Formulation Development and Characterization of Floating Drug Delivery System of Rosiglitazone Maleate

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***Abstract*—Background: Rosiglitazone Maleate exhibits a short elimination half-life (3–4 hours) and pH-dependent solubility that decreases as physiological pH increases. This study aimed to design and optimize an effervescent gastroretentive floating drug delivery system (FDDS) to prolong gastric residence time and sustain drug release over 12 hours, thereby enhancing bioavailability.**

Methods: Floating tablets were prepared via wet granulation using HPMC K15M and Xanthan gum as matrix polymers, sodium bicarbonate and tartaric acid as gas-generating agents, and dicalcium phosphate as a diluent. Drug-polymer compatibility was evaluated using FTIR and DSC. Formulations were subjected to pre- and post-compressional testing, in vitro buoyancy profiling in 0.1M HCl (37°C), dissolution kinetic modeling, and standard ICH stability studies.

Results: FTIR and DSC confirmed complete drug-excipient compatibility. Granules exhibited good flow (angle of repose: 20.10°–23.9°) and compressibility. Compressed tablets possessed high mechanical strength, low friability (1%), and uniform drug content. All batches maintained continuous buoyancy for up to 12 hours. While single-polymer matrices failed to sustain delivery for the full duration, the optimized formulation F9, utilizing an HPMC to Xanthan gum ratio of 1:2, successfully controlled release, achieving a cumulative drug dissolution of 98.38% at the 12th hour. F9 followed zero-order kinetics via Korsmeyer-Peppas anomalous (non-Fickian) transport, driven by coupled matrix diffusion and erosion. Stability testing showed no significant changes in physicochemical parameters over time.

Conclusion: The optimized floating matrix tablet successfully prolonged gastric retention and achieved sustained 12-hour delivery of Rosiglitazone Maleate, offering a reliable approach to maximizing therapeutic efficacy.

***Index Terms*—Rosiglitazone Maleate, Gastroretentive systems, Floating tablets, HPMC K15M, Xanthan gum, Zero-order release.**

I. INTRODUCTION

The primary objective of advanced oral drug delivery systems is to optimize therapeutic outcomes by ensuring predictable, reproducible, and enhanced drug bioavailability while maximizing patient compliance through reduced dosing frequencies.[1] Over the past few decades, significant formulation breakthroughs have led to the development of controlled release drug delivery systems (CR-DDS). Despite their success, the clinical efficacy of conventional CR-DDS is often severely compromised by unavoidable physiological constraints within the gastrointestinal tract (GIT). Chief among these challenges are highly variable gastric emptying rates and the brief gastric transit time in humans, which typically averages only 2 to 3 hours.[2] When a conventional sustained-release dosage form transits rapidly past its primary absorption zone, it frequently results in incomplete drug release, shortened therapeutic windows, and reduced structural bioavailability.[3]

To circumvent these biological limitations, localized placement and prolonged retention of a dosage form

within a specific region of the upper GIT represents a highly advantageous strategy.[4] This approach is particularly vital for drugs categorized by a narrow absorption window in the stomach or upper small intestine, or those exhibiting poor stability and solubility when subjected to the higher pH environments of the lower intestinal tract.[5]

Among the diverse anatomical and physiological strategies engineered to extend gastric residence time such as mucoadhesive, swelling, high-density, and osmotic systems Floating Drug Delivery Systems (FDDS) offer a highly elegant, non-invasive solution. FDDS possess a bulk density lower than that of gastric fluid (< 1.0g/cm^3). Consequently, they remain buoyant on the gastric contents within the stomach without affecting the natural gastric emptying rate.[6] While floating, the system continuously and systematically releases the therapeutic agent at a predetermined rate. Once drug release is complete, the remaining bioerodible matrix shell is emptied from the stomach, minimizing the risk of systemic accumulation or local mucosal irritation.[7]

However, designing an effective FDDS requires a meticulous balancing act between the gastric motility forces of the fasted and fed states. During fasting, the stomach undergoes the interdigestive migrating myoelectric cycle (MMC). Specifically, the intense, regular contractions of the Phase III "housekeeper wave" actively sweep undigested material out through the pyloric sphincter every 1.5 to 2 hours.[8] In contrast, the ingestion of food delays the MMC and initiates continuous digestive contractions that grind particles down to less than 1 mm before emptying them.[9] An optimal floating tablet must rapidly achieve buoyancy to escape both fasting and fed emptying patterns, relying on a robust polymer matrix to maintain structural integrity and control release over an extended duration.[10]

