Research Article

Formulation and *In-Vitro* Evaluation of Fast Disintegrating Rosiglitazone Sublingual Tablets

Bhanja Satyabrata*, Hardel Danendra K and Sudhakar Muvvala

Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Andhra Pradesh, India.

ABSTRACT

The objective of the current study was to develop and optimize sublingual tablets of Rosiglitazone which is an effective drug in the treatment of type II diabetes mellitus. Rosiglitazone containing tablets were prepared by direct compression method using different ingredients such as Crospovidone, Sodium saccharin, Mannitol, Microcrystalline cellulose, Talc and Magnesium stearate. The tablets were evaluated for physical properties including Hardness, Weight variation, Thickness, Friability, Drug content, Wetting time, Water absorption ratio, *In-vitro* disintegration time, *In-vitro* dissolution study and also Drug release kinetic study. The Hardness, Weight variation, Thickness, Friability and Drug content of tablets were found to be acceptable according to pharmacopoeial limits. An optimized tablet formulation i.e. F4 was found, which provided short wetting time of 21 sec, water absorption ratio of 53 and *In-vitro* disintegration time of 93 sec. From the above results, it indicated that the amount of superdisintegrant i.e. crospovidone was significantly affected the dependent variables like wetting time, Water absorption ratio and *In-vitro* disintegration time. The best *in-vitro* drug release was found to be in formulation F4 i.e.99.88% during the end of 08 min.All the formulations i.e. F1 to F4 followed the zero order release kinetics with diffusion mechanism.

Keywords; Sublingual, Wetting time, Water absorption ratio, *In-vitro* dissolution study.

INTRODUCTION

Diabetes mellitus is a group of syndrome characterized by hyperglycemia, altered metabolism of lipids, carbohydrates, proteins and an increased risk of complications from the vascular disease[1].

Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablets disintegration in oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through sublingual blood vessels bypass the hepatic first-pass metabolic processes[2-4].

Rosiglitazone is an anti-diabetic in the thiazolidinedione class of drug. It is mainly used in the management of type II diabetes mellitus[5-6]. When administered orally, frequent dosing is needed due to its short biological half life (3-4hr).Secondly drug undergoes high hepatic first pass metabolism.

Various techniques can be used to formulate rapidly disintegrating or dissolving tablets[7-8]. Direct compression is one of these techniques which require incorporation of a superdisintegrant into the formulation, or use of highly water soluble excipients to achieve fast tablet disintegration.

Extremely fast tablets disintegration would be required to enhance the release of Rosiglitazone from tablets for rapid absorption by the sublingual mucosa blood vessels. It was decided that Rosiglitazone could be formulated into

fast-disintegrating tablets for sublingual administration as potential emergency treatment of type II diabetes mellitus.

MATERIALS AND METHODS

Rosiglitazone was obtained as gift sample from Sharan Biomedicine Pvt. Ltd., Mumbai. Crospovidone was obtained from Amit Cellulose Products, Pune. Sodium saccharine, Mannitol, Micro crystalline cellulose, Talc and Magnesium stearate were obtained from S.D. Fine Chemicals. Pvt. Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade.

Preparation of sublingual tablets

Rosiglitazone sublingual tablets were prepared by the direct compression method using different excipients. The excipients used were Micro crystalline cellulose (binding agent), Mannitol(diluents), saccharine sodium (sweetening agent), crospovidone (super disintegrant). Different concentration of excipients was used to prepare different group of sublingual tablets. Compositions of various formulations are shown in Table 01. All the ingredients of the sublingual tablets of Rosiglitazone were weighed and mixed in mortar with the help of pestle. Then the blended material was slightly compressed on the 8mm flat–biconvex punch using a Rimek MINI PRESS-I MT tablet machine (Karnawati Engg. Ltd., Mehsana, India). The total weight of the formulation was maintained 200mg.

EVALUATION OF FORMULATED SUBLINGUAL TABLETS OF ROSIGLITAZONE

The evaluations of physicochemical parameters of Rosiglitazone sublingual tablets were done as per standard procedures The following parameters were evaluation**.**

Hardness[9]

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation (F1 to F4) was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in Kg/cm^2. The results are presented in Tables 2.

