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Design, Formulation, Optimization and Evaluation of Rosiglitazone Bilayer Mucoadhesive Tablet by Using Different Polymer

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ABSTRACT

The Rosiglitazone maleate mucoadhesive tablet was prepared with objective of avoiding first pass metabolism and prolonging the duration of action. The Rosiglitazone maleate mucoadhesive bilayered tablets were prepared by direct compression method using bioadhesive polymer such as corbopol 940, PVP and PVA along with ethyl cellulose as a backing layer. The interaction between Rosiglitazone maleate and excipients was also studied through FTIR spectroscopy. Tablets were evaluated for their physical properties like hardness, friability, and weight variation, uniform thickness, content uniformity and *in-vitro* swelling study. *In-vitro* release study of formulation was performed and data obtained from *in-vitro* release study were fitted to various kinetics models. The prepared formulations were passed the evaluation tests and the mechanism of drug release from tablets was found to be Quasi- Fickian diffusion transport.

INTRODUCTION

Rosiglitazone maleate (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy] phenyl] methyl]-2, 4-thiazolidinedione, (Z)-2-butenedioate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. It is effective only in the presence of insulin. Primary objectives of Controlled drug delivery system are to ensure the safety and to improve efficiency of drug as well as patient compliance. This is achieved by better control over plasma drug level and less frequent dosing. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT avoided. Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) a bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) a vehicle to release the drug at an appropriate rate under the conditions prevailing in the mouth and strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery system promotes the residence time and act as controlled release dosage forms. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site. In addition, there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period. Prolonged release of the drug and increased bioavailability leads to the significant reduction in the dose and hence dose related side effects. Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for Rosiglitazone maleate using different mixtures of polymers in order to avoid extensive first pass metabolism, degradation in the stomach and prolonged effect.

MATERIALS AND METHODS

Experimental

Materials:

Rosiglitazone maleate was a gift sample from Micro Lab Pvt. Ltd., Bangalore. Carbopol was gift sample from Glenmark Pvt. Ltd, Mumbai. PVA and PVP were purchased from Loba chemicals, Mumbai. All other reagents used were of analytical grade.

Micromeritics studies of blend

The blend were characterized by their Micromeritics properties, such as, bulk density, tapped density, Carr's compressibility index, Hausner ratio and flow property.

Bulk Density

The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm^3. The sample of about 10 cm^3 of powder was carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$\mathbf{D_f = M / Vp}$$

Where, D_f = bulk density

M = weight of samples in grams

Vp = final volumes of granules in cm^3.

Tapped Density

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. The sample of about 10 cm^3 of powder is carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$\mathbf{D_o = M / Vp}$$

Where, D_o = Tapped density

M = weight of samples in grams

Vp = final tapped volumes of granules in cm.^{3}

Carr's Index:

The percentage compressibility of microspheres was calculated according to equation given below:

$$\% \text{ Compressibility} = \frac{D_o - D_f}{D_o} \times 100$$

Where, D_f = bulk density; Do = Tapped density

Table No. 1: Relationship between % compressibility and flowability

% Compressibility	Flowability
5 - 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 - 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

Hausner ratio

The Hausner ratio of a microsphere was calculated according to equation given below:

$$\textbf{Hausner ratio} = D_o / D_f$$

D_o = Tapped density

D_f = bulk density

The Angle of repose

The Angle of repose (θ) i.e. Flow property of the microspheres, which measures the resistance to particle flow, was calculated as

$$\tan \theta = 2H / D$$

Where, 2H / D is the surface area of the free standing height of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