Type 2 Diabetes Mellitus represents a major global health burden, accounting for more than 75% of all diabetic cases worldwide, and is characterized by peripheral insulin resistance and progressive pancreatic β-cell secretory defects.[11] Rosiglitazone Maleate, a potent thiazolidinedione oral antidiabetic agent, is highly effective in managing Type 2 diabetes. However, its optimal delivery via traditional oral routes is hindered by distinct biopharmaceutical and pharmacokinetic limitations.[12] It possesses a remarkably short elimination half-life of 3 to 4 hours, which demands frequent daily dosing to maintain steady-state plasma levels. Furthermore, Rosiglitazone Maleate exhibits highly pH-dependent solubility; while it is highly soluble in the acidic environment of 0.1M HCl (11.803mg/mL), its solubility decreases drastically as the physiological pH rises through the distal parts of the GIT. These factors make Rosiglitazone Maleate an ideal candidate for an effervescent, gastroretentive floating system.[13]

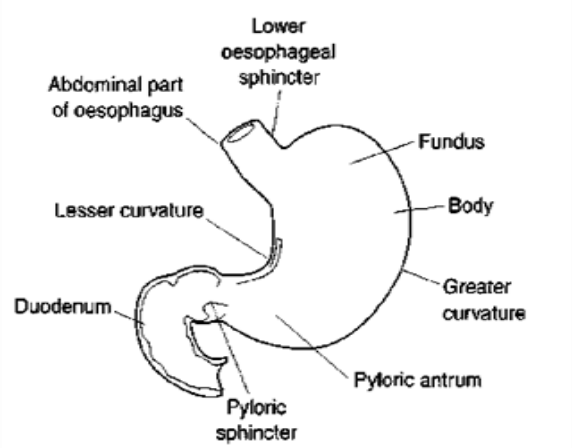

Fig 1: Anatomy of stomach

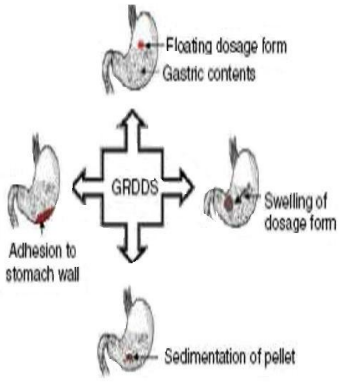

Fig 2: Mechanism of floating drug delivery

The present study was systematically designed to formulate and characterize gastroretentive floating matrix tablets of Rosiglitazone Maleate using a wet granulation approach. To achieve an optimal balance between rapid buoyancy lag time and a sustained 12-hour zero-order release profile, a synergistic interpenetrating polymer network consisting of hydrophilic Hydroxypropyl Methylcellulose (HPMC K15M) and natural Xanthan gum was evaluated. [14] Effervescence was controlled via a gas-generating

system composed of sodium bicarbonate and tartaric acid. Comprehensive pre- and post-compressional parameters were scrutinized, drug-polymer compatibility was validated using Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC), and the optimized formulation was subjected to rigorous ICH stability testing to ensure its long-term industrial and therapeutic viability.[15]

1.1 Aim:

The primary aim of this research was to develop, characterize, and optimize a pharmaceutically stable, effervescent gastroretentive floating drug delivery system (FDDS) of Rosiglitazone Maleate. This delivery system was designed to prolong gastric residence time, maximize drug dissolution within its highest solubility environment (the stomach), and achieve a controlled, zero-order therapeutic release profile over a 12-hour period. This localized approach serves to overcome the biopharmaceutical challenges associated with the drug's short biological half-life and pH-dependent solubility.

1.2 Objectives:

Gastroprotective systems can remain in the gastric region for several hours and hence significantly prolong the GRT of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.[16],[17] It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[18]. Rosiglitazone Maleate has a half-life of (3-4 hrs) and it reaches a peak plasma concentration after 1hrs. It is highly soluble in 0.1M/HCL (11.803 mg/ml) and solubility decreases with increasing pH over the physiological range[19, 20], which makes Rosiglitazone Maleate as a suitable candidate for FDDS in order to prolong the GRT. [21,22]

Plan of the work

- ✓ Selection of a suitable anti diabetic agent and polymers.
- ✓ Formulation of Rosiglitazone Maleate FDDS using polymers like HPMC K15M and Xanthan gum.
- ✓ To evaluate the precompression parameters like compatibility, angle of repose, bulk density, tapped density and compressibility index.
- ✓ To evaluate the post compression parameters like thickness, weight variation, drug content, Buoyancy Lag Time and total buoyancy time.
- ✓ To carry in vitro dissolution studies and release mechanism by using different release kinetic models.
- ✓ To carry out stability studies

