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Histological and mucoadhesion studies on transpalatal mucoadhesive disks of Rosiglitazone maleate

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Abstract

The present research is aimed to develop a mucoadhesive drug delivery system exhibiting a unique combination of mucoadhesion and controlled drug release in systemic manner to prolong residence in the soft palatal mucosa using rosiglitazone maleate as a model drug. In this study, a mucoadhesive disks formulation for palatal delivery were designed using a simplex lattice design with a mixture of various mucoadhesive polymers (Cp, SCMC, or HPMC, Guar gum and DPP), followed by optimization of the evaluation parameters was employed to get final optimized formulation. In vitro mucoadhesion and mucoretentability property of the formulated disks were examined and histological study was carried out to examine an ex-vivo interaction between the disks and tissue. The optimized F-11 composition showed a force of adhesion (N) > 3 and a mucoadhesion time >12 hours with zero order release profile as best fit model closer to the target release profile and followed anomalous mediated release of rosiglitazone maleate .The different concentration of mucoadhesive polymer significantly affects the drug release rate, force of adhesion and mucoretentability characteristics of the disks. No more histological changes were observed in the excised palatal mucosa after 12 h contact with the disks. This kind of disks extends the residence time of a dosage form at a particular site and controlling the release of drug in systemic manner from the dosage form and useful especially for achieving controlled plasma level of the drug as well as improving bioavailability with reduced side effects.

Keywords: Rosiglitazone maleate; Mucoadhesive disks; Force of adhesion; Date Palm Polysacchride (DPP), Transpalatal route.

Introduction

Oral administration is the most convenient, widely utilized, and preferred route of drug delivery for systemic action. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism [1-2], as a result of which low systemic bioavailability and shorter duration of therapeutic activity and/or formation of inactive or toxic metabolites have been reported [3-4]. Further, the quick passage of dosage forms through the absorptive segment of GIT often leads to unutilized drug, particularly in case of extended delivery of narrow absorption window drugs [5]. Much attention has been focused, recently on targeting a drug delivery system to a

particular region of the body for extended period of drug release, not only for local targeting of drugs but also for the better control of systemic delivery. The concept of mucoadhesion was introduced into controlled drug delivery in the early 1980s. Mucoadhesives are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin constituting a major part of the mucus. Drug delivery using mucoadhesive dosage form via transmucosal route, bypasses hepato-gastrointestinal first pass elimination associated with oral administration, thereby increases the bioavailability and produces longer therapeutic effect [6-7]. Rosiglitazone - a potent, novel antidiabetic agent is used in management of type-II diabetes mellitus. After 8 to 12 weeks of Rosiglitazone monotherapy, the dose may be doubled in case of insufficient response and this leads to higher incidence of dose dependent side effects [8] such as gastro-intestinal disturbances, headache, altered blood lipids, oedema, hypoglycaemia [9]. Further, adverse events of clinical significance which are reported frequently with conventional instant release dosage forms of the drug are edema, anemia, and weight gain [10]. Clinical studies showed that 4-mg twice-per-day regimen compared to 8 mg once a day provides statistically greater improvement in glycemic control [11]. Thus, there is a need to maintain Rosiglitazone at its steady state plasma concentration which makes Rosiglitazone maleate as suitable candidate for mucoadhesive transpalatal drug delivery system. Hence, this study was carried out to formulate and evaluate mucoadhesive transpalatal dosage form of rosiglitazone maleate as a model drug and optimize the formulation parameters to finally get optimized formulations which would control blood glucose level for prolonged period to achieve better glycemic control over immediate-release dosage formulation. In the literature, very few reports of RZM formulations such as carbopol-based mucoadhesive tablet [12] and intragastric floating sustained-release tablet [13] based on hydrodynamically balanced system are available. The efficacy of carbopol-based mucoadhesive dosage is restricted by its nonspecific mucoadhesion and mucin turnover in GIT [14]. Single-unit floating dosage form like tablet is associated with all-or-nothing emptying nature or dose-dumping phenomenon. However, no attempt has been reported yet to develop mucoadhesive transpalatal of rosiglitazone maleate for its controlled- release drug delivery having sufficient bioadhesive strength, bioadhesion time, and desired release profile. Palatal route offers many advantages over conventional routes of delivery with an improved bioavailability due to the avoidance of degradation in the gastrointestinal tract and hepatic first-pass metabolism [15-16].