Thickness[9]

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. The results are presented in Table 2.

Uniformity of Weight[9]

Weight variation test was done as per standard procedure. Ten tablets from each formulation (F1 to F4) were weighed using an electronic balance and the average weight was calculated. The results are shown in Table 2.

Friability[9]

The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted and reweighted. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%. The results are shown in table 2.

$$\%\text{Friability} = \frac{(\text{initial weight} - \text{final weight})}{(\text{initial weight})} \times 100$$

Drug Content

Ten randomly selected tablets from each formulation (F1 to F4) were finely powdered and powder equivalent to 4 mg of Rosiglitazone was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer(pH 6.8). The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with phosphate buffer pH 6.8 and filtered. One ml of the filtrate was suitably diluted and Rosiglitazone content was estimated at 315 nm using a double beam UV-visible spectrophotometer. This procedure was repeated thrice and the average value was

calculated. The results are presented in Table 3.

Wetting Time[10]

The tablets wetting time was measured by a procedure modified from that reported by Bi et al. The tablet was placed at the centre of two layers of absorbent paper fitted into a dish .After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. The results are presented in Table 3 and Fig 1.

Water absorption ratio[10]

A piece of tissue paper folded twice was placed in a small Petri dish Containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$R = Wa - Wb/Wa \times 100$$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption

The results are presented in Table 03 and Fig 02.

***In- vitro* Disintegration Time[10]**

Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temp was 37± 2 °C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured. The results are presented in Table 3.

***In- vitro* drug release study[11]**

In-vitro release rate of Rosiglitazone sublingual tablets was carried out using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus (Paddle method). The dissolution test was carried out using 900 ml of 6.8 pH phosphate buffer, at 37± 2^0C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8, 10, 12 and 14min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through Whatman filter paper No 40 and analysed for Rosiglitazone after appropriate dilution by UV spectrophotometer at 315nm. The percentage drug release was calculated using an equation obtained from the calibration curve. The results are presented in fig 3.

Drug release kinetics

To examine the release mechanism of Rosiglitazone from the prepared sublingual tablets, the results were analyzed according to the following equation

$$\frac{M_t}{M_\infty} = k.t^n$$

Where M_t / M_∞ is the fractional drug released at time *t*, *k* is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system [device], and *n* is the diffusional exponent that characterizes the mechanism of drug release. It is known that for non-swelling tablets, the drug release can generally be expressed by the Fickian diffusion mechanism, for which *n* = 0.5, whereas for most erodible matrices, a zero-order release rate kinetics is followed, for which *n* = 1. For non-Fickian release, the *n* value falls between 0.5 and 1.0 [0.5 < *n* < 1.0]; whereas in the case super case II transport *n* > 1.

The data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Rosiglitazone from sublingual tablets. The kinetic models used were zero-order equation[12] (eq. 1), first-order equation[13] (eq. 2), Higuchi equation[14] (eq. 3) and Krosmeyer-Peppas equation[15] (eq. 4).

$$Q_t = K_0 t \text{---------- (1)}$$
$$Q_t = Q_0 (1 - e^{-k1}t) \text{---------- (2)}$$
$$Q_t = K_H . t^{1/2} \text{---------- (3)}$$

$$Q_t / Q_\infty = K_k \text{ ------- (4)}$$

Where,

Q_t ------- is the amount of drug release in time t

Q_0 ------- is the initial amount of the drug

n ------- Exponent value

And K_0, K_1, K_H, and K_k are release rate constants for Zero-order, First-order, Higuchi, and Krosmeyer-Peppas model respectively.

Zero order represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs. First order is applicable to study hydrolysis Kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. Higuchi Matrix is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water-soluble drug. Krosmeyer-Peppas equation is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved. Data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Rosiglitazone from sublingual tablets. The data are presented in Table 4.

