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Formulation and characterisation of repaglinide buccal tablets

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ABSTRACT

The objective of this study was to develop effective buccal tablets of Repaglinide. Tablets of Repaglinide were prepared by direct compression method using bioadhesive polymers like Chitosan, Guar gum, Xanthan gum. Buccal tablets were prepared by taking polymers in different ratios. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, surface pH, *in-vitro* drug release, *ex vivo* drug permeation, *in vivo* mucoadhesive performance studies. *In vitro* assembly was used to measure the bioadhesive strength of tablets with fresh porcine buccal mucosa as model tissue. The tablets were evaluated for *in vitro* release in pH 6.8 phosphate buffer for 8 hr in standard dissolution apparatus. In order to determine the mode of release, the data was subjected to Zero order, First order, Higuchi, Korsmeyer and Peppas diffusion model. The formulation F3 showed maximum drug release (89.06%) in 8 hrs. The optimised formulation F3 showed a surface pH of 6.18. This formulation was following Zero order mechanism with regression value of 0.981. FT-IR studies revealed the absence of any chemical interaction between drug and polymers used. Repaglinide buccal tablets for buccal delivery could be prepared with required *in-vitro* release properties.

Keywords: Repaglinide, Buccal tablets, Chitosan, Guargum, Xanthan gum, *in-vitro* drug release.

INTRODUCTION

BUCCAL DRUG DELIVERY SYSTEMS

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs. But after oral drug administration many drugs are subjected to pre

systemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability[1-5]. Within the oral route, the Buccal cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism [6].

Buccal Delivery involves the administration of drug through buccal mucosal membrane (the lining in the oral cavity). ⁽¹⁾ The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability [7]. A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. Bioadhesive formulations have been developed to enhance the bioavailability [8,9] of drugs that undergo substantial first pass hepatic effect and to control the drug release to a constant rate [10] In addition, it should release the drug in a controlled and predictable manner to elicit the required therapeutic response [11-13] Various buccal mucosal dosage forms are suggested for oral delivery which includes: buccal tablets, buccal patches and buccal gels [14,15].

Advantages [17-21]

- Significant reduction in dose related side effects.
- It provides direct entry of drug into systemic circulation.
- Drug degradation in harsh gastrointestinal environment can be circumvented by administering the drug via buccal route.
- Drug absorption can be terminated in case of emergency.
- It offers passive system, which does not require activation.
- Rapid cellular recovery following local stress or damage.
- Ability to withstand environmental extremes like change in pH, temperature etc. Sustained Drug Delivery.
- The potential for delivery of peptide molecules unsuitable for the oral route.

Disadvantages [17,22,23]

- Once placed at the absorption site, the dosage form should not be disturbed.
- Eating and drinking are restricted.
- There is ever present possibility that the patient may swallow the formulation.
- Drug swallowed with saliva is lost.
- Drugs which are unstable at buccal pH and which irritate the mucosa or have a bitter or

unpleasant taste or an obnoxious odor cannot be administered by this route.

- Over hydration may lead to formation of slippery surface and structural integrity of formulation may get disrupted.

TERMINOLOGIES [16]

Buccal delivery

It is defined as drug administration through the mucosal membranes lining the cheeks (buccal mucosa).

Adhesion

It is defined as the bond produced by contact between a Pressure-sensitive adhesive and a surface.

Bioadhesion

It 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 to biological surface for an extended period of time. In the case of polymer attached to the mucin layer of a mucosal tissue, the term “mucoadhesion” is used.

BIOADHESIVE DELIVERY OF DRUG SYSTEM IN ORAL CAVITY [16]

Sublingual delivery

Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth,

Buccal delivery

Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa) and

Local delivery

Which is drug delivery into the oral cavity [24]

STRATEGIES FOR BUCCAL DRUG DELIVERY SYSTEMS

The buccal route has been one of the areas studied as a part of the effort to explore alternative administration routes that might be deficient in

enzymatic degradation, particularly for drugs, which show acceptable permeation characteristics.