Materials and methods

Rosiglitazone Maleate was received as a gift sample from Sun Pharma Ltd, Jammu. Carbopol 934 (Loba cheme Pvt. limited, Mumbai), H P M C – K4M (Central drug house, Delhi) , Date Palm fruit pulp isolated from Phoenix sylvestris taken from local market (Authentified from National Botanical Research Institute, Lucknow), carboxymethyl cellulose sodium salt (high viscosity) were purchased from Fluka Chemie GmbH CH-9471 Buchs. Mannitol (Central drug house, Delhi) and other chemicals used were procured commercially and were used as received.

Dose calculation

For controlled drug release up to 12h, the total dose of drug required was calculated based on the fact that the conventional dose was calculated using the following equation [17]. For Rosiglitazone maleate: Dt= Dose (1+0.693×12/3.5), Dt =6.752mg Rosiglitazone and 8.943mg of Rosiglitazone maleate is equivalent to 6.752mg Rosiglitazone.

Dt= Dose (1+0.693×t/t ½), Dt =Total dose, Dose=Immediate release dose, t=Total time period for which controlled release is required, t½ = Half life of drug.

Preparation of Discs by Direct Compression

Formulations were developed following a simplex lattice design [18] after setting the individual excipient levels through preformulation studies. We developed a series of formulations mentioned in the table1. Discs were prepared by directly compressing 150 mg of finely powdered mixtures of bioadhesive polymers, Rosiglitazone Maleate and other excipients in the ratios given in Table I at a pressure of 5,000 kg for 15 s using the infrared hydraulic press (Shimadzu, Japan). The 50 discs of each batch no. (F1- F15) were prepared using the 13-mm diameter set [19].

Drug excipient compatibility study

Binary mixture approach was used to screen the compatibility of drug with selected polymers. 10 mg drug was mixed thoroughly with the selected excipients to form physical mixtures. The physical mixtures were then kept in sealed vials at 55°C/ 25 % RH for 2 weeks in the ratio 1:1 and 1:10 and the vials examined daily at regular interval for discoloration, caking, liquefaction. After 2 weeks the mixtures were subjected to thin layer chromatographic studies of 2 mcg/ml drug content by using silica gel 60 G254 as stationary phase and Toluene: ethyl acetate: methanol: Diethylamine (6:3:0.5:0.15) as mobile phase. The R_f value was determined and compared with the R_f value of the pure drug [20].

Evaluation of Mucoadhesive Palatal Discs

Friability- A sample of ten formulation was selected. The sample was accurately weighed and placed in the drum of tablet friability apparatus (Roche friabilator -Model DFI-1, Veego, Bombay, India). The samples underwent 25 rpm, for 4 min, and were then reweighed. This process was repeated for all formulations and the percentage friability was calculated using the following equation [21].

$$F = \frac{(W1-W2)}{W1} \times 100$$

F, the percentage weight loss and W1 and W2 are the initial and final discs weights, respectively. If obviously cracked, cleaved, or broken discs are present in the disc sample after tumbling, the sample fails the test. A maximum weight loss of not more than 1% of the weight of the discs being tested is considered acceptable. This procedure was used to determine friability of formulations prepared by direct compression

Disc Thickness

The thickness of the buccal discs was determined using a digital caliper. The thickness of six discs was measured and the average thickness was determined.

Drug Content Uniformity

Six formulations of each batch no. (F1-F11) were dissolved in 50 mL phosphate buffer (pH 7.4). and filtered through whatman filter paper. (110 mm Φ) The amount of drug in each disk was determined uv spectrophotometrically at there λmax. 242nm.

