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Stability And Invivo Studies Of Mucoadhesive Buccal Tablets (Repaglinide) For Management Of Diabetes

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Abstract:

Repaglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus. The main objective of the study was to formulate and evaluate bioadhesive buccal tablets to avoid the first pass metabolism in liver. Bioadhesive buccal tablets were prepared by direct compression method using bioadhesive polymers like HPMC K4 M, HPMC K15 M, Chitosan, HPMC K100 M, Sodium CMC, Carbopol 974 P, Sodium Alginate, Gum karaya and Carbopol 941NF in different ratios. *In vivo* mucoadhesive behavior of optimized formulation was performed in New Zealand rabbits and pharmacokinetic parameters were evaluated. The Stability studies were carried out for best formulation.

Keywords: Repaglinide, buccal tablet, Stability studies, *In vivo* permeation.

INTRODUCTION

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 presystemic 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 gastrointesinal tract as well as first pass hepatic metabolism.[6]

The primary objectives of mucoadhesive dosage forms[7]are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body including the buccal mucosa, gastrointestinal tract, the urogential tract, the airways, the ear, nose, and eye. It represents potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system includes

- Buccal delivery system
- Gastrointestinal delivery system
- Nasal delivery system
- Ocular delivery system
- Vaginal delivery system
- Rectal delivery system

Buccal Delivery System[7]

The unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach, or which are extentensively metabolized in the liver (first pass effect).

Delivery through Sublingual Mucosa

Sublingual delivery traditionally involves systemic administration of drug via membranes of the floor of the mouth or the ventral surfaces of the tongue. The sublingual mucosa is relatively permeable due to thin membrane and large veins, hence allows rapid absorption and acceptable bioavailability of many drugs. Moreover, the sublingual mucosa is a smooth surface and free of mucous and undigested food, therefore, it is conveniently accessible for application of dosage forms.

Local Delivery to Mouth[(8)]

Local delivery to mouth includes any system that is applied to the oral mucous membrane in order to treat conditioning of the mouth such as periodontal diseases, gingivitis, oral candidisis and other chronic lesions or topical fungal infections. Traditional methods of delivery to the diseased site include chewing gums, mouthwashes, ointments and gels.

Gastrointestinal drug delivery system[(7-8)]

The ideal of mucoadhesive began with the clear need to localize a drug at certain sites in the GIT. Therefore, a primary objective of using mucoadhesive system orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit one daily dosing.

Nasal drug delivery system[(9)]

The nasal mucosa provides a potentially good route for systemic drug delivery. With a surface area of 150 cm^2, a highly dense vascular network, and relatively permeable membrane structure, the nasal route has good absorption potential. One of the most important features of the nasal route is that it avoids first-pass hepatic metabolism, thereby reducing metabolism**.**

Ocular drug delivery system[(6)]

Mucin is secreted by conjuctival goblet cells, but there are no goblet cells on the cornea. On this basis, a mucoadhesive polymer will firmly attach to conjuctival mucus but only loosely, if at all, to corneal mucus. Ophthalmic dosage forms can be improved by increasing the time the active ingredient remains in contact with eye tissues.

Vaginal drug delivery system[(7)]

Vaginal mucoadhesive preparations have been developed as new type of controlled release form for the treatment of both topical and systemic diseases. For drugs that are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal delivery may offer a number of advantages over the other routes of administration.

Rectal drug delivery system[(10)]

Another way to deliver the drug by using mucoadhesive polymers is through the mucous membrane of the rectum. Hydrogels administered rectally have proven to be useful for drug deliver.

Materials & Methods

Materials

HPMC K4M, HPMC K15M, HPMC K100M, Chitosan, Sodium CMC, Carbopol 974P, sodium alginate, Gum karaya, Carbopol 941NF. All other chemicals used in the study were of analytical grade which are obtained from SURA Labs Pvt Ltd.

Method

Preparation of Buccal Tablet

Table 1: Composition of buccal tablets

Ingredients (mg)	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9	RF10	RF11	RF12
Repaglinide	2	2	2	2	2	2	2	2	2	2	2	2
HPMC K4 M	12	16	20	-	-	-	-	-	-	-	-	-
HPMC K15 M	-	-	-	12	16	20	-	-	-	-	-	-
Chitosan	-	-	-	-	-	-	12	16	20	-	-	-
HPMC K100 M	-	-	-	-	-	-	-	-	-	12	16	20
Sodium CMC	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 974 P	-	-	-	-	-	-	-	-	-	-	-	-
Sodium Alginate	-	-	-	-	-	-	-	-	-	-	-	-
Gum karaya	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 941NF	6	6	6	6	6	6	6	6	6	6	6	6
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
MCC pH 102	71	67	63	71	67	63	71	67	63	71	67	63
Mg. Stearate	1	1	1	1	1	1	1	1	1	1	1	1
Aerosil	3	3	3	3	3	3	3	3	3	3	3	3
Total Weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Composition of buccal tablets

