ORIGINAL ARTICLE

FORMULATION AND EVALUATION OF MUCOADHESIVE DOSAGE FORM CONTAINING ROSIGLITAZONE MALEATE

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ABSTRACT

Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving bioavailability. The objective of this study was to extend the GI residence time of the dosage form and control the release of rosiglitazone using mucoadhesive tablet to achieve controlled plasma level of the drug which is especially useful after 8 to 12 weeks of monotherapy using conventional dosage forms when dose is doubled and plasma level also doubles. Direct compression method using simplex lattice design, followed by optimization of the evaluation parameters was employed to get final optimized formulation. The optimized formulation showed a mucoadhesive strength >40 gm-f, and a mucoadhesion time >12 hours with release profile closer to the target release profile and followed Non-Fickian diffusion mediated release of rosiglitazone maleate.

Keywords: Mucoadhesive tablet, rosiglitazone maleate, formulation.

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 (Gupta *et al*., 1990 and Madsen *et al*., 1998), 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 (Jay *et al*., 2002 and Jimenez *et al*., 1993). 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 (Akiyama *et al*., 1999).

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 (Harris *et al*., 1989 and Smart *et al*., 1984).

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 (Diamant *et al*., 2003) such as gastro-intestinal disturbances, headache, altered blood lipids, oedema, hypoglycaemia (BNF 51, 2006). 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 (Werner *et al*., 2001). Thus, there is a need to maintain Rosiglitazone at its steady state plasma concentration. Hence, this study was carried out to formulate and evaluate mucoadhesive dosage form of rosiglitazone maleate as a model drug and optimize the formulation parameters to finally get optimized formulations having sufficient bioadhesive strength, bioadhesion time, and desired release profile.

MATERIALS AND METHODS

Materials

Rosiglitazone maleate was donated by Nicholas Piramal India Limited, Hyderabad. Carbopol 934 (Loba cheme Pvt. limited, Mumbai), Ethylcellulose (EC; 18-22 cP; Ethoxyl content 48-49.5%; SD Fine Chemicals, Mumbai) and Cellulose Acetate Phthalate (CAP; Anilax Enterprises, Columbia, USA) and other chemicals used were procured commercially and were used as received.

Methods

Formulations were developed following a simplex lattice design (Bolton, 1997) after setting the individual excipient

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levels through preformulation studies. We developed a series of formulations mentioned in the table 1 and statistically evaluated the effects of two formulation variables viz., percentage of ethylcellulose and percentage of cellulose acetate phthalate on tablet parameters.

The optimized formulations were obtained by subjecting the evaluation parameters to ANOVA and numerical optimization using the software 'Design Expert'. Table 2 contains the formulae of the optimized formulations.

Tablet preparation

The mucoadhesive tablets were prepared by direct compression method using Rimek Minipress-I rotary tablet machine to obtain the tablets of desired specification (Ahuja *et al*., 1997).

Weight variation and hardness

Weight variation test was conducted according to USP and the hardness was measured with Monsanto hardness tester.

Mucoadhesive strength and mucoadhesion time

These were measured by 'modified balance method (Chien, 1992). Briefly, a balance was taken and its left pan was replaced with a weight to the bottom of which a tablet was attached. Both sides were balanced with weight. Porcine gastric mucosa (obtained from local piggery) having a thick layer of mucus was fixed to a rubber cork, which was already attached to the bottom of the beaker containing corresponding medium with a level slightly above the mucosa. The weight, which was attached to the tablet, was brought into contact with the porcine mucosa, kept undisturbed for 5 minutes and then the pan was raised. Weights were continuously added on the right side pan in small increments and the weight at which the tablet detached from the mucosa was recorded as the mucoadhesive strength. For measuring mucoadhesion time a 10-gram weight was put on right side pan after raising it and the detachment time was noted. The time period throughout which the tablet remained attached to the mucosa is mucoadhesion time.

In vitro release study

The *in vitro* release study for all the formulations were carried out for 12 hrs using a USP-Dissolution Test Apparatus Type-II (DISSO 2000, LabIndia, India). The temperature of the dissolution medium (0.1N HCl, 500 ml) was maintained at 37°C ± 1°C with a stirring rate of 50 rpm. At predetermined intervals 4 ml sample was withdrawn and equal volume was replaced to maintain sink condition. The sample was further diluted with methanol and absorbance measured in a UV spectrophotometer (PharmaSpec UV-1700; Shimadzu, Japan) at 228 nm against suitable blank. The absorbance was converted to drug concentration using a calibration curve (ABS = 0.036xCONC + 0.245; R^2 = 0.9999) and then cumulative %drug released was calculated with the help of dilution factor.