RESULTS AND DISCUSSION

The powder blend for all the formulations containing various concentrations (2%, 4%, 6% & 8%) as superdisintegrant and other exciepients were used. The Rosiglitazone sublingual tablets were prepared by direct compression method using Rimek Mini Press-1MT tablet punching machine. The tablets were evaluated for Weight variation, Hardness, Thickness, Friability, Drug content, Water absorption ratio, Wetting time, *In-vitro* disintegration time, *In-vitro* dissolution rate and also Drug release kinetic study.

It was observed that all the tablets from each formulation passed the test for weight variation, as the percentage of weight variation was within the pharmacopoeial limits. The weight variations in all formulations (F1 to F4) were found to be in the range of 201.08 mg to 199.98 mg, which was within the acceptable limits.

The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 4.0 to 2.8 kg/sq.cm. The tablet mean thickness was almost uniform in all formulations. The thickness varies between 3.9 to 3.8 mm.

The friability varies between 0.28 to 0.18 %. The friability values between 1% were an indication of good mechanical resistance of tablets.

The drug content in all formulations (F1 to F4) was highly uniform and in the range of 100.58 to 98.52 %.The wetting time was found to be in the range of 113 sec to 21 sec. The water absorption ratio in all formulations (F1 to F4) was found to be in the range of 53 to 19.It was observed that wetting time and water absorption ratio increased as the concentration of crospovidone increased. The disintegration time in all formulations were observed within fraction of second. The disintegration time in all formulations (F1 to F4) was found to be in the range 483 sec to 93 sec. It was observed that concentration of crospovidone increases disintegration time not decreased significantly but the formulation F4, containing 8% crospovidone as superdisintegrant showed faster disintegration rate as compared to other formulations.

The *in-vitro* dissolution studies of all formulations (F1 to F4) were conducted and the results are shown in table 03.The percentage of drug release for formulation, F1 was found to be 31.38 % during 2min. And maximum percentage of drug release was found to be 97.81% during 14 min. The percentage of drug release for formulation, F2 was found to be 36.63 %

during 2min. And maximum percentage of drug release was found to be 98.01% during 12 min. The percentage of drug release for formulation, F3 was found to be 42.13 % during 2min. And maximum percentage of drug release was found to be 98.76 % during 10 min. The percentage of drug release for formulation, F4 was found to be 55.76% during 2min. And maximum percentage of drug release was found to be 99.88 % during 08 min .From the above studies, it was observed that increase in concentration of superdisintegrant i.e. crospovidone, the percentage of drug release increased. Among the all formulations (F1toF4) , the best in-vitro drug release observed in formulation, F4 was found to be 99.88 %, as increase the concentration of crospovidone that is due to result of rapid disintegration. During the dissolution studies, it was observed that the tablets were initially swelled and erodible over period of time.

The *in-vitro* drug release data of all Rosiglitazone sublingual tablets were subjected to goodness of fit test by linear regression analysis according to Zero order equation, 1st order equation, Higuchi's equation and Krosmeyer-Peppas equation to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficient are presented in table 04.Among the regression correlation co-efficient (R^2) values of zero order equation was found to be higher, similarly among the Higuchi's equation and Krosmeyer-Peppas equation, the (R^2) values of Higuchi's equation was found to be higher. Hence the drug release followed the zero order release kinetics with diffusion mechanism.

CONCLUSION

An optimized formulation of Rosiglitazone sublingual tablets was found and prepared in this study by direct compression method. The best *in-vitro* drug release observed in formulation F4 was found to be 99.88% which contain the drug Rosiglitazone and crospovidone as superdisintegrant agent with other excipients. The formulation, F4 was found to be best among all other formulations because it has exhibited good wetting time, water absorption ratio and faster disintegration time when compared to all other formulations.

ACKNOWLEDGEMENT

The authors wish to give thanks to Principal, Malla Reddy College of Pharmacy**,** for providing suitable research work laboratory to carry out this project work and my deep greatness to Sharan Biomedicine Pvt. Ltd, Mumbai, India for providing Rosiglitazone as gift sample.