Weight Uniformity

Six formulations were randomly selected and accurately weighed using an electronic balance. The results are expressed as the mean values of six determinations.

In Vitro Mucoadhesive Strength Measurement

MS of selected polymer with palatal mucosa was measured using a modified 2-arm balance [22]. Goat palatal tissue were obtained from a local slaughterhouse and stored in Krebs buffer upon collection using ice box. The experiments were performed within hours of procurement of tissue. The tissue was fixed to the stainless steel piece with cynoacrylate adhesive and then placed in a beaker by facing the mucosal surface upperside. Krebs solution was added into the beaker up to the surface of the palatal mucosa to maintain palatal mucosal viability during the experiments and aeration maintained throughout the experiment by using aerator pump. The prepared polymer disc was attached to the upper clamp of the apparatus and then the pan was raised slowly until contact between mucosa and disc was established. A preload of 50 g was placed on the clamp for 5 minutes (preload time) to establish

adhesion bonding between disc and palatal mucosa. The preload and preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp, and the weight were placed on the another pan starting from 10 gm and the continousally increased the weight untill disc was detached mucosa. The weight required to detach disc from mucosa was noted as force of mucoadhesion, and these experiments were repeated three times with fresh mucosa in an identical manner for each formulation of F1- F15 batch no.

$$\text{Force of adhesion} = \frac{\text{Mucoadhesive strength}}{100} * 9.81$$

In Vitro Mucoretentability Measurement

Mucoretentability property measured in terms of duration of time in which the disc is detached from to the mucus. The in vitro mucoretentability studies were conducted using a dissolution apparatus assembly. Prepared disc of given polymer was lowered onto the palatal mucosa which is already adhered to the lower tip of basket and studies carried out at 150 rpm and 37 ^{0}C to simulate saliva movement [23] . The time necessary for complete erosion or detachment was taken as an indication of the in vitro adhesion time.

In Vitro Dissolution Study

In vitro dissolution study was carried out in a basket type dissolution test apparatus (TDT-06P, Electrolab, India) with stirring speed of 150 rpm using 900 ml Phosphate buffer pH 7.4 as dissolution medium under sink conditions. Prepared disks of RZM were added to dissolution medium kept at 37±0.5°C. Periodically, 5 ml solution withdrawn from the dissolution medium, Same volume of dissolution medium was replaced back after each sampling in order to maintain sink condition. Concentration of drug was determined using uv spectroscopy. After the dissolution study, disks were dried at room temperature and observed under the SEM to examine any changes in surface topography. . The drug release data obtained from the release rates were also evaluated by fitting into different kinetic models.

Scanning electron microscopy

Prepared disks obtained before and after complete dissolution of core content were examined for their porous structure and topography using F 3000N SEM (Hitachi, Japan). After dissolution, disks were dried at 50^{0}C for 8 hours and stored in dessicator before examination . disks were sputter coated for 5 to 10 minutes with gold by using fine coat ion sputter (Hitachi E-100, Japan) and examined under SEM.

Histology of isolated palatal tissue

The histology of the isolated tissue before and after in vitro mucoretentability was examined by photomicroscopy At the end of in vitro mucoretentability study [24], the disks was removed from the isolated tissue. Then tissue was taken and after a classical fixation, dehydration and embedding procedure [25], sections were cut, stained with eosin and examined under a light microscope (Nikon, Japan).

Results and discussions

RZM belongs to class 1 drugs of Biopharmaceutical Classification System [26]. The drug is highly soluble in aqueous solution at pH1.2. So a good release retardant is necessary to control the release of RZM from the mucoadhesive disk, by the use of mucoadhesive polymers the active ingredient is released slowly by diffusion. It shows pH-independent release profile, which means that drug release takes place independently of individual variation. For this reason, these mucoadhesive polymers have been used to prolong RZM release from the mucoadhesive disks formulation.