General criteria for candidate's drug [22-24]

One of the drug properties required for the practical buccal formulation will be high pharmacological activity or a low dose requirement. The Limit size of the dosage form should not exceed 12 cm² for buccal application or 3cm² for sublingual or gingival application. The following properties will make the drug suitable candidate for buccal delivery:

- ✓ In general, any drug with a daily requirement of 25mg or less would make a good candidate
- ✓ Relatively short biological half-life:- Drugs with biological half-life 2-8 hr will in general be good candidates for sustained release dosage forms
- ✓ The maximal duration of buccal delivery is approximately 4–8 hr
- ✓ Drug must undergo first pass effect or it should have local effect in oral cavity.
- ✓ Drugs susceptible to degradation:-Drug degradation either by stomach/intestinal enzymes or by first pass hepatic metabolism will be assured protection in buccal dosage form.
- ✓ Drug must undergo first pass effect or it should have local effect in oral cavity.

MATERIALS AND METHOD

MATERIALS

Repaglinide was Procured From Torrent Pharmaceutical Ltd., Ahmedabad, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Chitosan, Guar gum, Xanthan gum, Magnesium stearate, Talc, Microcrystalline cellulose, Potassium Dihydrogen *ortho* phosphate Purified LR, Sodium hydroxide pellets, Agar – agar powder.

METHOD

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Chitosan, guar gum and Sodium carboxy methyl cellulose are the mucoadhesive and biodegradable polymers used in

this preparation of buccal mucoadhesive drug delivery systems.

Repaglinide was mixed manually with different ratios of chitosan, guar gum and sodium carboxy methyl cellulose and microcrystalline cellulose as diluent for 10 min. The blend was mixed with talc and magnesium stearate for 3-5 min.

EVALUATION PARAMETERS

Evaluation of Pre-Compression Blend

The quality of tablet, once formulated, by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characterization of blends produced. Prior to compression, granules were evaluated for their characteristic parameter such as Tapped density, Bulk density, Carr's index, Angle of repose, Hausner's ratio. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus.

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

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

Where, θ = angle of repose

h = height of the cone

r = radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density ρ_b , is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment. 30 gm of

powder blend introduced into a dry 100 mL cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume V_0 , was read. The bulk density was calculated using the formula:

$$\rho_b = M/V_0$$

Where, ρ_b = Apparent bulk density.

M = Weight of the sample.

V_0 = Apparent volume of powder.

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm per mL, using the formula:

$$\rho_{tap} = M/V_f$$

Where, ρ_{tap} = Tapped density.

M = Weight of the sample.

V_f = tapped volume of the powder.

Carr's index

The compressibility index (Carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measure of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index which is calculated using the following formula:

$$\text{Carr's index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] \times 100$$

Where, ρ_b = bulk density

ρ_{tap} = tapped density

Hausner's ratio

It is the ratio of tapped density to the bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to

predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

$$\text{Hausner's Ratio} = \rho_{tap} / \rho_b$$

Where, ρ_{tap} = Tapped density.

ρ_b = Bulk density.

EVALUATION OF BUCCAL TABLETS:

Physicochemical characterization of tablets

The prepared Repaglinide buccal tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation

The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity.

The percent deviation was calculated using the following formula:

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Tablet Thickness

The Thickness and diameter of the tablets from production run is carefully controlled. Thickness can vary with no change in weight due to difference in the density of granulation and the pressure applied to the tablets, as well as the speed of the tablet compression machine. Hence this parameter is essential for consumer acceptance, tablet uniformity and packaging. The thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets is calculated and presented with standard deviation.

Tablet Hardness

Tablet hardness is defined as the force required to breaking a tablet in a diametric compression test. Tablets require a certain amount

of strength, or hardness and resistance to friability, to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm².

