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FORMULATION AND EVALUATION OF BUCCAL MUCOADHESIVE TABLETS OF REPAGLINIDE

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ABSTRACT

Aim: The present work was performed to develop and evaluate buccal tablet containing antidiabetic drug (Repaglinide). **Background:** Repaglinide is poorly water soluble drug which comes under BCS Class II. By formulating as buccal tablets using polymers can enhance the solubility and bioavailability of drug in biological fluids yields therapeutic window. **Method:** By Direct Compression method prepared buccal tablets. Ethyl cellulose was used as backing membrane and Carbopol 934p, Polyoxwsr N-80 NF, HEC and HPC was used as bucco adhesive polymer. Aspartame was used as sweetener. **Results:** F5 formulations showed maximum amounts of drugs release (87.18%) at the end of 10 h dissolution study. F5 also showed maximum bioadhesion (0.0754N) and the resident time of F5 formulation was 9.2 h. It shows 41.52% drug release after 10 h permeation study through porcine buccal mucosa mounted in Franz cell. The tablet also found stable in human saliva after 10hr. The tablet was not showed any type of physical changes after the completion of 10 h. **Conclusion:** The results of the study suggested that new buccal tablet formulations of combined bucco-adhesive polymers can be suitably developed as an alternate to conventional dosage forms.

KEYWORDS: Buccal tablets, Carbapol 934p, Direct compression, Repaglinide.

INTRODUCTION

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption. Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery, because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect). The medicament is placed between the cheek and the gum. The barrier to drug absorption from this route is the epithelium of oral mucosa. Passive diffusion is the major mechanism for absorption of drugs. Drugs with short biological half-lives, requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via bioadhesive buccal delivery systems.

RELEVENT WORK

Vaishali A. Chaudhari al.,(2014) The objective of the study was to develop mucoadhesive buccal tablet of Flurbiprofen. Tablets of Flurbiprofen were prepared by direct compression method using mucoadhesive polymers like Carbopol 934P, HPMC K4M and Sodium Alginate in different ratios. Buccal tablets were evaluated by different methods for parameters such as thickness, hardness, weight uniformity, drug content uniformity, swelling index, matrix erosion, surface pH, mucoadhesive strength, in vitro drug release, stability studies. The tablets were evaluated for in vitro release in pH 6.8 phosphate buffer for 10 hr in standard dissolution apparatus. Mucoadhesion strength was increased with increase in the concentration of carbopol.

BALAGANI PAVAN KUMAR et.al., (2014) The tablets were prepared using Carbopol 934 in varying concentration with secondary polymers like HPMC K4M, HPMC K15M and sodium alginate by direct compression method. The tablets were further evaluated for their mucoadhesive characteristics such as surface pH, swelling index, ex vivo residence time, mucoadhesive strength, ex vivo permeation, in vitro drug release and also for the effect of Carbopol concentration on mucoadhesive parameters. The surface pH of the tablet was 6.48 to 6.75 which fall in the range of salivary pH and all the tablet of batch C containing sodium alginate as secondary polymer showed ex vivo residence time of 10 to 12.30 hrs indicated

good mucoadhesive capacity of tablet. The buccal tablets showed good swelling up to 8 hrs maintaining the integrity of polymers.

MATERIALS AND METHODOLOGY

Drugs and chemicals

Repaglinide was purchased from Dr.Reddys Labs Ltd, Hyderabad and other chemicals used were Carbopol 940P (Nihar traders pvt Ltd), HPMCK15M (Finar chemicals Ltd), HPMCK100M (Finar chemicals Ltd), Magnesium stearate (Himedia Laboratories Ltd), Potassium dihydrogenortho phosphate ((Finar chemicals Ltd).

METHODOLOGY

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. HPMCK4M, HPMCK15M, HPMCK100M and Carbopol934P are the mucoadhesive and biodegradable polymers used in this preparation of buccal mucoadhesive drug delivery systems. Repaglinide was mixed manually with different ratios of HPMCK4M, HPMCK15M, HPMCK100M and carbopol 934P and Microcrystalline Cellulose as diluent for 10 min. In every formulation constant amount of PVPK30 was added as binding agent. The blend was mixed with talc and magnesium stearate for 3-5 min. Then the powder blend was compressed into tablets by the direct compression method using 8 mm flat faced punches. The tablets were compressed using 8 station Cemach rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge.