Disks Formation and Morphology

Mucoadhesive disks were prepared by direct compression method. The surface structure of the disks produced by the direct compression method was found spherical as observed visually

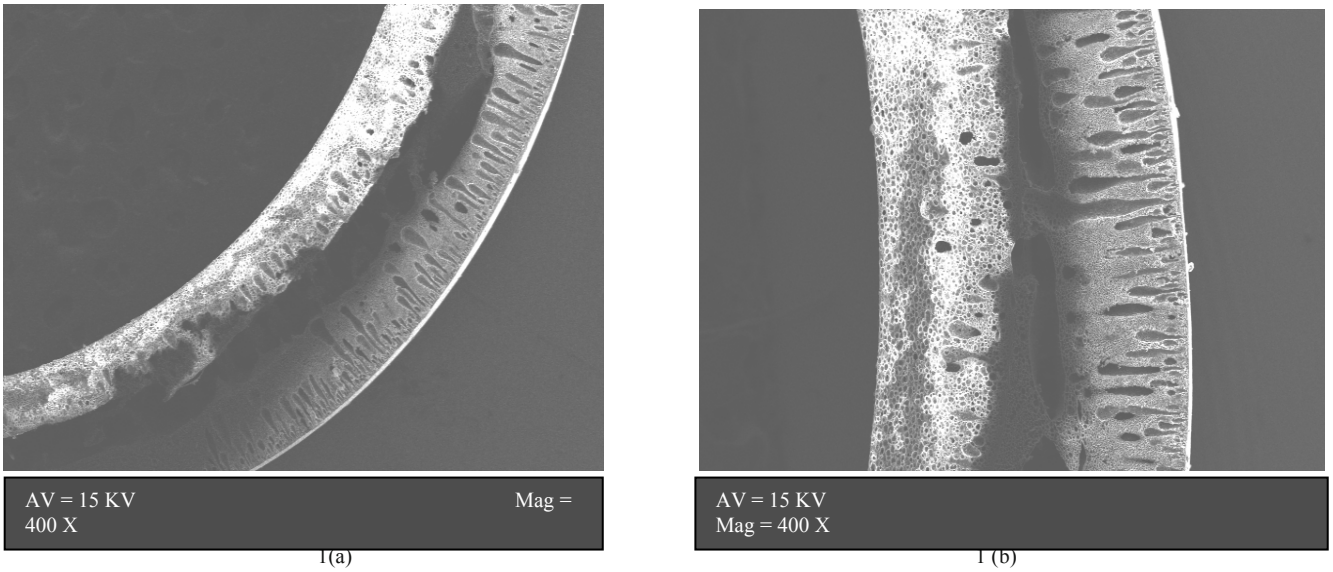

Fig: 1- Scanning electron micrograph of disks (a) before and (b) after dissolution

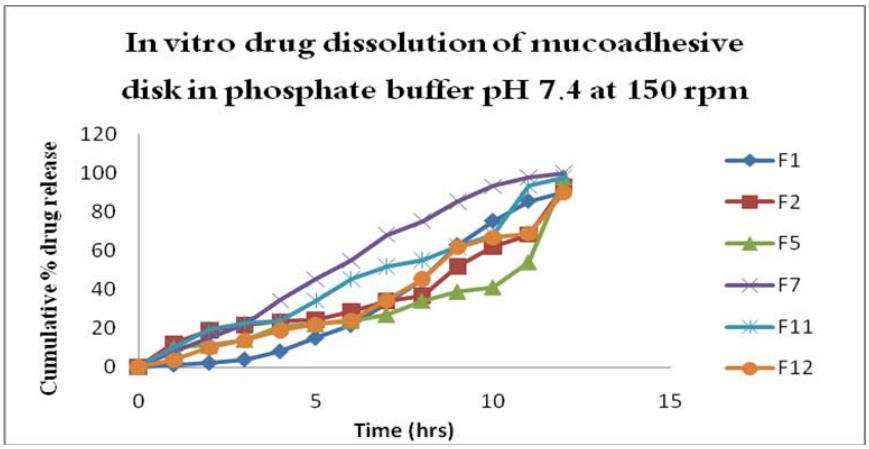

Fig. 2. In vitro drug dissolution profile of mucoadhesive disks.