Friability

Tablet hardness is not an absolute indicator of the strength because some formulations when compressed into very hard tablets lose their crown positions. Therefore another measure of the tablet strength, its friability, is often measured. Tablet strength is measured by using Roche friabilator. Test subjects to number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as

Friability (%) = $\frac{\text{Initial weight of 10 tablets} - \text{final weight of 10 tablets}}{\text{Initial weight of 10 tablets}} \times 100$

Initial weight of 10 tablets

$F(\%) = \frac{W_0 - W}{W_0} \times 100$

Where, W_0 is the initial weight of the tablets before the test and

W is the final weight of the tablets after test.

Assay

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45 μ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 241 nm using pH6.8 phosphate buffer.

IN VITRO RELEASE STUDIES

The drug release rate from buccal tablets was studied using the USP type II dissolution test

apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 241nm.

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppas's model – Log cumulative % drug released versus log time.

Zero order kinetics

Zero order release would be predicted by the following equation:-

$$A_t = A_0 - K_0 t$$

Where, A_t = Drug release at time 't'.

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr⁻¹).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K_0 .

First Order Kinetics

First – order release would be predicted by the following equation:-

$$\log C = \log C_0 - K t / 2.303$$

Where, C = Amount of drug remained at time 't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr⁻¹).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D \square / \square (2 A - \square Cs) Cst]^{1/2}$$

Where, Q = Amount of drug released at time 't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

$\square$ = Porosity of the matrix.

$\square$ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes:

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer equation / Peppas's model

To study the mechanism of drug release from the buccal tablets of Repaglinide, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppas's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_a = Kt^n$$

Where, M_t / M_a = the fraction of drug released at time 't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get

$$\log M_t / M_a = \log K + n \log t$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for

anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0.

In vitro bioadhesion strength

Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced force gauge equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK) according to method describe as it is fitted with 25kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the buccal tablet to be tested was adhered to another cylindrical stainless steel adaptor similar in diameter using a cyanoacrylate bioadhesive. Mucin 100 μ l of 1 %w/v solution was spread over the surface of the buccal mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5mm/sec until the tablet was completely detached from the mucosa. The work of adhesion was determined from the area under the force distance curve.

The peak detachment force was maximum force to detach the tablet from the mucosa.

Force of adhesion = Bioadhesion strength $\times$ 9.8

1000

Bond strength = Force of adhesion

surface area

Surface pH

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffer (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3)

Moisture absorption

Agar (5% m/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of

the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Initial weight

Ex vivo residence time

The Ex vivo residence time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 ml of phosphate buffer, pH 6.8, at 37°C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (figure 10). The time for complete erosion or detachment from the mucosa was recorded.

Ex vivo permeation studies through porcine buccal mucosa

The aim of this study was to investigate the permeability of buccal mucosa to Repaglinide. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption.

Tissue permeation

Buccal tissue was taken from Pigs slaughter-house. It was collected within 10 minutes after slaughter of pig and tissue was kept in Krebs buffer solution. It was transported immediately to the laboratory and was mounted within 2hrs of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove the adherent material. The buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from underlying connective tissue. Sufficient care was taken to prevent any damage to the epithelium.

PROCEDURE

Ex vivo permeation study of Sodium carboxy methyl cellulose through the porcine buccal mucosa was performed using Franz diffusion cell

and membrane assembly, at 37°C ± 0.2°C and 50 rpm. This temperature and rpm was maintained by magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughter house and used within 2 hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. After the buccal membrane was equilibrated for 30 min with the buffer solution between both the chambers, the receiver chamber was filled with fresh buffer solution (pH 6.8), and the donor chamber was charged with 5 mL (1mg/mL) of drug solution. Aliquots (5mL) were collected at predetermined time intervals up to 8 hr and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 241 nm using a UV spectrophotometer. The medium of the same volume (5 mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber.