1.3 Drug Profile:

Rosiglitazone Maleate[62-66]

Rosiglitazone Maleate is an anti-diabetic drug in the thiazolidinedione class of drugs.[23,24] It is marketed by the pharmaceutical company GlaxoSmithKline as a stand-alone drug (Avandia) and in combination with metformin (Avandamet) or with glimepiride (Avandaryl). Chemical structure

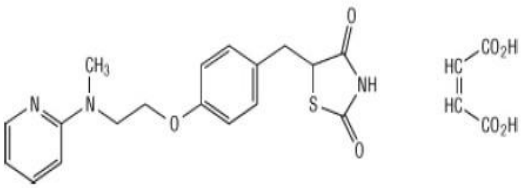

Fig 3: Rosiglitazone Maleate

Molecular formula: $C_{18}H_{19}N_3O_3S$, $C_4H_4O_4$

Molecular weight: 473.5 gm

Chemical name: 5-{p-[2-(Methyl-2-pyridylamino) ethoxy] benzyl}-2, 4thiazolidinedione maleate.

Solubility: soluble in ethanol and a buffered aqueous solution with a pH of 2.3; solubility decreases with increasing pH in the physiologic range.

Category: Anti diabetic agent

Description: A white to off- white crystalline powder.

pka: 6.8 and 6.1

Pharmacology

Rosiglitazone Maleate, a member of the drug group known as the thiazolidinediones or 'insulin sensitizers', is not chemically or functionally related to the alpha-glucosidase inhibitors, the biguanides, or the sulfonylurea. Rosiglitazone Maleate targets insulin resistance and, hence, is used alone or with Metformine or Sulfonylurea to improve glycemic control in patients with type II diabetes mellitus.[25]

Mode of action

Rosiglitazone Maleate acts as an agonist at peroxisome proliferator activated receptors (PPAR) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In this way, enhances tissue sensitivity to insulin. [26]

Pharmacokinetics

Absorption: Bioavailability is 99%. t_{max} is 1 hr. When administered with food, C_{max} is lowered 28%, with a delay in t_{max} by 1.75 hrs. Administration with food does not affect the AUC, but the C_{max} may be decreased by approximately 28% and the t_{max} delayed by 1.75 hrs. However, ROSIGLITAZONE MALEATE may be taken without regard to meals. [27]

Distribution: V_d is about 17.6 L. Protein binding is 99.8%, primarily to albumin.

Metabolism: Extensively metabolized by isoenzyme CYP2C8, with CYP2C9 as minor pathway.

Elimination: Eliminated in urine (64%) and feces (23%). Plasma half-life is 103 to 158 hrs. Elimination half-life is 3 to 4 hrs. [28]

Indications and usage: Improved glycemic control of type II diabetes mellitus as monotherapy and as an adjunct to diet and exercise.

Unlabeled uses: Increased ovulation frequency in women with polycystic ovary syndrome; reduced in-stent restenosis in patients with diabetes.

Dosage and administration: Individualize therapy.

Contraindications: Established New York Heart Association class III or IV heart failure; hypersensitivity to any component of the product. [29]

Combination therapy

Metformin: In combination with Metformin, initiate therapy with Rosiglitazone Maleate 4 mg as a single dose or 2 divided doses. Following 8 to 12 weeks of treatment, dosage may be increased to 8 mg daily if needed. [30]

Sulfonylureas: In combination with sulfonylureas, the recommended dose of Rosiglitazone Maleate is 4 mg as a single dose or 2 divided doses. Following 8 to 12 weeks of treatment, dosage may be increased to 8 mg daily if needed. If patient reports hypoglycemia, decrease the sulfonylurea dose. [31]

Sulfonylurea and Metformin: In combination with a sulfonylurea and Metformin, initiate therapy with Rosiglitazone Maleate 4 mg as a single dose or 2 divided doses. Following 8 to 12 weeks of treatment, dosage may be increased to 8 mg daily if needed. If patient develops hypoglycemia, decrease the sulfonylurea dose. [32]

Hepatic function impairment: Treatment should not be initiated in patients exhibiting evidence of active liver disease or increased serum transaminase levels.

Monotherapy: Initiate therapy at 4 mg/day, administered as a single dose or 2divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment, the dosage may be increased to 8 mg daily. [33]

Over dose: Rosiglitazone Maleate has been administered at single oral doses of up to 20 mg and was well-tolerated.