Table No. 2. Micromeritics Analysis of Blend

Batch Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	% Compressibility Index	Angle of Repose
F1	0.385±0.003	0.440±0.001	1.117±0.004	14.96±0.003	23.35±0.001
F2	0.395±0.025	0.449±0.004	1.109±0.002	1.109±0.002	23.50±0.002
F3	0.401±0.004	0.452±0.003	1.115±0.003	14.60±0.002	24.50±0.003
F4	0.388±0.002	0.510±0.003	1.120±0.003	14.90±0.002	23.90±0.004
F5	0.420±0.002	0.420±0.002	1.16±0.002	15.2±0.003	24.10±0.004
F6	0.396±0.003	0.449±0.004	1.210±0.003	14.90±0.004	24.01±0.003
F7	0.366±0.004	0.463±0.003	1.178±0.003	15.1±0.002	23.98±0.004
F8	0.402±0.005	0.482±0.002	2.014±0.002	14.78±0.003	24.20±0.004
F9	0.420±0.002	0.443±0.004	1.120±0.003	14.92±0.004	24.52±0.003

* Each sample was analyzed in triplicate (n = 3).

Compatibility studies

The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra red spectra of pure drug and mixture of drug and excipients were recorded.

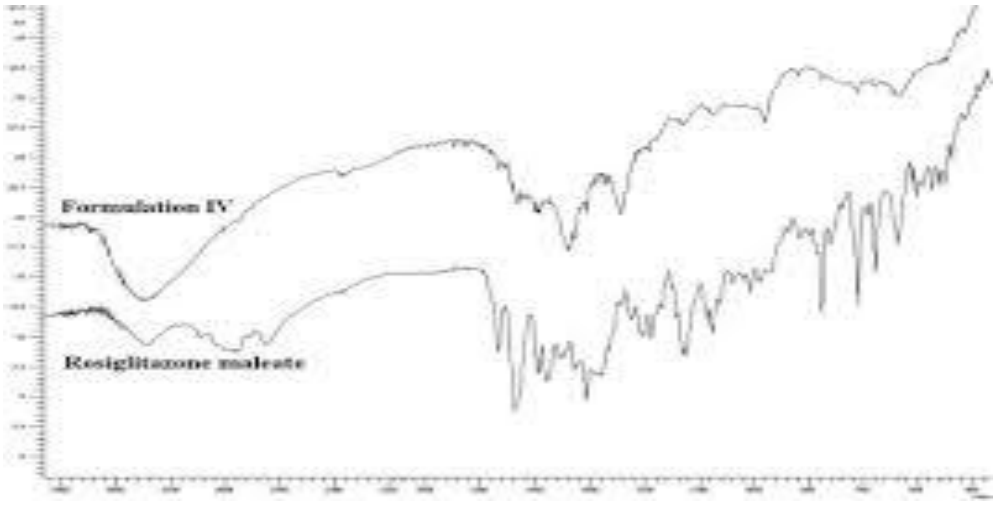

Fig No. 1: FTIR Data of Pure Drug and Excipients

Formulation of mucoadhesive buccal tablets

The drug, polymers and excipients were mixed homogeneously in a glass mortar for 15 min. The mixture (230 mg) was then compressed using an 8 mm, bi-flat punch in a single-stroke using 10-station rotary machine. Upper punch is raised 30 mg backing layered of ethyl cellulose is added to above compact mass.

Table No. 3: Formulation of mucoadhesive buccal tablets

Name of Ingredient	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Rosiglitazone	4	4	4	4	4	4	4	4	4
Corbopol 940	120	120	120	100	100	100	80	80	80
PVP	60	40	20	60	40	20	60	40	20
PVA	40	40	40	40	40	40	40	40	40
Mannitol	40	60	80	60	80	100	80	100	120
Mg.stearate	4	4	4	4	4	4	4	4	4
β-cyclodextrin	2	2	2	2	2	2	2	2	2
Backing Layer									
Ethyl cellulose	30	30	30	30	30	30	30	30	30

Evaluation of mucoadhesive buccal tablets

Rosiglitazone maleate mucoadhesive buccal tablet was evaluated for

Weight variation

Eight tablets from each formulation (F1 to F9) were weighed using an electronic balance and the average weight was calculated.

Hardness

Hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability

Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss was determined.

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a Vernier Caliper (Pico India). The average values were calculated.

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 10 mg of Rosiglitazone equivalent of mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 245 nm. This procedure was repeated thrice and this average was chosen.