The experiments were performed in triplicate (n = 3) and mean values were used to calculate flux (J) and permeability coefficient (P).

$$J = (dQ/dt)$$

A

$$P = (dQ/dt)$$

ΔC

Where,

J is Flux (mg.hrs-1cm-2)

P is permeability coefficient (cm/h)

dQ/dt is the slope obtained from the steady state portion of the curve

ΔC is the concentration difference across the mucosa and A the area of diffusion (cm²)

RESULTS

Drug – excipient compatibility studies by physical observation

Repaglinide was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.

FTIR

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Repaglinide drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Repaglinide

are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

EVALUATION

Characterization of pre-compression blend

The pre-compression blend of Repaglinide buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio. Angle of repose was less than 28° , carr's index values were less than 11 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Evaluation of buccal tablets

Physical evaluation of Repaglinide buccal tablets

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 22. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.6 to 5 kg/cm² and the friability values were less than 0.561% indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 2.71 - 2.91 mm. All the formulations satisfied the content of the drug as they contained 98-100% of Repaglinide. Thus all the physical

attributes of the prepared tablets were found to be practically within control limits.

In vitro release studies

The *in vitro* drug release studies Sodium CMC in the Polymer concentration 30% of the total tablet weight (F10), is showing better result 89.73 % drug release when compared with other three formulations. In case of F9 formulation the polymer was to produce required bioadhesion strength and the maximum drug was released in 8 hrs. where as in F11, F12 formulations the concentration become high and the drug release was retarded more than 8 hrs, hence it was not taken in to consideration.

DISCUSSION

Based on the all studies F3 formulation was found to be better when compared with all other formulations. F3 formulation has shown more residence time when compared with other formulations. F3 formulation shown good moisture absorption. The surface pH of the F3 formulations was found to be 6.81 and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations were not irritant to the buccal mucosa. Peak detachment force (N) and work of adhesion were calculated and they were found to be good for the formulation F3. Swelling index value was also found to be good for this formulation. F3 formulation was showing maximum flux value, permeability coefficient value i.e., 418.445 (µg.hrs-1cm-2), 0.4122 (cm/hrs) respectively. This formulation was following Zero order release mechanism with regression value of 0.981 and n value was found to be 0.612 which indicates it follows non fickian drug release pattern..

Table 1: Formulation Chart

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Repaglinide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Chitosan	2	4	6	8	-	-	-	-	-	-	-	-
Guargum	-	-	-	-	2	4	6	8	-	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	2	4	6	8
MCC pH 102	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Physical properties of pre-compression blend

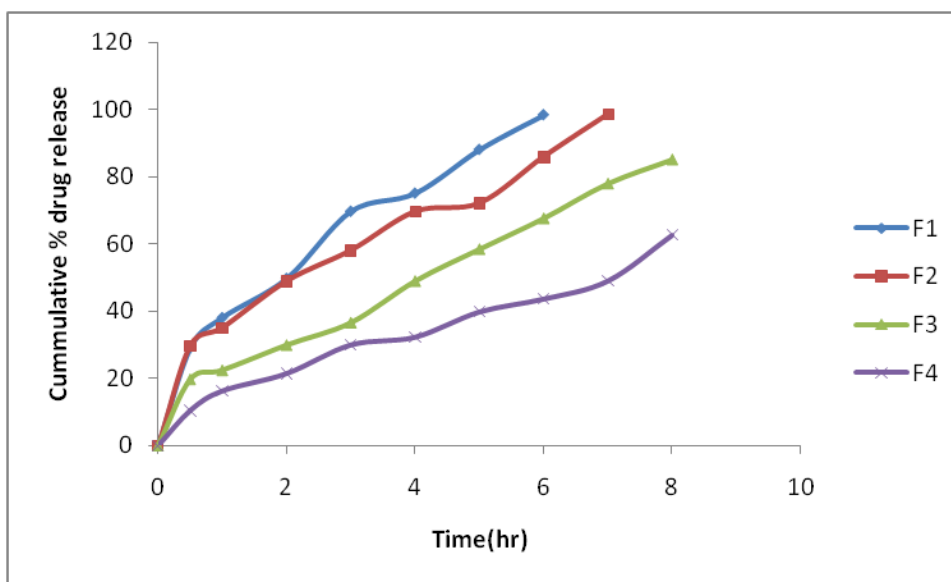
Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's Index (%)	Hausner's ratio
F1	25.10°	0.52	0.60	13.33	1.15
F2	25.43°	0.52	0.62	16.12	1.19
F3	25.41°	0.50	0.59	15.25	1.18
F4	26.40°	0.53	0.62	14.51	1.16
F5	27.12°	0.56	0.64	12.50	1.14
F6	25.31°	0.58	0.68	14.70	1.17
F7	26.11°	0.55	0.64	14.06	1.16
F8	26.15°	0.52	0.59	11.86	1.13
F9	26.10°	0.53	0.62	14.51	1.16
F10	25.95°	0.53	0.60	11.69	1.13
F11	25.43°	0.52	0.59	11.86	1.14
F12	25.41°	0.51	0.57	10.52	1.11