Ingredients (mg)	RF13	RF14	RF15	RF16	RF17	RF18	RF19	RF20	RF21	RF22	RF23	RF24
Repaglinide	2	2	2	2	2	2	2	2	2	2	2	2
HPMC K4 M	-	-	-	-	-	-	-	-	-	-	-	-
HPMC K15 M	-	-	-	-	-	-	-	-	-	-	-	-
HPMC K100 M	-	-	-	-	-	-	-	-	-	-	-	-
Chitosan	-	-	-	-	-	-	-	-	-	-	-	-
Sodium CMC	12	16	20	-	-	-	-	-	-	-	-	-
Carbopol 974 P	-	-	-	12	16	20	-	-	-	-	-	-
Sodium Alginate	-	-	-	-	-	-	12	16	20	-	-	-
Gum karaya	-	-	-	-	-	-	-	-	-	12	16	20
Carbopol 941NF	6	6	6	6	6	6	6	6	6	6	6	6
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
MCC pH 102	71	67	63	71	67	63	71	67	63	71	67	63
Mg. Stearate	1	1	1	1	1	1	1	1	1	1	1	1
Aerosil	3	3	3	3	3	3	3	3	3	3	3	3
Total Weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Stability studies:

Stability studies for 3 months were carried out for the best formulation; the best formulation is kept under two different conditions like at 30 ± 2°C & 65 ± 5 % RH and other at 40 ± 2°C & 75 ± 5 % RH. After 30 days first month stability studies were carried out for important parameters like dissolution, *Ex vivo* residence time, drug content, Surface pH. The same study is repeated after completion of 60, and 90 days.

In vivo studies

In vivo studies were carried out in white New Zealand rabbits were taken with a mean weight of 1.85-2.25 kg. The animals were fasted overnight and kept in individual cages before the study and the study animals were anesthetized by giving xylazine 4 mg/kg and ketamine 100 mg/kg intradermal injection upon the introduction of anesthesia, a drop of water was placed on the surface of the tablet, the tablet was applied to the oral cavity by pressing for 30 sec, ensure that the tablet was placed carefully in between the check and gingiva to prevent the animal from spitting out. Blood samples of 0.5 mL were withdrawn from the ear vein of a rabbit using a gauze needle at a regular time interval of 0.5 h, 1 h, 2 h, 4 h, 8 h, 10 h, 12 h, and 24 h. Collected blood samples were taken in heparinized tubes and shaken well their samples were centrifuged at 3000 rpm for 15 min to separate the plasma. The clear supernatant plasma layer was collected in an Eppendorf tube and stored immediately at -20°C until analysis.

RESULTS & DISCUSSION

1. Stability Studies: Stability studies are done for best formulation (RF11) as per ICH guideline as follows Acceleration stability studies intermediate storage condition has been changed from 30°C ± 2°C and 60% RH ± 5% RH and 40°C ± 2°C and 75% RH ± 5% RH. It focuses that there's no change in Drug content shown in Table 3 & Figure 1& 2.

Table 3: Acceleration stability studies of formulation RF11

Time in (Min)	30°C ± 2°C and 60% RH ± 5% RH (INTERMEDIATE)				40°C ± 2°C and 75% RH ± 5% RH (ACCELERATED)		
	Initial	30 Days	60 Days	90 Days	30 Days	60 Days	90 Days
0	0	0	0	0	0	0	0
1	52.15	52.10	52.01	49.89	52.10	52.02	49.91
2	61.83	61.75	61.70	61.27	61.71	61.60	61.30
3	74.19	74.12	74.05	74.10	74.16	74.10	74.08
4	84.43	84.40	84.38	84.10	84.31	84.26	84.05
5	96.19	96.15	96.11	96.05	96.11	96.03	98.95
6	99.43	99.41	99.35	99.24	99.38	99.28	99.14