Swelling study

Six Buccal tablets were individually weighed (W1) and placed separately in Petri dishes with 5 ml of phosphate buffer of pH 6.8. At the time interval of 1, 2, 4, 6 and 8 h, tablet was removed from the Petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W2) and the percentage hydration were calculated using the following formula.

$$\text{Percentage hydration} = [(W2-W1)/ W1] \times 100$$

***In-vitro* dissolution studies**

The In-vitro dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, at a rotation of speed of 50 rpm. 5 ml samples were withdrawn at predetermined time intervals (1 to 12 h) and the volume was replaced with fresh medium. The samples were filtered through Whatman filter paper No. 40 and analyzed for after appropriate dilution by UV spectrophotometer at 317 nm. The % drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8.

Assay: Rosiglitazone maleate was estimated using an UV spectrophotometer method. Solutions of Rosiglitazone maleate (5 to 50 µg/ml) were prepared in and absorbance was measured on Shimazdu UV spectrophotometer at 317 nm. The method obeys Beer's law in the range of 5- 300 µg/ml. The regression coefficient was found to be 0.998.

***In vitro* mucoadhesive strength study**

In present study, sheep buccal mucosa was used as a model mucosal surface for bioadhesion testing. Immediately after slaughter, the buccal mucosa was removed from the sheep and transported to laboratory in tyrode solution and kept it at 40ºC. The composition of tyrode solution (g/L) is sodium chloride 8, potassium chloride 0.2, calcium chloride dihydrate 0.134, sodium bicarbonate 1.0, sodium dihydrogen phosphate 0.05 and glucose 1.0.

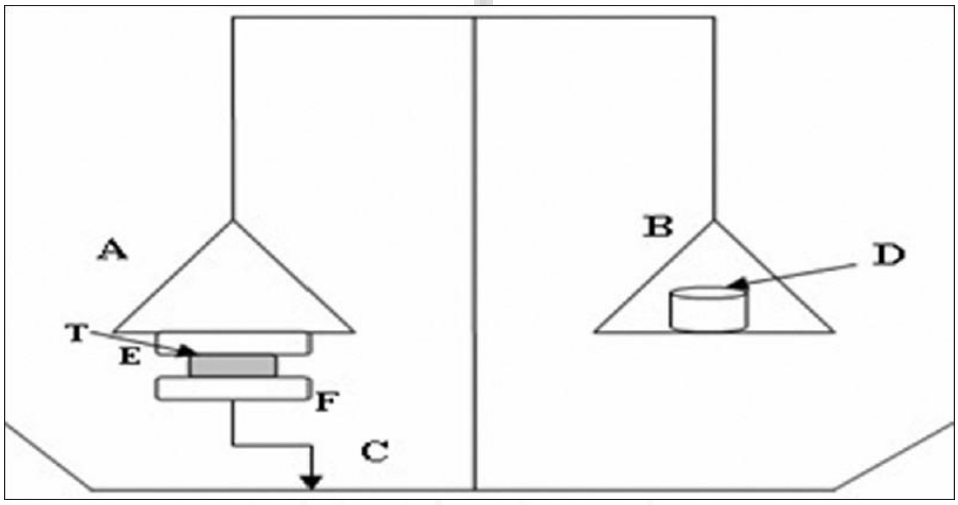

Fig. No. 2. Measurement of bioadhesive strength

A-glass vial; E-sheep buccal mucosa; T-Mucoadhesive tablet; F-adjustable pan; G-weight

