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# FORMULATION AND EVALUATION OF ROSIGLITAZONE MOUTH DISSOLVING TABLET

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## ABSTRACT

To improve patient compliance, mouth dissolving tablets have emerged as an alternative to conventional dosage forms. Rosiglitazone and Sulfonylurea are given in combination for treatment of type 2 Diabetes Mellitus for long term therapy. During this therapy, it is observed that there is uncontrolled increase of blood glucose level. Therefore, mouth dissolving tablets of Rosiglitazone were prepared to overcome this unusual problem and to make use of the inherent advantages of the novel drug delivery system. Rosiglitazone with Sodium Starch Glycolate, Cross povidone & Cross carmellose sodium were tableted with a view to obtain mouth dissolving tablets. Rosiglitazone mouth dissolving tablets containing Cross povidone & Cross carmellose sodium in the ratio 1:1 showed maximum drug release. Formulations were subjected to stability studies. Formulations are stable for 4 weeks at 40 $^{o}$C / 75 % RH with insignificant change in the hardness, disintegration time and in vitro drug release pattern.

## KEY WORDS

Mouth dissolving tablets, sodium starch glycolate, Crosscarmellose sodium, Crospovidone.

## INTRODUCTION

Oral route of drug administration have wide acceptance, up to 50-60% of solid dosage forms are popular because of natural, uncomplicated, convenient, ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms being tablets and capsules, one important drawback of these dosage forms for patient is the difficulty to swallow. Swallowing of solid dosage forms like tablets and capsules and improper dosing of suspension and emulsion may produce difficulty for young children because of incomplete development of muscular and nervous system and elderly patients suffering from dysphasia, Parkinson's disorder and tremor. Other

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groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled patients, patients who are uncooperative, or on reduced liquid intake plans or nauseated, patients having a persistent cough or a gag-reflex, and travelers who may not have access to water[1].

Recent development in technology have presented viable dosage forms alternative for patients who may have difficulty in swallowing tablets or liquids, traditional tablets and capsules administered with glass of water may be inconvenient for some patients[2].

A constant focus on Novel Drug Delivery systems that offer greater patient compliance, effective dosages and minimal chances of side effects has led to the development of Mouth Dissolving Tablets[3]. Mouth dissolving tablets are gaining more demand and popularity from last few years because Pharmaceutical industry has become increasingly aware of the need that elderly be considered as a separate and unique medicare population. Though geriatric patients constitute a minor proportion of the population, its growth rate is high and hence will have significant impact on development of drug delivery system[4].

Mouth Dissolving Tablets are those when put on tongue disintegrate instantaneously, releasing the drug, which dissolves or disperses in the saliva. The faster the drug goes into solution, the quicker the absorption and the onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[5].

Various techniques can be used to formulate rapidly disintegrating or dissolving tablets[6-7.] Direct compression is one of the techniques, requires the incorporation of a suitable superdisintegrant into the formulation, or the use of highly water soluble excepients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat labile medications. Conventional equipment, commonly available excepients and a limited number of processing steps are involved in direct compression. Disintegrant efficiency is strongly affected by tablet size and hardness. Large and hard tablet have disintegration time more than that usually required. As a consequence, product with optimal disintegration properties often have medium to small size and/or high friability and low hardness. Disintegrants have major role in disintegration and dissolution of mouth dissolving tablets made by direct compression. Disintegration efficiency is based on force equivalent concept, which is combined measurement of swelling force development and amount of water absorption. The simultaneous presence of disintegrant with high swelling force called disintegrating agent and substances with low swelling agent are claimed to be key factor for rapid disintegration of tablet; which also offer physical resistance.

Rosiglitazone is an anti-diabetic drug in the thiazolidinedione class of drugs. Like other thiazolidinediones, the mechanism of action of Rosiglitazone is by activation of the intracellular receptor class of the peroxisome proliferator-activated receptors (PPARs), specifically PPARγ. Rosiglitazone is a selective ligand of PPARγ, and has no PPARα-binding action[8]. Rosiglitazone and Sulfonylurea is given in combination for treatment of type 2 Diabetes Mellitus for long term therapy. During this therapy it is some time observed that

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there is uncontrolled increase of blood glucose level. To overcome this unusual problem mouth dissolving tablets of Rosiglitazone is preferred. The aim of this study is to formulate and evaluate Rosiglitazone mouth dissolving tablet.