Fig-3a Fig-3b

Fig-3 Palatal mucosa before and after in vitro mucoretentability study

Table 1. Simplex lattice design for various formulations.

Formulae	Drug (mg)	Polymer compositions (mg)					Excipients (mg)	
		CP	SCMC	HPMCK4M	Guar Gum	DPP	PEG	Mannitol
F1	10	15	100	-	-	-	10	15
F2	10	15	-	100	-	-	10	15
F3	10	15	-	-	100	-	10	15
F4	10	15	-	-	-	100	10	15
F5	10	15	50	50		-	10	15
F6	10	15	50	-	50	-	10	15
F7	10	15	50	-	-	50	10	15
F8	10	15	-	50	50	-	10	15
F9	10	15	-	50	-	50	10	15
F10	10	15	-	-	50	50	10	15
F11	10	15	33.3	33.3	-	33.3	10	15
F12	10	15	33.3	33.3	33.3		10	15
F13	10	15	33.3	-	33.3	33.3	10	15
F14	10	15	-	33.3	33.3	33.3	10	15
F15	10	15	25	25	25	25	10	15

Table. 2. Observation of drug excipient compatibility study

Mixture	Rf value	Discoloration		Caking		Liquefication	
		1:1	1:10	1:1	1:10	1:1	1:10
Drug:SCMC	0.46	-	-	-	-	-	-
Drug:HPMCK4M	0.46	-	-	-	-	-	-
Drug: Carbopol	0.46	-	-	-	-	-	-
Drug: Guar Gum	0.46	-	-	-	-	-	-
Drug: Date palm polymer	0.46	-	-	-	-	-	-
Drug: PEG	0.46	-	-	-	-	-	-
Drug: Mannitol	0.46	-	-	-	-	-	-

- Compatible + Incompatible

Table-3 In Vitro Mucoadhesive strength (Mean adhesive force %) and Adhesion Time of RZM Mucoadhesive Palatal D iscs.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F11	F12	F14
Mean Adhesive Force (%)	2.68 ± 0.065	2.57 ± 0.090	1.69 ± 0.037	2.28 ± 0.037	3.15 ± 0.026	2.07 ± 0.020	2.38 ± 0.142	2.05 ± 0.023	1.97 ± 0.020	3.02 ± 0.060	3.51 ± 0.020	1.88 ± 0.011
In vitro Adhesion time (Hrs)	13.24± 0.035	13.14± 0.045	8.06± 0.015	11.53± 0.028	16.42± 0.025	11.32± 0.025	12.47± 0.025	11.47± 0.025	11.37± 0.026	14.39± 0.096	18.44± 0.045	10.54± 0.015

(Fig.1a). The surface of the disks was smooth and revealed the presence of larger pores in disks after dissolution which, in part, might be responsible for their drug release behaviour (Fig.1b). Before and after the dissolution study, disks were dried, and observed under the SEM. SEM revealed that the disks retained their size intact. They were spherical in nature with smooth surface. There is no significant change in their surface topography

Drug–Excipient Interaction Study

Drug excipient compatibility was performed by using binary mixture approach. Physical mixtures were observed for 2 weeks and the results obtained are listed in table 2. Results showed that drug was found to be compatible with the selected polymers.

Physical Characterization of Mucoadhesive Palatal Discs

Friability test was applied to palatal discs prepared by direct compression. Several preliminary experiments were done to prepare RZM palatal discs containing several combinations of different polymers. Cp, HPMC, SCMC, Guar Gum, DPP were used to prepare palatal discs in different ratio (table 1). The friability test was conducted for all prepared formulae. All formulation showed friability values well below the 1% tolerance limit set by the British Pharmacopoeia for pharmaceutical tablets. except for the formulation F10, F13,F15 These formulae, having friability values above the 1% tolerance limit, were excluded. Disc thickness ranges of the discs prepared by direct compression were 1.82 – 1.98 mm. Disc weight ranges of the discs prepared by direct compression were 147– 152 mg. The RZM content was determined for each palatal disc. It was found that the RZM content in all palatal discs was in the range from 9.20 to 10.22 mg.

