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DEVELOPMENT, OPTIMIZATION AND INVITRO EVALUATION OF ROSIGLITAZONE MOUTH DISSOLVING TABLETS

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ABSTRACT
In the present work an attempt has been made to develop mouth dissolving tablets of Rosiglitazone. The objective of the current study is to develop and optimize mouth dissolving 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 superdisintegrants such as Crospovidone, croscarmellose sodium, sodium starch glycolate and other ingredients like mannitol, aspartame 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. Optimized tablet formulation F9 was found, which provided short wetting time of 52 sec, in-vitro disintegration time of 26 seconds. From the above results, it indicated that the amount of super disintegrant i.e. crospovidone was significantly affected the wetting time, water absorption ratio and in-vitro disintegration time. The best in-vitro drug release was found to be in formulation F9 i.e., 99% at the end of 29 sec .All the formulations followed the zero order release kinetics with diffusion mechanism.

KEYWORDS: Rosiglitazone, super disintegrants, Wetting time, Water absorption ratio, in-vitro dissolution study, zero order release kinetics.

INTRODUCTION
Diabetes mellitus is characterized by hyper glycemia, 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 Maleate was received as a gift sample from Sun Pharma Ltd, Mumbai. Sodium Starch Glycolate, Croscarmellose Sodium &Cross povidone 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.

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 single station tablet punching machine using 5mm standard concave punch.

Composition of Mouth Dissolving Tablets of Rosiglitazone

Table 1: Composition of Mouth Dissolving Tablets of Rosiglitazone

Ingredients (mgs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosiglitazone	2	2	2	2	2	2	2	2	2
SSG	6	8	10	-	-	-	-	-	-
CCS	-	-	-	6	8	10	-	-	-
CP	-	-	-	-	-	-	6	8	10
Mannitol	90	88	86	90	88	86	90	88	86
Aspartame	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	
Total	100	100	100	100	100	100	100	100	100

SSG-Sodium Starch Glycolate, CCS- Cross carmellose sodium, CP- Cross povidone

Evaluation of tablet Characteristics

Drug content uniformity: A physically 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 0.1NHCl 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 0.1NHCl and analysed spectrophotometrically at 277nm. 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.

In vitro disintegration time: The process of breakdown of a tablet into smaller particles is called as disintegration. The invitro 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^{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^{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.

Table 2: Pre-compression parameters

Form. No	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (%)	Hausner Ratio
F1	0.195±0.013	0.214±0.0165	8.695±0.888	1.09±0.012
F2	0.188±0.018	0.215±0.015	12.500±1.801	1.14±0.022
F3	0.193±0.014	0.223±0.009	13.02±2.169	1.15±0.029
F4	0.223±0.006	0.250±0.008	10.52±0.401	1.11±0.001
F5	0.225±0.004	0.250±0.009	10.00±0.033	1.11±0.001
F6	0.216±0.001	0.232±0.003	7.1428±1.986	1.07±0.026
F7	0.225±0.008	0.250±0.009	10.00±0.033	1.11±0.001
F8	0.232±0.013	0.252±0.010	7.6923±0.598	1.08±0.019
F9	0.225±0.007	0.250±0.008	10.00±0.033	1.11±0.001

****Each value represents mean ± S.D (n=3)***

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.Samples were withdrawn at various time intervals, diluted and assayed at 317 nm, using UV spectrophotometer.

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. ICH specifies the length of study and storage conditions, Long term testing 25^{0}C±2^{0}C /60% RH±5% for 12 months.[17] Accelerated testing 40^{0}C±2^{0}C /75% RH±5% for 6 months. In the present study, stability studies were carriedout at 40^{o}C/75% RH for a specific time period up to 30 days for selected formulations.