## MATERIALS AND METHODS

Rosiglitazone Maleate was received as a gift sample from Sun Pharma Ltd, Mumbai. Sodium Starch Glycolate, Croscarmellose Sodium & Crosspovidone were received as a gift sample from Sanofi-Aventis Pharma, Goa. Microcrystalline Cellulose, Magnesium Stearate, Lactose, Aspartame & Purified Talc were received as a gift sample from Aurobindo Pharmaceuticals, Hyderabad. All other materials were used of Pharma grade.

*1. Preparation of Rosiglitazone Mouth Dissolving Tablets:*

Mouth dissolving tablet containing Rosiglitazone maleate was prepared by direct compression technique using varying concentration of superdisintegrants**.** All ingredients except magnesium stearate were blended in a glass mortar uniformly. After sufficient mixing of drug and other components, magnesium stearate was added and further mixed for additional 1-2 minutes. The mixture of drug and excepients was compressed using cadmach single station tablet punching machine using 5mm standard concave punch.

**Table 1**

***Composition of Mouth Dissolving Tablets of Rosiglitazone.***

| Ingredients (mgs) | Formulation Nos. | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| Rosiglitazone | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium Starch Glycolate | 2 | - | - | 1 | - | 1 |
| Cross povidone | - | 2 | - | 1 | 1 | - |
| Cross carmellose sodium | - | - | 2 | - | 1 | 1 |
| Microcrystalline cellulose | 71.5 | 71.5 | 71.5 | 71.5 | 71.5 | 71.5 |
| Lactose | 20 | 20 | 20 | 20 | 20 | 20 |
| Magnesium Stearate | 1 | 1 | 1 | 1 | 1 | 1 |
| Talc | 1 | 1 | 1 | 1 | 1 | 1 |
| Aspartame | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

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In the present work total six formulations were prepared. The weight of the tablet was kept constant for all the formulation.

*2. Evaluation of Tablet Characteristic:*

(i) Drug content uniformity

A physical sound tablet may not produce the desired effects. To evaluate a tablet's potential for efficacy; the amount of drug in a tablet needs to be monitored.

Tablet was weighed and dissolved in phosphate buffer pH 6.4 taken in a 100ml volumetric flask, made up to the mark. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 1 ml of filtrate was taken in a 25 ml volumetric flask and diluted up to the mark with phosphate buffer pH 6.4 and analyzed spectrophotometrically at 317nm. The concentration of Rosiglitazone maleate (in µg/ml) was calculated by using the standard calibration curve of Rosiglitazone maleate. Drug content studies were carried out in triplicate for each formulation batch.

Drug content in mg was calculated by using formula = $\frac{\text{Concentration in µg/ml x 100 x 25}}{1000}$

(ii) Wetting time:

**Simple Method for the Measurement of Wetting Time of a Tablet**

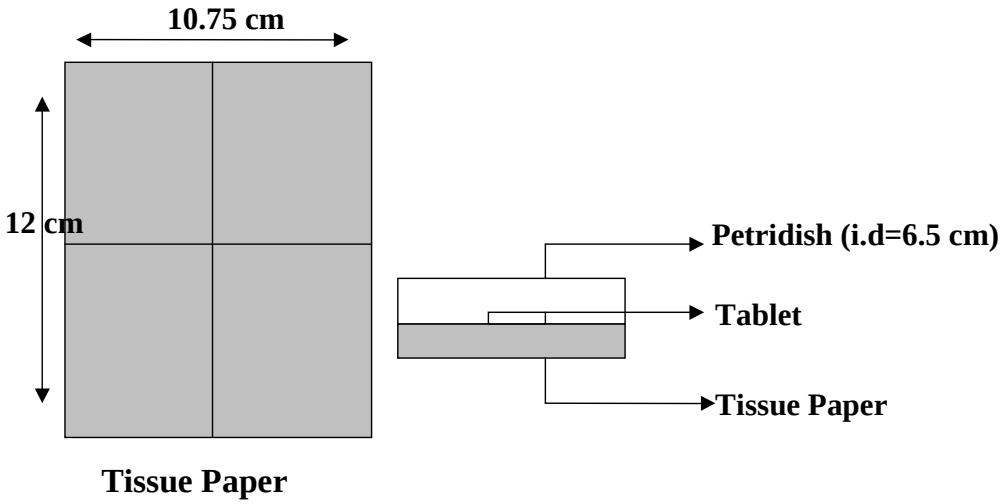


**Figure 1** ***Simple Method for the Measurement of Wetting Time of a Tablet***

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The method was reported by Schmid P, et al. A conventional method was used to measure wetting time and capillarity of the oral dispersible tablets. The tablet was placed in a petridish of 6.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

(iii) In vitro disintegration time:

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.4 (simulated saliva fluid) maintained at 37 ± 0.2 $^{o}$C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in pH 6.4 maintained at 37 ± 0.2 $^{o}$C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

(iv) In vitro dissolution studies:

In vitro release studies were carried out using tablet dissolution test apparatus USP XXIII at 50 rpm, using Phosphate buffer pH 6.4 as a dissolution medium maintained at 37$^{0}$C± 0.1$^{0}$C. Samples were withdrawn at various time intervals, diluted and assayed at 317 nm, using UV spectrophotometer. Two objectives in the development of in vitro dissolution tests are to show (1) that the release of the drug from the tablet is as close as possible to 100% and (2) that the rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.

The following procedure was employed throughout the study to determine the in vitro dissolution rate for all the formulations.

The various parameters related to dissolution which are evaluated in the present work are as follows:

1. Drug release
2. Cumulative percentage drug release
3. Cumulative percentage drug retained

(v) Stability studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established. ICH specifies the length of study and storage conditions: Long term testing 25$^{0}$C±2$^{0}$C /60% RH±5% for 12 months. Accelerated testing 40$^{0}$C±2$^{0}$C / 75% RH±5% for 6 months. In the present study, stability studies were carried out at 25$^{o}$C/60% RH and 40$^{o}$C/75% RH for a specific time period up to 30 days for selected formulations.

## RESULTS AND DISCUSSION

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The content uniformity was performed for all the six formulations. Five trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 3.88 mg to 3.97 mg of Rosiglitazone. The cumulative percentage drug released by each tablet in the *in vitro* release studies were based on the mean content of the drug present in the respective tablet.

Wetting is closely related to inner structure of tablets. All formulations showed quick wetting. This may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling. This parameter also duplicates disintegration time in oral cavity as tablet is kept motionless on tongue.

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance suggested mechanism of disintegration. All formulations showed disintegration time less than 60 seconds. Formulation F2, F4 & F5 showed fast disintegration compared to formulation F1, F3 & F6. A disintegration characteristic of tablet.

All the six formulations were subjected for in vitro dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed at 317 nm. Cumulative drug release and cumulative % drug retained were calculated on the basis of mean amount of Rosiglitazone present in respective tablet. The results obtained in the in vitro drug release for the formulations F1 to F6 are tabulated in **Table 2.**

**Table 2**

**Cumulative % drug Released of Rosiglitazone from Formulation F1 to F6.**

| Time in Min | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| 2 | 32.853 | 54.857 | 38.644 | 54.857 | 60.648 | 38.644 |
| 4 | 53.401 | 63.766 | 63.76 | 79.890 | 78.738 | 45.339 |
| 6 | 66.846 | 74.862 | 73.717 | 86.315 | 88.605 | 73.717 |
| 8 | 78.997 | 84.691 | 88.108 | 97.218 | 99.496 | 88.108 |
| 10 | 97.801 | 95.356 | 96.669 | - | - | 94.404 |
| 12 | 99.497 | 99.385 | 98.371 | - | - | 97.246 |

The cumulative percentage of Rosiglitazone released as a function of time (t) for formulations F1 to F6 are shown in Figure 2.