Mechanism of release

The mechanism of release was determined by fitting the release data into various kinetic equations such as Zero-order, First-order, Higuchi, and Korsemeyer-Peppas and finding the R^2 values of the release profile corresponding to each model (Kim, 2000).

RESULTS AND DISCUSSIONS

Weight variation and assay

The percentage weight variation of each tablet from average weight was less than 5%, which provided good uniformity. The assay for drug content was found to be uniform among different batches of tablets and ranged from 95 % to 99%.

Table 1: Simplex lattice design for formulations

Formula code	Rosiglitazone Maleate (%)	Carbopol 934 (%)	Ethylcellulose (%)	Cellulose acetate phthalate (%)
DF1	10	80	4	6
DF2	10	80	2	8
DF3	10	80	0	10
DF4	10	80	3	7
DF5	10	80	1	9
DF6	10	80	0	10
DF7	10	80	4	6
DF8	10	. 80	2	8

Hardness

The hardness of all formulations was kept constant at 5 ± 0.5 Kg/cm^2.

Mucoadhesive strength and Mucoadhesion time

The mucoadhesive strength ranged from19 gm-f to 45gm-f, and the mucoadhesion time ranged from 9 to 15 hours for the formulations made at preformulation stage. The mucoadhesive strength ranged from 40 to 41 gm-f and mucoadhesion time ranged from 12 to 13 hours for the designed formulations. These parameters were kept constant during optimization. These results for mucoadhesive strength and time are encouraging keeping in view the dynamic conditions under which the tablet has to adhere to the gastric mucosa *in vivo*. It is expected that electrolytes present in the gastric fluid would reduce the viscosity of the adhering gel layer and hence bring down both the mucoadhesive force and time so that ultimately a bioadhesion time of about 8 hr minimum is expected.

In vitro release profile

In preformulation stage carbopol 934, HPMC and ethylcellulose, were used for making tablets of different formulae. The tablets obtained exhibited i*n vitro* release profile having large deviation from target. The target release profile was obtained by dividing the controlled release dose

Table 2: Composition of optimized formulations

Optimized Formula code	Rosiglitazone Maleate (%)	Carbopol 934 (%)	Ethylcellulose (%)	Cellulose acetate phthalate (%)
OF1	10	80	1.58	8.42
OF2	10	80	1.92	8.08
OF3	10	80	1.66	8.34
OF4	10	80	1.66	8.34
OF5	10	80	0.59	9.41
OF6	10	80	2.06	7.94
OF7	10	80	0.45	9.55
OF8	10	80	0.51	9.49
OF9	10	80	1.93	8.07

Table 3: Model equations

Parameter	M. Eq	Eq. No.
CDR1	Logit (CDR1) = Ln [(CDR1-4.77)/(10.94-CDR1)] = (0.61352 x EC) – (0.15572 x CAP)	1
CDR2	Logit (CDR2) = Ln [(CDR2 – 11.50)/(19.34 – CDR2)] = -(0.22705 x EC) – (0.19835 x CAP) + (0.15848 x EC x CAP)	2
CDR3	$(CDR3 – 19.00)^3$ = (322.78710 x EC) – (7.52703 x CAP)	3
CDR5	$(CDR5 – 31.00)^{-3}$ = (1.80949E-003 x EC) + (4.17461E-004 x CAP) - (3.98533E-004 x EC x CAP)	4
CDR8	$(CDR8 – 54.00)^{-2}$ = (1.34568 x EC) + (0.20383 x CAP) - (0.27198 x EC x CAP)	5
CDR12	Logit (CDR12) = Ln [(CDR12-61.00)/(83.50-CDR12)] = (1.27616 x EC) – (0.26788 x CAP)	6
f_2	$(f_2 – 40.00)^{-3}$ = (9.300E-005 x EC) + (0.027 x CAP) – (0.055 x EC x CAP) + (0.046 x EC x CAP x (EC - CAP))	7
K	K = (0.025238 x EC) + (8.10497E-003 x CAP) - (1.46569E-003 x EC x CAP)	8
n	$(n – 0.80)^{-3}$ = (29396.08534 x EC) + (494.14830 x CAP) - (3859.73411 x EC x CAP)	9

Table 4: Model statistics

Parameter	M.Eq. No.	F	P<F	LOF	R^2adj	R^2pred
CDR1	1	204.39	0.0001	1.86	0.9667	0.9512
CDR2	2	102.36	0.0001	2.28	0.9666	0.9409
CDR3	3	119.26	0.0001	5.43	0.9441	0.9179
CDR5	4	47.91	0.0003	6.35	0.9306	0.8891
CDR8	5	42.24	0.0006	2.38	0.9218	0.8575
CDR12	6	92.54	0.0001	3.52	0.9290	0.8873
f_2	7	283.18	0.0001	0.64	0.9918	0.9789
K	8	395.82	0.0001	5.38	0.9912	0.9862
n	9	10.93	0.0147	1.89	0.7394	0.5086

Table 5: Predicted, target, and observed values of response parameters of the optimized formulations.