The mucoadhesive forces of the tablets were determined by means of mucoadhesive measuring device shown in Fig. 2. The sheep buccal mucosa was cut into strips/pieces and washed with tyrode solution. At the time of testing a section of sheep buccal mucosa (E) was secured keeping the mucosal side out, on the upper glass vial (A) using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1 cm. The vial with the sheep buccal mucosa (A) was stored at 37°C for 10 min. Then one vial with section of sheep buccal mucosa (A) and another vial were fixed on height adjustable pan (F). To a lower vial a tablet (T) was placed with the help of bilayered adhesive tap, adhesive side facing downward. The height of the lower vial was adjusted so that a tablet could adhere to the sheep buccal mucosa on the upper vial. A constant force was applied on the upper vial for 2 min,

after which it was removed and the upper vial was then connected to the balance. Then the weight on right side pan was slowly added in an increment of 0.5 g, till the two vials just separated from each other. The total weight (G) required to detach two vials was taken as a measure of Mucoadhesive strength. From this Mucoadhesive strength, the force of adhesive was calculated.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.81}{100}$$

Table No. 4: Evaluation of the prepared formulation batches

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (Kg/Cm^2)	3.8± 0.02	3.6±0.03	3.6±0.01	3.6±0.02	3.4±0.01	3.5±0.02	3.4±0.02	3.4±0.02	3.3±0.01
Friability (%)	0.6±0.05	0.6±0.02	0.64±0.03	0.56± 0.02	0.71±0.01	0.6±0.05	0.88±0.03	0.61±0.03	0.6± 0.02
Wt. variation (%)	1.25±0.05	1.30±0.01	1.35±0.03	1.10±0.05	1.5± 0.02	1.51±0.05	1.25±0.01	1.6± 0.02	1.28±0.03
Thickness (mm)	3.5±0.025	3.5±0.03	3.4± 0.02	3.5±0.03	3.5±0.05	3.5± 0.02	3.4±0.05	3.5±0.03	3.5± 0.02
Content uniformity (%)	98.6±0.01	10.99± 0.02	94.0± 0.02	92.0±0.01	98.22± 0.5	96.1±0.03	97.14±0.2	10.4±0.05	10.0±0.03
Surface pH	6.9± 0.02	6.8±0.03	7.2±0.01	7.0±0.03	7.1± 0.02	7.1±0.05	7.1±0.02	7.1±0.03	7.0±0.01
Swelling index (%)	15.1±0.05	16.2±0.01	120±0.02	15.2±0.01	104±0.02	11±0.05	136±0.01	11.8±0.02	10±0.05
Assay (%)	92.0± 0.02	11.6±0.03	96.0±0.05	95.22±0.01	14.12± 0.2	11.12±0.05	99.23±0.03	99.0±0.01	96.40± 0.02

* Each sample was analyzed in triplicate (n = 3).

Table No. 5: % drug release of prepared formulation batches (F1 to F9)

TIME (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	3.5± 0.02	3.4± 0.05	3.0± 0.01	7.1± 0.05	6.3± 0.02	6.1± 0.02	9.2±0.03	8.4±0.03	7.9± 0.02
2	7.2± 0.01	7± 0.02	5.6± 0.02	13.2± 0.04	12.5±0.02	11.3± 0.02	17.2±0.04	16.9±0.02	13.5± 0.02
3	12.8±0.02	11± 0.01	9.3± 0.04	19.2± 0.03	18.5±0.04	15.8± 0.05	23.6±0.02	21.3±0.02	17.8± 0.02
4	19.8±0.02	17± 0.05	15.2±0.02	24.1± 0.02	23.9±0.02	22.8± 0.03	30.2±0.03	26.3±0.02	25.8± 0.05
5	29.5±0.02	26.± 0.02	23.4±0.04	29.3± 0.03	32.5±0.04	28.9± 0.04	33.7±0.02	32.6±0.02	30.1± 0.02
6	33.8±0.04	31.5± 0.05	27.8±0.04	36.2± 0.02	38.6±0.01	33± 0.02	41± 0.02	39.6±0.02	37.8± 0.02
7	39.4±0.02	37.5± 0.02	34.2±0.02	44.1± 0.02	42.3±0.02	42.1± 0.02	49.5±0.02	46.8±0.02	45.1± 0.02
8	47.8±0.02	42.2± 0.02	39.6±0.02	51.8± 0.02	52.1±0.02	50.2± 0.02	58.4±0.02	53.7±0.02	52.7± 0.02
9	55.2±0.05	49.8± 0.04	47.2±0.02	62.5± 0.02	60.1±0.02	59.6± 0.02	68.2±0.05	63.4±0.02	64± 0.02
10	65± 0.01	58.2± 0.02	56.3±0.04	71.2± 0.02	68.9±0.04	67.4± 0.01	79.2±0.02	71.3±0.01	71.2± 0.01
11	72.5±0.04	64.3± 0.02	62.2±0.06	79.6± 0.04	76.2±0.03	74.4± 0.02	88.4±0.05	83.2±0.04	82.6± 0.03
12	79.2±0.01	73.2± 0.03	69.3±0.04	86.8± 0.06	84.2±0.05	80.6± 0.01	98.2±0.02	94.3±0.02	91.2± 0.03