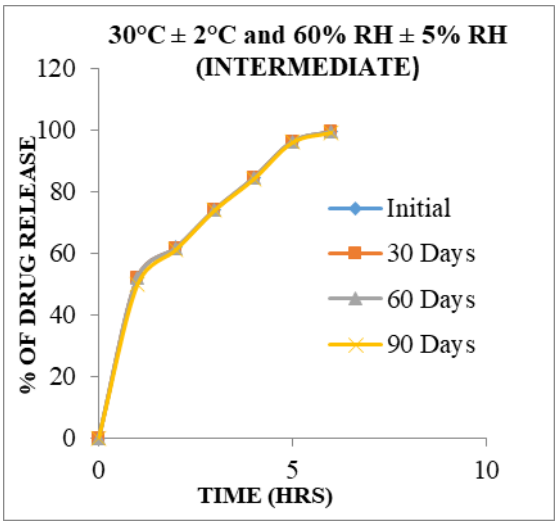

Fig1: RF11 Intermediate stability studies

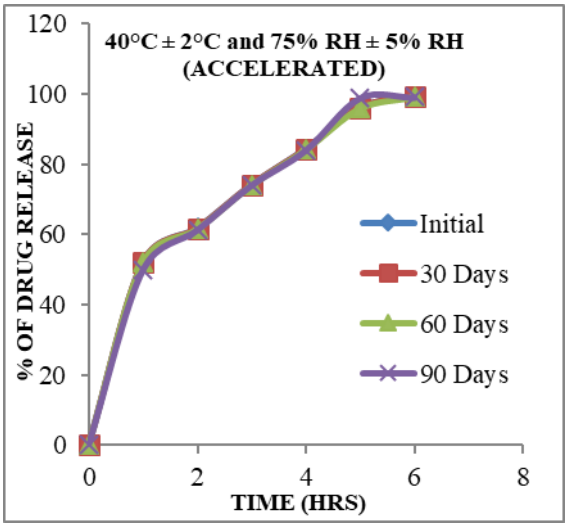

Fig2: RF11 Acceleration stability studies

***2. In vivo* results:** The mean plasma concentration–time curves of Repaglinide pure drug Suspension and optimized buccal tablets (RF11) following the application of the bioadhesive buccal tablet and oral suspension to pigs are shown in Table 4 & Figure 3

The mean peak plasma concentrations (C_{max}) and time to reach peak plasma concentration (T_{max}) for pure drug Suspension, RF11 were calculated to be 46.11 and 131.54 ng/mL respectively, 1 hr, 4hr respectively after administration of oral suspension and bioadhesive buccal tablet. The AUC0–α were found to be, respectively, 340.00 and 1672.64 ng/h/mL. The results of bioavailability study (Table 5) reveal that Repaglinide were released and permeated well from the bioadhesive buccal tablet, as compared with oral suspension. The C_{max}, T_{max}, and AUC profiles were compared, C_{max} was found to be higher by the buccal route than oral route, greater C_{max} values could be attributed due to avoidance of first pass hepatic metabolism after buccal administration.

Table 4: Plasma concentration data for Repaglinide pure drug suspension, Repaglinide optimized buccal tablets

Time (h)	Plasma drug concentration (ng/mL)	
	Repaglinide pure drug Suspension	Repaglinide optimized buccal tablets (RF11)
0	0.00	0.00
0.5	23.29	35.98
1	46.11	62.67
2	33.55	79.22
4	24.75	131.54
8	23.66	57.34
10	12.21	42.06
12	6.05	31.15
24	2.11	28.77

Each value represents the mean value (n =6)

Table 5: Pharmacokinetic parameters of Repaglinide pure drug suspension, Repaglinide optimized buccal tablets

Pharmacokinetic parameter	Repaglinide pure drug Suspension	RF11 optimized buccal tablets
C_{max} (ng/mL)	46.11	131.54
t_{max} (h)	1	4
AUC_t (ng-h/mL)	321.21	1225.25
$AUMC_t$ (ng-h/mL)	2062.13	10848.97
AUC_i (ng-h/mL)	340.00	1672.64
$AUMC_i$ (ng-h/mL)	2680.55	28543.40
Clearance (CL) (mL/min)	0.0058	0.0011
V_d (mL)	0.052	0.018

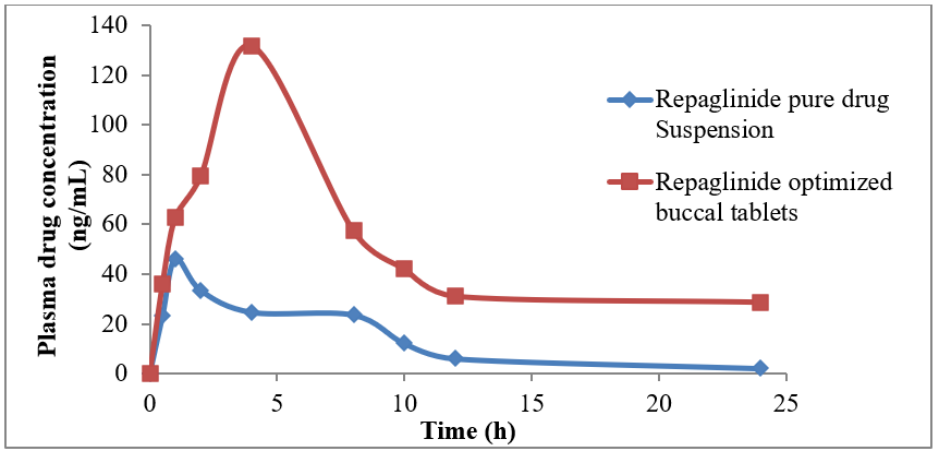

Figure 3: Plasma concentration data for repaglinide pure drug suspension, repaglinide optimized buccal tablets

CONCLUSION:

From the results it was conclude that an improvement of bioavailability by the buccal tablet higher than that of the oral route for Repaglinide, respectively, was obtained. Hence, the development of a bioadhesive buccal tablet in tablet dosage form for Repaglinide may be a promising one, as the necessary dose of Repaglinide drug may be decreased, and thus side-effects may be reduced. The Stability of the Repaglinide Buccal tablet(RF11) under accelerated stability condition remains unchanged in Drug content.

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