RESULTS

Calibration curve of Repaglinide in phosphate buffer pH 6.8 (λ_{max}=416nm)

Table 1: Calibration curve of Repaglinide in phosphate buffer pH 6.8 (λ_{max}=416nm).

Concentration(µg/ml)	Absorbance
5	0.112
10	0.324
15	0.567
20	0.628

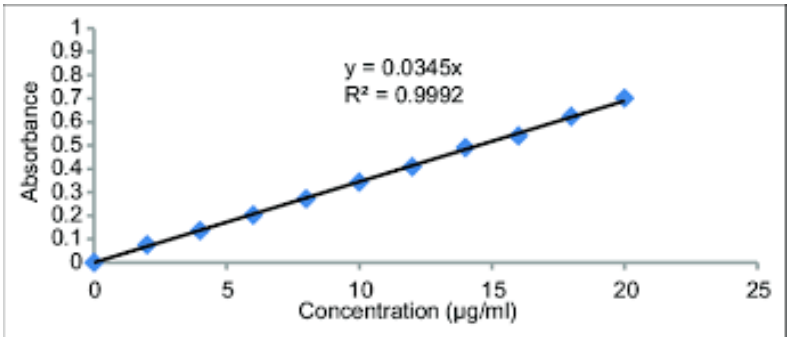

Fig 1: calibration curve in phosphate buffer of Repaglinide.

Formulation and preparation of tablets

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Table 2: Composition of buccal tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	2	2	2	2	2	2	2	2	2
HPMCK15M	10	20	30	-	-	-	-	-	-
CARBOPAL 972	-	-	-	10	20	30	-	-	-
CARBOPAL 940	-	-	-	-	-	-	10	20	30
PVPK30	15	15	15	15	15	15	15	15	15
MCC pH 102	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Mg. Stearate	3	3	3	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3	3	3	3
Total Weight (mg)	60	60	60	60	60	60	60	60	60

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.

A. 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:

% Deviation = (Individual weight – Average weight / Average weight) X 100

The average weight of tablets in each formulation was calculated and presented with standard deviation.

Table 3: Pharmacopoeial specifications for tablet weight variation.

Average weight of tablets (mg)	Maximum % of difference allowed
80 or less	10
More than 80 but less than 250	7.5
250 or more	5

B. 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. 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.

C. 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/cm^2.

D. 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:

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

$F\ (\%) = [Wo\text{-}W/W_O]\ X100$

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

W is the final weight of the tablets after test.

E. 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 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 272 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 272nm.

a. Release kinetics

Data of *invitro* release was fit into different equations to explain the release kinetics of candesartan release from buccal tablets. The kinetic equations used were zero – order and first order equations.

Swelling Studies

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.8) solution. At regular intervals (0.5,1, 2, 3, 4, 5 and 6hr), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2**)** (Ritthidej et al., 2002). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq**.**

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} X\ 100$$

***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 µl 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.

$$\text{Force of adhesion} = \frac{\text{Bioadhesion strength}}{1000} x\ 9.8$$

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\text{Surface area}}$$

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:

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

***In vitro* residence time**

The *in vitro* 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 37^0C. 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.

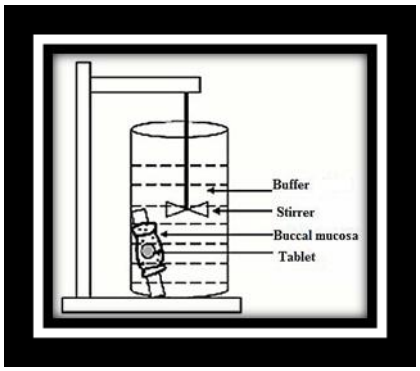

Fig 2: Schematic representation of *in vitro* residence time study.

Ex vivo permeation studies through porcine buccal mucosa

The aim of this study was to investigate the permeability of buccal mucosa to candesartan. 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 candesartan 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 inter wells up to 8 hr and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 272 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).

$$J = \frac{(dQ/dt)}{A}$$

$$P = \frac{(dQ/dt)}{\Delta CA}$$

Where, J is Flux ($mg.hrs^{-1}cm^{-2}$)

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 (cm^2)

CONCLUSION

The present study was aimed at an attempt to develop sustained release drug delivery system for Repaglinide. Repaglinide tablets were formulated into a sustained release dosage form using the optimum amount of PEG, HPMC and Carbopol along with other common tabulating occupants to sustain as well as extend the drug release over a period of 24 hours. The present study was undertaken to develop sustained release matrix tablets of 4 mg.