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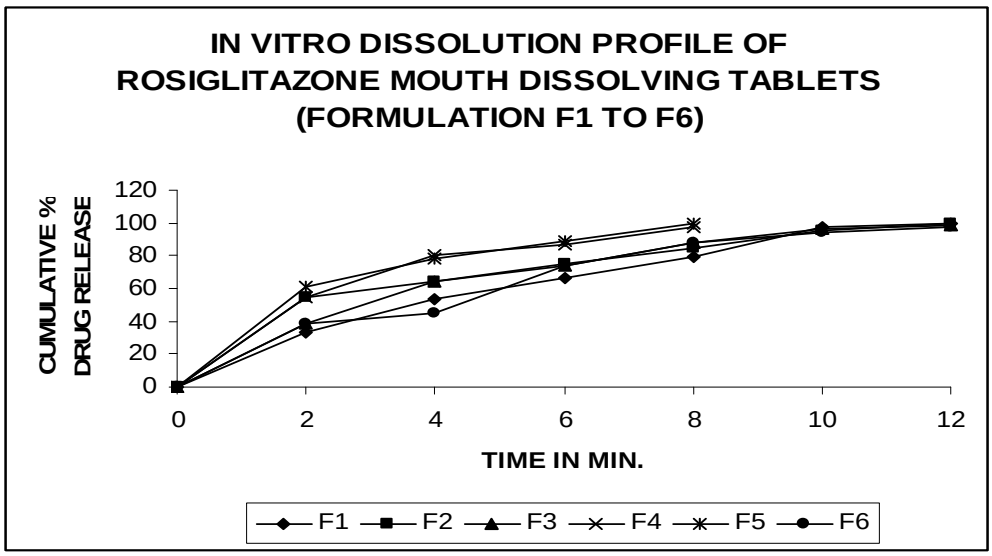


**Figure 2** ***Cumulative % Drug Released v/s Time of Formulation F1 to F6.***

*Formulation F1, F2, F3 F4, F5 and F6 prepared by direct compression method was found to release 99.50 %, 99.39 %, 98.37 %, 97.22 %, 99.50 % and 97.25 % respectively, at end of 12 minutes. This rapid dissolution might be due to fast breakdown of particles of superdisintegrants and porous structure of the tablet.*

In all formulations the drug release was nearer to 100 % within 12 minutes. F1 and F5 showed good drug release than other formulations.

The formulations F4, F5 were selected for stability studies on the basis of their high cumulative % drug release and also results of in vitro disintegration time, wetting time, and in vivo disintegration time. The stability studies were carried out at 25 $^{o}$C / 60 % RH and 40 $^{o}$C / 75 % RH for all the selected formulations up to 30 days. For every 10 days time interval the tablets were analyzed for drug content uniformity, hardness, in vitro disintegration time, friability and wetting time up to 30 days. These formulations showed not much variation in any parameter. From these results it was concluded that, formulations F4 & F5 are stable and retained their original properties.

## CONCLUSION

From the experimental results it can be concluded that the mouth dissolving system can be formulated using different superdisintegrants like Sodium Starch Glycolate, Crosspovidone, Cross Carmellose Sodium by Direct Compression technique.

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The IR Spectra revealed that, polymers and excepients used were compatible with the drug. The formulated tablets showed compliance for various physiochemical parameters viz. tablet dimensions, hardness, friability, weight variation, content uniformity and disintegration. The drug content was within acceptable range which ensured dose uniformity in the formulation. The in vitro studies revealed that formulation F5 showed maximum drug release and drug content. The water absorption ratio revealed that Formulation F5 showed best wetting time results. On the basis of drug release disintegration and wetting studies it can be concluded that the formulation F5 is the optimum formulation. The result of stability studies indicated that all six formulations were stable at 25 $^{o}$C and 60 % RH and there was no significant change in evaluated parameters of formulated

In summary, present work was satisfactory in design and development of Rosiglitazone mouth dissolving tablets. This study clearly demonstrated that one could develop a mouth dissolving tablets by using direct compression method.

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