Table 3 : Physical evaluation of Repaglinide buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Content uniformity (%)
F1	102	2.76	4.6	0.430	99
F2	103	2.74	4.3	0.391	101
F3	101	2.71	4.0	0.383	103
F4	97	2.80	4.6	0.491	108
F5	98	2.81	3.9	0.522	98
F6	97	2.74	4.2	0.563	97
F7	98	2.76	5.1	0.532	99
F8	100	2.71	4.7	0.492	98
F9	99	2.73	4.2	0.482	100
F10	300	2.95	4.1	0.513	99
F11	301	2.74	3.9	0.521	99
F12	295	2.78	4.2	0.492	98

Table 23 : *In vitro* dissolution data for formulations F1 - F4 by using Chitosan Polymer

Time (hrs)	% Cumulative drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	29.04	29.73	19.73	10.42	19.28	13.56	10.75	8.53	28.42	17.42	15.06	9.56
1	38.06	35.04	22.42	16.23	22.93	15.58	12.54	12.60	36.57	28.89	19.73	15.24
2	49.72	48.92	29.90	21.40	33.78	21.99	19.59	18.70	48.91	37.59	25.07	21.65
3	69.68	58.06	36.56	29.91	46.97	28.77	22.94	21.35	57.07	46.35	37.45	28.78
4	75.06	69.57	48.93	32.23	52.43	37.42	28.72	26.87	62.74	52.75	42.09	32.67
5	88.06	72.08	58.40	39.73	58.74	45.97	35.23	31.55	76.72	67.58	49.56	37.72
6	98.36	85.90	67.58	43.56	66.56	53.23	42.06	39.72	87.91	79.23	53.48	41.35
7	-	98.56	77.92	48.94	78.73	67.58	52.43	42.97	95.23	82.42	62.74	43.23
8	-	-	89.06	62.56	89.90	75.83	62.40	48.73	-	89.73	73.42	48.84