Response parameter	OF1			OF2		
	Predicted	Target	Obtained	Predicted	Target	Obtained
CDR1	7.327	7.866	7.260	-	7.866	7.665
CDR2	15.564	15.732	15.616	-	15.732	16.099
CDR3	26.634	23.598	26.481	-	23.598	26.831
CDR5	40.751	39.330	40.784	-	39.330	41.621
CDR8	50.096	62.928	56.058	-	62.928	62.395
CDR12	70.869	94.392	70.951	-	94.392	74.083
f_2	49.056	Max	49.758	55.978	Max	53.501
K	0.088	0.080	0.088	0.091	0.080	0.089
n	-	0.830	0.880	0.920	0.920	0.906

of rosiglitazone maleate with time period throughout which constant level is to be maintained. The controlled release dose was calculated from pharmacokinetic parameters of Rosiglitazone using data from an earlier study (Cox *et al*., 2000). Briefly, the steady state drug concentration (C_{ss}) to be maintained in human plasma was calculated to be ≈ 244 ng/ml using the equation $C_{ss} = AUC_{0-\infty}/\tau$ and the dose required to maintain that level was calculated to be ≈ 8 mg since Dose = $C_{ss} \times \tau \times Cl_T$ (Gibaldi *et al*., 1982), where τ = dosing interval.

The types and the lower and upper limits of excipients were obtained during preformulation study. Based on this a simplex lattice design was developed by taking two formulation variables viz. % of ethylcellulose and % of cellulose acetate phthalate as the independent variables of the simplex lattice design and evaluated for their influence on various response parameters. The percent of drug released at different intervals from various formulations, their similarity factor (f_2) (USFDA, 1997), and 'k' and 'n' values from korsemeyer-peppas kinetic model (Ritger *et al*., 1987) were subjected to numerical optimization (Lewis *et al*., 1999) using polynomial models (tables 3 & 4), which resulted in nine optimized formulae (table 2). From those, two optimized formulae were selected for preparation and evaluation based on the predicted and target values of the evaluation parameters that were taken into consideration in optimization process. The formulation OF2 showed least percent deviation of evaluation parameters both from predicted and target values and was selected as the final optimized formula (table 5).

The release was found to be influenced by the presence of both the rate limiting polymers – EC and CAP. CAP uniformly retarded the drug release from the matrix due to its enteric properties (figures 1 & 2) so that formulations

with higher CAP content released less (DF3 ≈ DF6 > DF5 > DF2 ≈ DF8 > DF4 > DF1 ≈ DF7). The opposite trend could be observed in case of EC where the release increased with increasing polymer concentration. EC is a hydrophobic polymer known to release independent of pH of environment. It just helped in modulating the solvent penetration so that the drug (pKa=6.8) having good solubility inside the tablet matrix (due to acidic microenvironment since dissolution was carried out in 0.1 N HCl and carbopol 934 is an acidic polymer) could not be leached out quickly and hence a steady release was observed.

It may further be observed from the release profiles of the designed formulations (figures 1 & 2) and specifically from Figure 3 for the optimized formulations that the biphasic nature of release is being followed. The phase transition occurs between 5–8 hours of dissolution for all formulations. This period might be the equilibration period for the carbopol hydrogel formed by solvent imbibitions, after which the effect of gel-diffusion barrier becomes constant and the rate is subsequently controlled by the hydrophobic polymers, release being Fickian in nature.

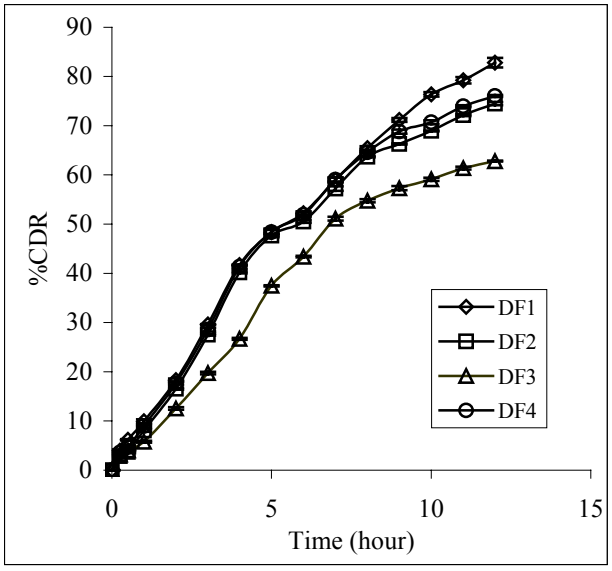

Fig. 1: *In vitro* release profile of formulations made at formulation stage.

