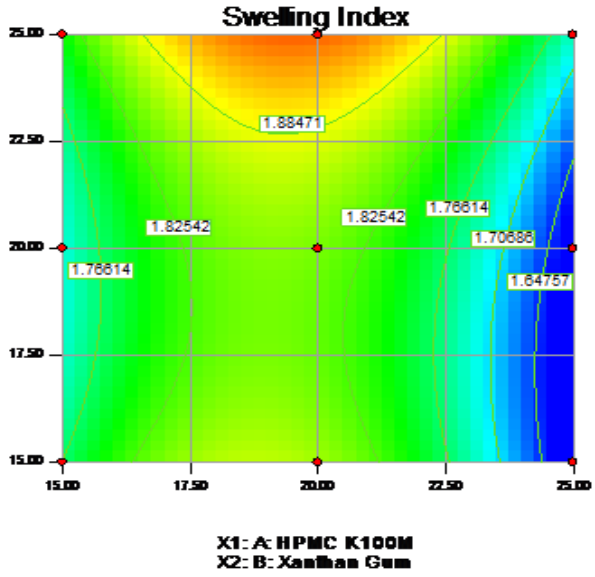

Figure 13: Counter plot showing effect of HPMC K100M and Xanthan Gum on swelling index

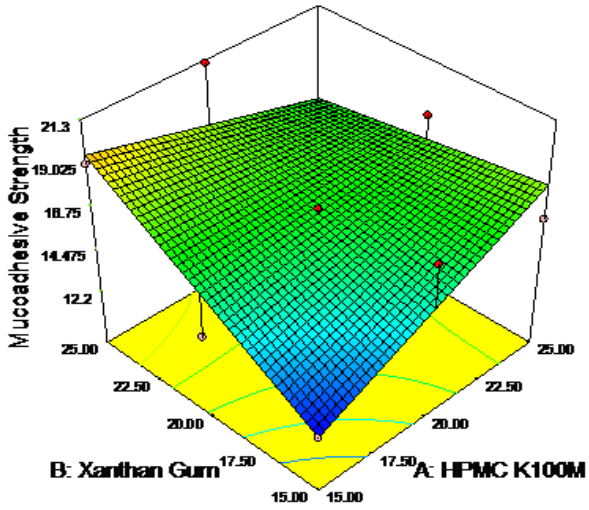

Figure 14: surface response plot showing effect HPMC K100M and Xanthan Gum on mucoadhesive strength

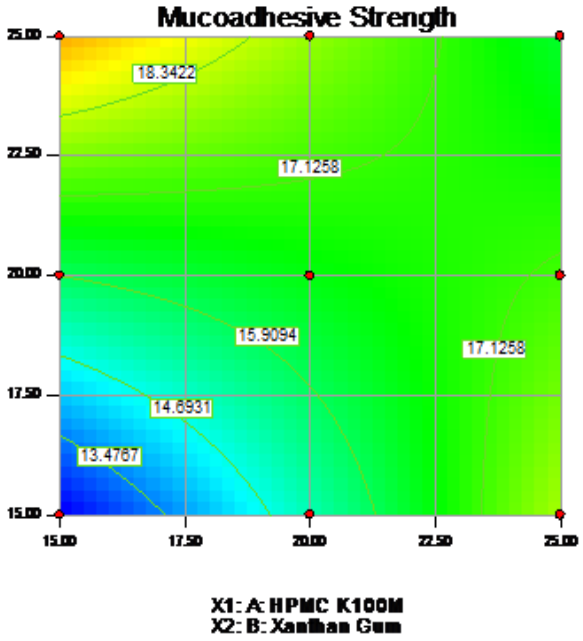

Figure 15: Counter plot showing effect of HPMC K100M and Xanthan Gum on mucoadhesive strength

From design expert optimum batch of HPMC K100M and Xanthan Gum was found to be optimized. From this data **F7** was selected as optimized formulation.

Kinetic Study

In the present study, the drug released mechanism from all formulation and evaluation of mucoadhesive tablet formulation different kinetic models was analyzed using factorial design batches followed zero order , first order model kinetic, Highuchi and Korsemeyer's Peppas model kinetics.

Table 10: R^2 values of Korsemayer's peppas model kinetics

Batch	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
R^2	0.923	0.994	0.914	0.909	0.925	0.986	0.939	0.967	0.979
N Value	0.523	0.562	0.589	0.526	0.549	0.563	0.578	0.512	0.545

The classical zero order released curved was found to be linear the curve plotted according to first order and Highuchi were also found to be linear respectively. For the Korsemeyer's Peppas released curves r^2 was found to be ≥ 0.90 for all formulation and n value was found to be ≥ 0.5 which indicate that all the formulation show anomalous or non-fickian diffusion. The drug release occurs probably by diffusion, erosion and dissolution follows.

Stability studies of Mucoadhesive buccal tablet of Repaglinide

Table 11: Stability study of optimized formulation

Sr .No.	Observations	Before Stability	Stability testing interval days	
			1 months	2 months
1.	General appearance			
	Color	No change	No change	No change
	Odor	No change	No change	No change
2.	Ph	6.4	6.5	6.4
3.	% Drug release	96.35	96.15	95.80
4.	% Drug content	96.50	97.05	96.87

Optimized formulation F_7 at 25 ^{0}c temperature was found to be stable up to 2 months. There was no significant change in appearance, drug release and drug content.

CONCLUSION

It was planned in this investigation to formulate and evaluate mucoadhesive buccal tablet of Repaglinide to release the drug in buccal cavity for extended period of time in order to avoid first pass metabolism to reduce the dosing frequency and to improve the patient compliant. Experiments were conducted to investigate the influence of polymer like HPMC K100M and xanthan gum bioadhesion strength and release kinetic of mucoadhesive tablet of Repaglinide. In vitro dissolution studies were conducted in apparatus II at 50 rpm for 12 hr. Drug content of all formulation were found to be more than 96.55%. The pH of all mucoadhesive formulation was in between 6.7 to 6.8. In vitro drug release result of all the formulation were conducted for 12 hrs of all tablet formulation **F1 -F9.** The formulations **F7** were taken as an optimized batch. It can be seen that by increasing the concentration of HPMC K100M and xanthan gum in the formulation, the drug release rate was found to be increased. The in vitro release kinetic indicate that all the formulation show anomalous or non-fickian diffusion. The drug release occurs probably by diffusion, erosion and dissolution follows. The data was statically analyzed and mechanism of release kinetic studied. All the studies were conducted at least 6 times and average was computed and tabulated.

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CONFLICT OF INTERESTS

Declared None.

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