* Each sample was analyzed in triplicate (n = 3).

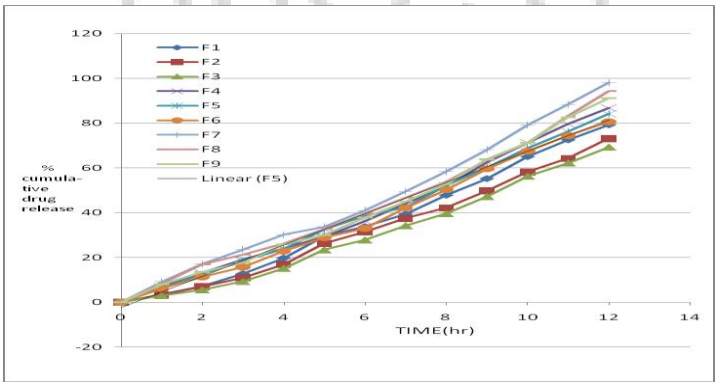

Fig No. 2: % drug release of prepared formulation batch

Table No. 6: *In vitro* mucoadhesive strength study

Batch code	Mucoadhesive strength* (g)	Mucoadhesion force (N)
F1	17.27±0.45	1.69
F2	23.22+0.56	2.25
F3	26.28±0.45	2.56
F4	18..28±0.17	1.79
F5	17.87±0.55	1.75
F6	24.27±0.49	2.36
F7	26.77±0.45	2.76
F8	18.95±0.32	1.85
F9	22.27±0.65	2.10

* Each sample was analyzed in triplicate (n = 3).

RESULTS AND DISCUSSION

It was observed that all the prepared tablets fulfill the I.P requirements for physicochemical properties and results were given in Table 4, 5, 6. The measured hardness of all formulations i.e. F1 to F9 were ranged between 3.3 to 3.8 Kg / cm^2. The friability test data indicates that it was less than 1% in all formulations ensuring that the tablets were mechanically stable. The thickness of all formulations was found to be in the range of 3.40 to 3.56 mm. All the batches showed drug content above 92%. The highest swelling 136% was observed with the formulation F7 (Table 4). pH of all the formulation batch was found in promising range (6.9 to7.1). It was also found that the batch F7 showed the maximum percentage of drug release i.e. 98.2 % at the end of 12 hr (Table 5). It can be concluded that stable mucoadhesive buccal tablets with desired properties could be prepared by using PVP and PVA in proper concentration along with carbopol 940. All the batches showed their results within standard range but results shown by F7 batch are very nearer to standard range. So Batch F7 was optimized batch based on good physicochemical properties and percentage drug release.

CONCLUSION

Rosiglitazone maleate mucoadhesive buccal tablets could be formulated using the drug, Carbopol 940 and PVA, PVP with Ethyl cellulose as backing layer can be seen that by increasing the concentration of Carbopol 940 in the formulation, the drug release rate from the

tablets was found to be decreased. But when the concentration of PVP, PVA increased drug release increased. The mucoadhesive buccal tablet of Rosiglitazone is a good way to bypass the extensive first pass metabolism and to improve the bioavailability of Rosiglitazone maleate through buccal mucosa.

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