Table 1: Formulation of Fast Dissolving Sublingual Tablets of Rosiglitazone

INGREDIENTS	F1	F2	F3	F4
Rosiglitazone (mg)	4	4	4	4
Crospovidone(mg)	4	8	12	16
Sodium saccharine(mg)	10	10	10	10
Mannitol(mg)	85	85	85	85
Micro crystalline cellulose(mg)	91	87	83	79
Talc(mg)	3	3	3	3
Magnesium stearate(mg)	3	3	3	3

Table 2: Weight variation, Hardness, Thickness and Friability of Rosiglitazone sublingual tablets

Formulation code	Weight Variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	200.25	3.5	3.8	0.18
F2	201.08	2.8	3.9	0.24
F3	200.86	3.5	3.8	0.22
F4	199.98	4.0	3.9	0.28

Table 3: Water absorption ratio, Wetting time, Disintegration time and Drug content of Rosiglitazone sublingual tablets

Formulation code	Water absorption ratio	Wetting time (Sec.)	Disintegration time (sec)	Drug content
F1	19	113	483	99.83
F2	37	65	219	98.52
F3	41	39	156	99.25
F4	53	21	93	100.58

Table 4: Regression analysis of formulations F1-F4

S.L NO.	Formulation Code	Drug Release kinetics			
		Zero-order	First-order	Higuchi	Korsemeyer-peppas
1	F_1	0.895	0. 664	0.937	0.784
2	F_2	0.969	0. 550	0.998	0.751
3	F_3	0.840	0. 657	0.993	0.768
4	F_4	0.950	0. 537	0.986	0.417

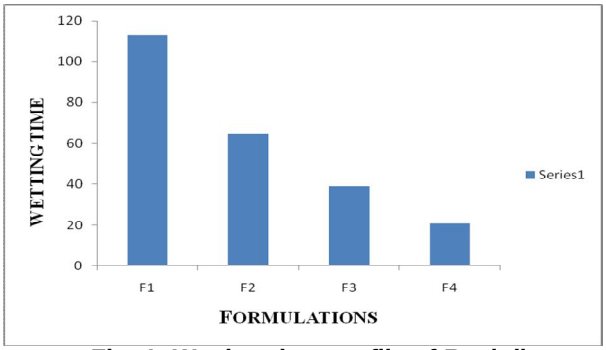

Fig. 1: Wetting time profile of Rosiglitazone formulations F1-F4

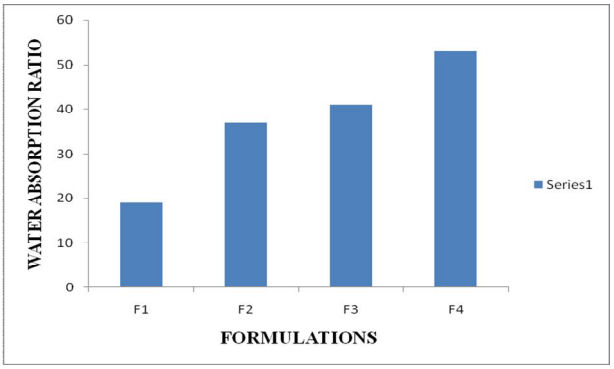

Fig. 2: Water absorption ratio profile of Rosiglitazone formulations F1-F4

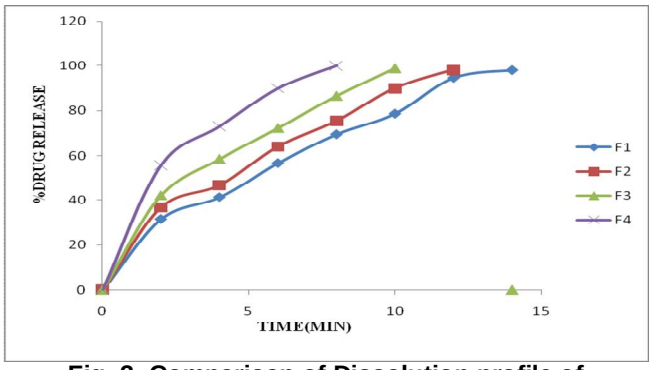

Fig. 3: Comparison of Dissolution profile of Rosiglitazone formulations F1-F4

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