Table 3: Post compression parameters

S. No	WT (sec)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	DT (sec)	WV(mg)
F1	54±1.021	2.7±0.196	1.50±0.025	0.56±0.047	33±1.0999	97.20±0.025
F2	55±0.314	2.3±0.086	1.48±0.039	0.55±0.054	31±0.314	97.66±0.299
F3	54±1.021	2.0±0.227	1.42±0.082	0.76±0.094	29±1.728	92.02±3.688
F4	56±0.392	2.8±0.267	1.58±0.030	0.38±0.174	35±2.514	98.83±0.796
F5	59±2.514	2.3±0.086	1.68±0.101	0.66±0.023	33±1.099	97.76±0.370
F6	54±1.021	2.6±0.125	1.71±0.005	0.97±0.242	29±1.728	97.77±0.377
F7	59±2.514	2.5±0.054	1.45±0.060	0.61±0.011	30±1.099	97.74±0.355
F8	56±0.392	2.2±0.157	1.36±0.124	0.50±0.089	29±0.314	97.45±0.150
F9	52±2.435	2.3±0.086	1.82±0.200	0.65±0.016	26±1.728	98.70±1.034

WT-Wetting time, DT-Disintegration time, WV-Weight variation

RESULTS AND DISCUSSION

Table 4: Calibration curve of Rosiglitazone

Concentration (µg/ml)	Absorbance
0	0
10	0.0535
20	0.1049
30	0.1592
40	0.2143
50	0.2655

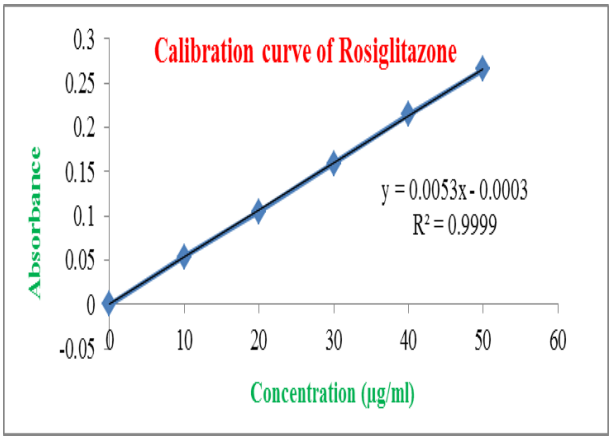

Figure 1: Calibration curve of Rosiglitazone

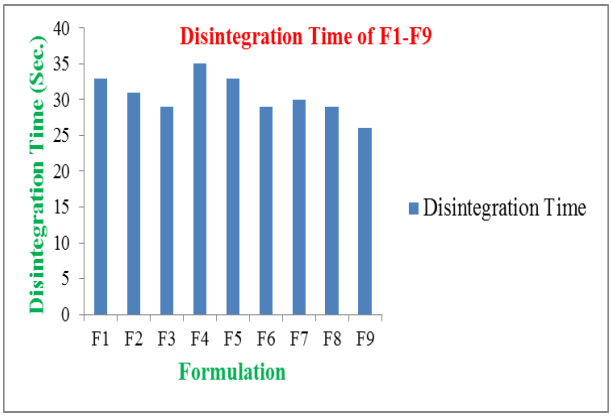

Figure 2: Disintegration Time of F1-F9

Table 5: Cumulative % drug released of Rosiglitazone F1 to F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	24	28	29	32	34	34	35	40	38
10	36	38	37	46	39	43	47	51	55
15	44	51	50	49	43	53	52	67	63
20	64	56	52	60	60	68	74	77	75
25	72	62	76	72	80	70	87	91	88
30	80	72	82	92	91	93	96	97	99

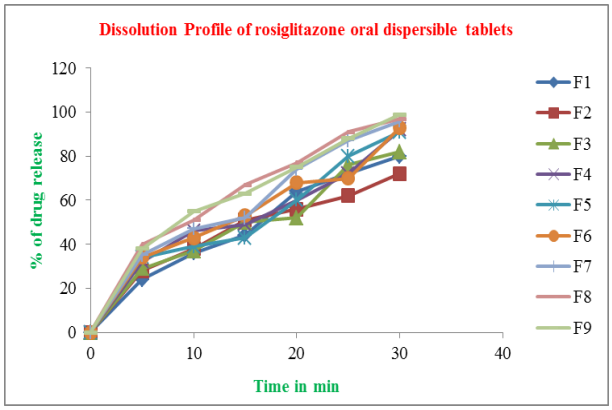

Figure 3: Comparative Dissolution Profile of rosiglitazone oral dispersible tablets.