**Fig 16: *In vitro* dissolution data for formulations F1 - F4 by using Chitosan polymer**

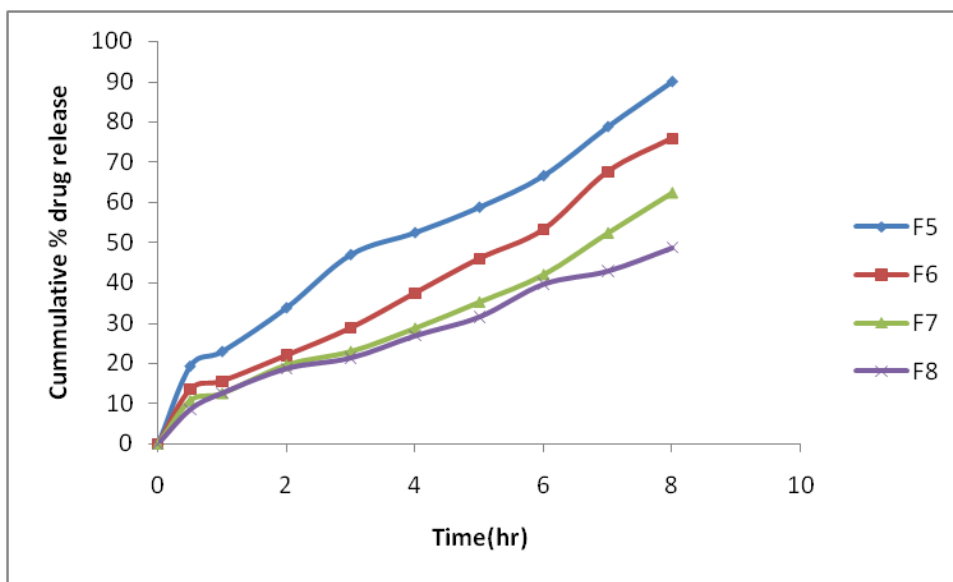


Fig 17: *In vitro* dissolution data for formulations F5 - F8 by using Guar gum polymer

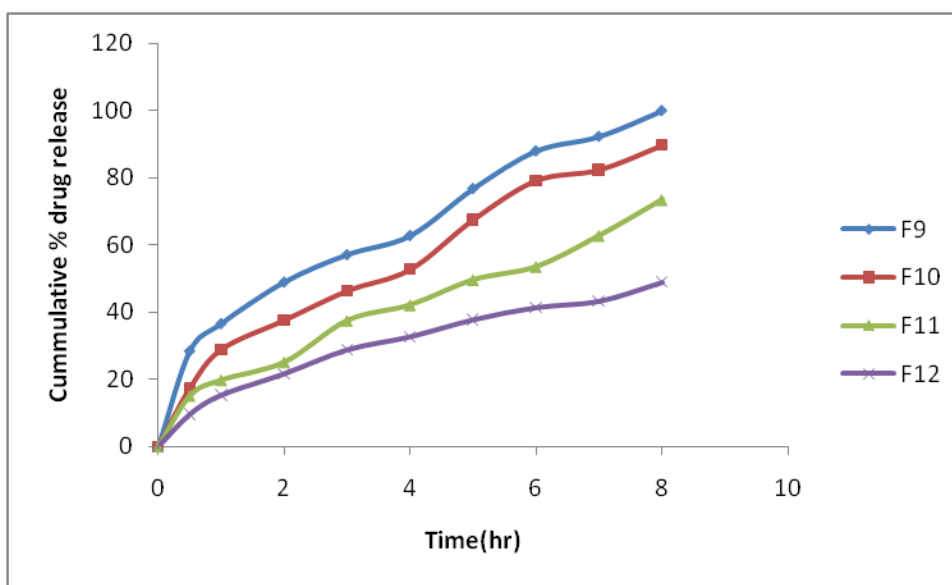


Fig 18 : *In vitro* dissolution data for formulations F9- F12 by using Sodium CMC polymer

Table 28 : *Ex vivo* residence time, moisture absorption, surface pH, bioadhesion strength values of selected formulations.

Formulation Code	<i>Ex vivo</i> residence time (hrs)	Moisture absorption	Surface pH	Bioadhesion strength	
				Peak detachment force (N)	Work of adhesion (mJ)
F3	7hr 51min	62	6.18	4.5	16.43
F5	7hr 34min	53	6.11	4.5	15.24
F10	6hr 33min	49	6.14	4.9	13.43

Ex vivo residence time

Is one of the important physical parameter of buccal bioadhesive tablets. The *ex vivo* residence time was determined by specially designed apparatus. Among the selected formulations F3 formulation has shown more residence time when compared with other formulations.