For optimized formulation OF1, this transition occurred fairly early, presumably due to lower EC content in the matrix, which allowed faster solvent penetration and hence quicker hydrogel swelling equilibration. Consequently, the release rate decreased at 5 hours, deviating significantly from the target profile. However, for OF2, the transition occurred at 8 hours, presumably due to higher EC content that resisted the solvent penetration velocity and thus deferred hydrogel equilibration.

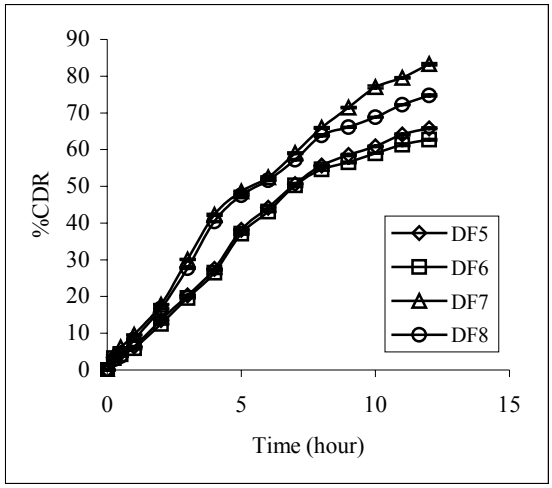

Fig. 2: *In vitro* release profile of formulations made at formulation stage.

Mechanism of release

The R^2 values of first order release as well as R^2 values of Korsemeyer-Peppas release pattern for all formulations were near one implying a mixed order kinetics being operative. The 'n' value for each formulation was above 0.5, indicating that mechanism of release is the Non-Fickian diffusion type (Chien, 1992). Although majority of the formulations followed non-fickian (anomalous) diffusion mediated drug release, the release exponent for optimized formulation is 0.906 (i.e., > 0.89)(Kim, 2000), which indicates that beyond the equilibration point of Carbopol hydrogel, the release mechanism is undergoing a change from non-fickian to Case II transport. This proposed change could be noticed in the changing slopes of the dissolution profile of OF2 in figure 3.

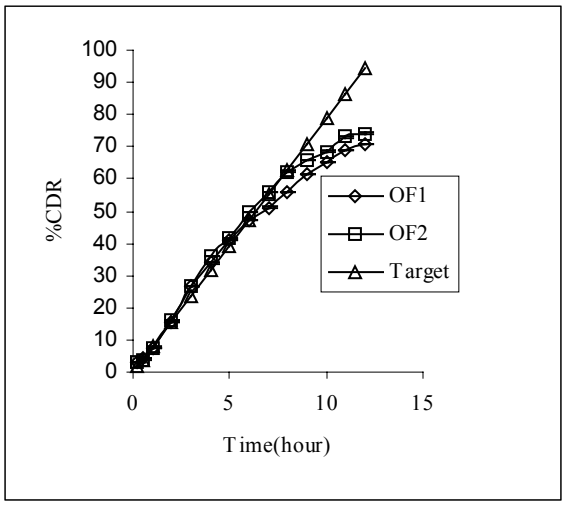

Fig. 3: Comparison of optimized formulations with target zero-order release profile.

The simplex lattice design mediated formulation development thus helped to develop and optimize the mucoadhesive tablet of Rosiglitazone Maleate with desired mucoadhesion time, strength, and release profile. Keeping in view the dynamic conditions existing in vivo under which mucoadhesion is supposed to occur in the stomach, it is expected that the units will be adhering to gastric mucosa at least up to 8 hrs and doing so would release the drug at a rate sufficient to maintain uniform plasma level for better therapy. Thus, it is expected to be a better clinical option to treat chronic NIDDM.

CONCLUSION

It may be concluded that that optimized formulation (OF2) with a composition of 10% rosiglitazone maleate, 80% carbopol 934, 1.92% ethylcellulose, and 8.08% Cellulose acetate phthalate was selected as the final optimized formulation that exhibited less percentage deviation of response parameters from both predicted and target responses in comparison to other predicted formulations. The mechanism of release of rosiglitazone maleate from the mucoadhesive dosage form was following First order as well as Non-Fickian diffusion. Hence, in the present study mucoadhesive rosiglitazone tablets could be developed with desirable mucoadhesion and release modulation for a once-daily administration.

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