Adhesion Time and Force of adhesion of RZM Mucoadhesive Palatal Discs

Palatal discs showed (Table-3) adhesion time ranging from 8.06 ±0.015 h for formula (F3) to 18.44±0.45 h for formula (F12) and force of adhesion ranging from 1.690N to 3.515N. The results revealed that the formulation F3, F4,F6,F8,F9 were not able to retain the formulation upto 12 hr and F10, F13,F15 These formulation, having friability values above the 1% tolerance limit, were excluded for in vitro mucoadhesive and in vitro mucoretentability study.

In Vitro drug Release and Kinetic Analysis of the Release Data of RZM from Different palatal Discs

The release of RZM from the various mucoadhesive polymers (Cp, SCMC, HPMC, Guar Gum, DPP in different ratio) and drug in different combinations as per simplex lattice design prepared by direct compression was studied (Fig. 2). Excipients like polyethylene glycol (PEG 6000) and mannitol were used to develop a palatal disc to ensure drug release in the palatal mucosa. It was reported that PEG 6000 could increase the release of drugs from the matrix and that mannitol had a sweet taste, a good mouth feel, negative heat of solution, and dissolution enhancing properties [27]. The effect of drug/polymer ratio and polymer/polymer ratio on the RZM release properties from the palatal discs prepared by direct compression with different polymer combinations was studied through validated PCP disso v2 08 soft ware (Poona College of Pharmacy, Pune, India). For most of the tested formulations, the values of n were >0.05, indicating anomalous (non-Fickian) diffusion where drug release is controlled by a combination of diffusion and polymer relaxation. .The release profiles up to 12 hrs of RZM from all formulations in the dissolution medium were statistically compared with each other by the help of statistical test one way ANOVA and nonparametric kruskal wallis test by using Graph pad Prism version 5 software. Results of statistical test showed that there was no significant difference in RZM release from all the formulations at 95% confidence interval with the

calculated F – value (1.255< 2.18) was found to be less than tabled F-value and F11 formulation has been selected as best formulation, as it follows the zero order drug release kinetics with R=0.9844 value and n=0.9063 (n>0.05) , which means that the release of RZM from F11 formulation is of anamalous type moreover it also follows the criteria of USP standard that there should be at least 80% release from formulation in the prescribed time.

Kinetic models of Drug Release

All the models for selecting the release profile were applied on all the formulations. Release models were applied on the selected formulation. Results showed that best fit model in all the case except F-2 could have followed the Zero order, first order, Matrix, peppas, Hixon crowell model and the Peppas and corsenmayer model. While considering higher correlation coefficient value (R), the release data seems to fit Peppas model better. According to correlation coefficient value (R) and maximum drug release with good mucoretentability F-11 seems to be the best formulation. Drug release data, For F-11 formulation further analyzed for curve fitting based on Power law and results (F-11: n = 0.9063, k = 0.0090, and R=0.9844) confirmed that release of RZM from F-11 formulation is of anamalous type.

Histological studies

Disks remained attached to the palatal mucosa during the 12 h period without any disintegration. Typical appearance of intact palatal mucosa is seen in Fig. 3a. After 12 h contact with the disks the surface layer of the mucosa was not smooth as the intact mucosa, showing a slight irregularity in Fig. 3b.

Conclusion

It may be concluded that that optimized formulation (F11) was selected as the finaloptimized formulation that exhibited less percentage deviation of drug release. The mechanism of release of rosiglitazone maleate from the mucoadhesive dosage form was following zero order as well as anamolous type. Hence, in the present study mucoadhesive rosiglitazone disks could be developed with desirable mucoadhesion and release modulation for a once daily administration.

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