Seven formulations of sustained release matrix tablets were developed and evaluated. The formulation F4 showed a drug release 98.4% whereas the other formulation showed that 83 to 94.6. In-vitro drug release studies revealed that the drug was sustained over a period of 24 hours.

To conclude the In-vitro dissolution profile of Formula 4 has shown the highest release of Repaglinide with the optimum amount of PEG, HPMC and Carbopol prepared by using direct compression method. Hence the further work of this formulation can bring a marketable product.

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REFERENCES

1. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003.
2. Vidyadhara S, Rao PR., Prasad JA., Indian J. Pharm Sci, 2004; 66: 188-192.
3. Reddy KR., Mutalik S, Reddy S, AAPS Pharm. Sci. Tech, 2003; 4: 1-9.
4. Mohammed AD., James LF., Michael HR., John EH., Rajabi-Siahboomi AR., Phar. Dev. Tech., 1999; 4: 313-324.
5. Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind. Pharm, 1999; 25: 493-501.

6. Gwen MJ and Joseph RR, In Banker GS and Rhodes CT, Eds., Modern Pharmaceutics, 3rd Edn, Vol. 72, Marcel Dekker Inc. New York, 1996; 575.
7. Salsa T, Veiga F And Pina M.E, Drug Develop. Ind. Pharm, 1997; 23: 931. Publication Ref No.:
8. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Revised and Expanded, Drugs and The Pharmaceutical Sciences, Vol 72., Marcell Dekker, Inc., New York, 1995; 575-609.
9. Altaf AS, Friend DR., MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology Marcell Dekker Inc., New York.
10. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Revised and Expanded, Drugs and The Pharmaceutical Sciences, Vol 72, Marcell.
11. Brahmankar HA, Jaiswal SB, Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, 2000; 348-357 and 337.
12. Venkatraman S, Davar A, Chester A, Kleiner L, Wise DL, An overview of controlled release systems, Handbook of Pharmaceutical Controlled Release Technology, New York, Marcel Dekker, Inc, 2000, 431-465. 14) Qiu Y, Zhang G and Wise DL.
13. Kamboj S, Gupta GD, Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms, 2009, 7 (6), www.pharmainfo.net/review.
14. Lieberman HA, Lachman L and Schwartz JB., Pharmaceutical Dosage Forms: Tablets, Volume 3, 2nd edition, 199-287. 1. Williams G. Management of non-insulin dependent diabetes mellitus. Lancet, 1994; 343: 95-100.
15. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet, 1998; 352: 837-53.
16. Gromada J, Dissing S, et al. The effects of the hypoglycemic drugs repaglinide and glibencamide on ATP-sensitive potassium-channels and cytosolic calcium levels in beta TC3 cells and rat beta pancreatic cells. Diabetologia, 1995; 38: 1025-32.
17. Balfour JA, Faulds D. Repaglinide. Drugs & Aging, 1998; 13: 173-80.
18. Fuhlendorff J, Rorsman P, et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes, 1998; 47: 345 51.

19. Hatorp V, Nielsen K, et al. Bioavailability of repaglinide after administration as either 2mg tablet or 2mg I.V. Infusion. J Clin Pharmacol, 1997; 37: 874 (Abstract 70).
20. European Agency for the Evaluation of Medicinal Products. European Public Assessment Report Novonorm CPMP/866/98.
21. Guay DRP. Repaglinide, a novel, short-acting hypoglycemic agent for Type 2 diabetes mellitus. Pharmacotherapy, 1998; 18: 1195-204.
22. Van Heiningen PNM, Hatorp V, et al. Disposition of one dose of 14C-repaglinide during non-labelled repaglinide multiple dosing. Diabetes, 1998; 47(suppl 1): A355 (abstract1374).
23. Hatorp V, Bayer T. Repaglinide bioavailability in the fed or fasting state. J Clin Pharmacol, 1997; 37: 875 (abstract 72).