Drug release kinetics study of F9

Table 6: Drug release kinetics study of F9

Time	Sqr of t	Log time	% drug released	Log % d rel	% d rel	Log % d rel
0	0	1	0	1	100	2
5	2.236068	0.69897	38	1.5797836	62	1.792391689
10	3.162278	1	55	1.7403627	45	1.653212514
15	3.872983	1.176091	63	1.7993405	37	1.568201724
20	4.472136	1.30103	75	1.8750613	25	1.397940009
25	5	1.39794	88	1.9444827	12	1.079181246
30	5.477226	1.477121	99	1.9956352	1	0

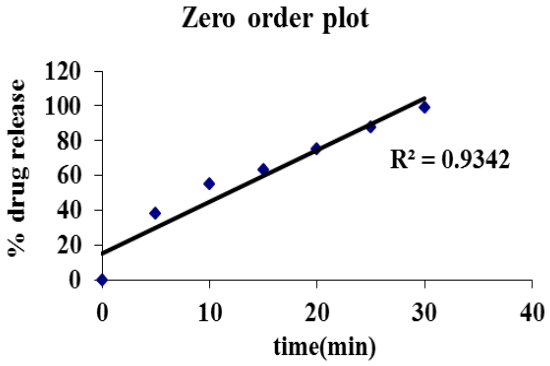

Figure 4: Zero order plot

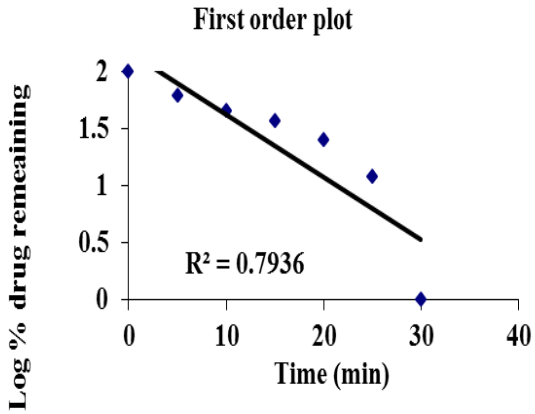

Figure 5: First order plot

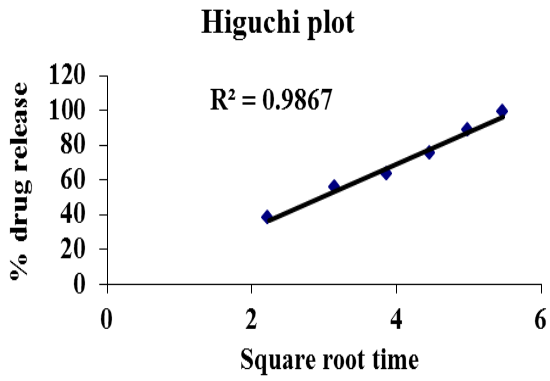

Figure 6: Higuchi plot

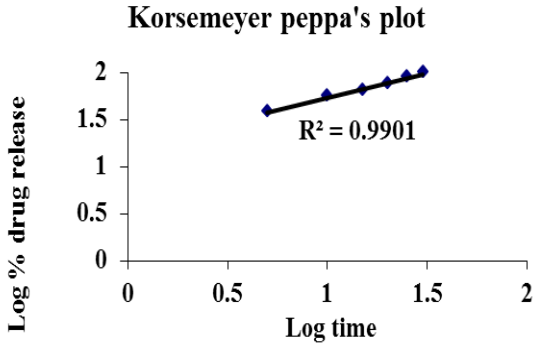

Figure 7: korsemeyer- peppa's plot

CONCLUSION

From the experimental results it can be concluded that the mouth dissolving tablets can be formulated using different superdisintegrants like sodium starch glycolate, crosspovidone, crosscarmellose sodium by direct compression technique. The IR Spectra revealed that, polymers and excepients used were compatible with the drug. The formulated tablets showed compliance for various physiochemical parameters like 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 F9 showed maximum drug release and drug content. The water absorption ratio revealed that formulation F9 showed best wetting time results. On the basis of drug release, disintegration and wetting studies it can be concluded that the formulation F9 is the optimum formulation. This study clearly demonstrated that one could develop a mouth dissolving tablets by using direct compression method for low dose drugs such as rosiglitazone.

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