The moisture absorption

Studies give important information of the relative moisture absorption capacities of polymers and it also give information regarding whether the formulations maintain the integrity or not. Among the selected formulations F3 formulation shown good moisture absorption.

The surface pH of

The buccal tablets was determined in order to investigate the possibility of any side effects. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The

surface pH of the selected formulations was found to be 6.71 to 6.81 and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations were not irritant to the buccal mucosa.

Bioadhesion strength

Was measured for the selected formulations. From this two parameters such as peak detachment force (N) and work of adhesion were calculated and they were found to be good for the formulation F3.

Ex vivo permeation studies through porcine buccal mucosa

The aim of this study was to investigate the permeability of buccal mucosa to Repaglinide. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption was shown in table 30 & fig 22.

Table 30: Ex vivo permeation studies of selected formulations through porcine buccal mucosa

Time (hrs)	F3	F5	F10
0	0	0	0
0.5	19.73	19.28	17.42
1	22.42	22.93	28.89
2	29.90	3378	37.59
3	36.56	46.97	4635
4	48.93	52.43	52.75
5	58.40	58.74	67.58
6	67.58	66.56	79.23
7	77.92	78.73	82.42
8	89.06	89.90	89.73
Flux ($\mu\text{g.hrs}^{-1}\text{cm}^{-2}$)	499.43	469.32	434.38
Permeability coefficient (cm/hr)	0.4994	0.2218	0.1525

From the Table it was evident that selected formulations were showing good flux and permeability coefficient values. Among the selected formulations F3 formulation was showing maximum flux value of 499.43 ($\mu\text{g.hrs}^{-1}\text{cm}^{-2}$) and permeability coefficient value was 0.4994 (cm/hrs).

CONCLUSION

Development of bioadhesive buccal drug delivery of Repaglinide tablets is one of the alternative routes of administration to avoid first pass hepatic metabolism effect and provide prolonged sustained release of drug.

Buccal tablets of Repaglinide were prepared by direct compression method using various bioadhesive polymers like Chitosan, Guar gum, xanthan gum in different ratios.

The formulated buccal tablets were evaluated for different parameters such as drug excipient compatibility studies, weight variation, thickness, hardness, content uniformity, *In vitro* drug release, surface pH, *ex vivo* residence time, moisture absorption studies, *ex vivo* drug solution and tablets permeation through porcine buccal mucosa. *In vitro* drug release studies performed in phosphate buffer pH 6.8 for 8hrs in standard dissolution apparatus the data was subjected to zero order, first order, Zero and First diffusion models.

The following conclusions could be drawn from the results of various experiments

- The feasibility of delivering Repaglinide was investigated by conducting *ex vivo* permeation studies using freshly prepared porcine buccal mucosal membrane.
- FTIR studies concluded that there was no interaction between drug and excipients.
- The physico-chemical properties of all the formulations prepared with different polymers like Chitosan, Guar gum, Xanthan gum were shown to be within limits.
- Properties and from the results, it was concluded that the *in vitro* drug release,

moisture absorption studies, surface pH, *ex vivo* residence time, swelling studies and *ex vivo* permeation studies of the optimized formulations is suitable for buccal delivery.

- *In-vitro* drug release studies demonstrated the suitability of developed formulations for the release of Repaglinide.
- Finally suitable formulations were selected and *ex-vivo* permeation studies were conducted by using freshly prepared porcine buccal mucosal membrane. Satisfactory drug release rates and final percentage of drug release could be obtained from the selected formulation.
- The present study concludes that buccal delivery of Repaglinide tablets can be a good way to bypass the first metabolism and to prolong duration of action of drug by reducing the frequency of dosing of Repaglinide. Present study concludes that buccal drug delivery system may be a suitable method for Repaglinide administration. The optimised formulation was found to be F3 formulation.

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