Adverse reactions

Cardiovascular: Hypertension (4%), CHF (post marketing).

CNS: Headache (6%), fatigue (4%).

Dermatologic: Pruritus, rash, Stevens-Johnson syndrome, urticaria (post marketing). [34]

ENT: Nasopharyngitis (6%), sinusitis (3%), macular edema (post marketing).

GI: Diarrhea (3%).

Hematologic-Lymphatic: Anemia (2%), decreased WBC, dose-related decreases in Hgb and Hct.

Hepatic: Hepatic enzyme elevation 3 or more × ULN, hepatitis (post marketing).

Metabolic-Nutritional: Hyperglycemia (4%); hypoglycemia (3%).

Musculoskeletal: Bone fractures (9%), arthralgia, back pain (5%).

Respiratory: Upper respiratory tract infection (10%), pleural effusion, pulmonary edema (post marketing).

Miscellaneous: Injury (8%), edema (5%), anaphylactic reactions, angioedema
(post marketing). [35,36]

II. METHODOLOGY

Table 1: Materials:

S.No.	Ingredients	Suppliers
1	Rosiglitazone Maleate	KAPL, Bangalore
2	HPMC K15M	KAPL, Bangalore
3	Xanthan gum	KAPL, Bangalore
5	Sodium bicarbonate	CDH, New Delhi

6	Tartaric acid	Colour corn pharmaceuticals
7	Lactose	KAPL, Bangalore
8	Talc	KAPL, Bangalore
9	Magnesium stearate	KAPL, Bangalore

Table 2: List of instruments used

S. No.	Instruments	Company Name
1	Hot air oven	C.S. medical PVT LTD 175-10
2	Tablet punching machine	Elit Jemkay engineers Pvt Ltd, Ahmedabad
3	Friability testing apparatus	Electrolab, EF 2
4	Dissolution test apparatus	Electro lab TDT-08L dissolution tester (USP) and USP-Type-II
5	UV –Visible spectrophotometer	Shimadzu (UV-1601)
6	FTIR	Shimadzu 8300

III. METHODS

Preformulation Studies

It is one of the important prerequisites in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies. [37]

Determination of melting point

Melting point of Rosiglitazone Maleate was determined by capillary method. Fine powder of Rosiglitazone Maleate was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermo meter and the thermometer was placed in fire. The powder at what temperature it will melt was noticed.[38]

Solubility

Solubility of Rosiglitazone Maleate was determined in methanol, acetone, water, 0.1M HCL.

Compatibility studies by FTIR

Compatibility with polymers was confirmed by carried out I R studies. The Rosiglitazone Maleate and its formulations along with polymers were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed. [39]

Compatibility studies by DSC

Individual coils that are heated and cooled at the same rate heat DSC in which sample and reference containers are not contiguous and heated them separately. Platinum resistance thermometers monitor the temperature of the sample and reference holders and electronically maintain the temperature of the two holders constant.[40] For thermal analysis of drug and drug-excipients mixtures, a DSC was used. Individual samples (drug and selected excipients (all passed through sieve 60-mesh) were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 50-300°C (at the heating rate of 10°C/ min) under an atmosphere of dry nitrogen. [41]

Determination of λ_{max}

A solution of Rosiglitazone Maleate containing the concentration 10 µg/ ml was prepared in 0.1 M HCL and UV spectrum was taken using Shimadzu (UV-1601) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm. [42]

Preparation of standard calibration curve of Rosiglitazone Maleate

Stock I: 100 mg of Rosiglitazone Maleate was accurately weighted into 100 ml volumetric flask, dissolved in 0.1M HCL and volume was made up with 0.1M HCL.

Stock II: Pipette 1ml of above solution into another 10 ml volumetric flask and the volume was made with 0.1M HCL. Aliquots of, 0.5 ml, 1.0 ml, 1.5 ml,2.0 ml,2.5 ml,3.0 ml from standard drug solution were diluted to 10 ml with 0.1M. The absorbance of these solutions was measured at 318 nm 0.1M HCL as a blank.[43]

Dose Calculation[44]

For sustained drug release up to 12hrs, the total dose of drug required was calculated based on the fact that the conventional dose was calculated using the following equation:

$D_t = \text{Dose}\ (1+0.693\times t/t_{½})$

D_t = Total dose, Dose= Immediate release dose, t= Total time period for which sustained release is required, $t_{½}$ = Half-life of drug. For Rosiglitazone Maleate: D_t= Dose (1+0.693×12/3.5), D_t =6.752mg Rosiglitazone and 8.943mg of Rosiglitazone Maleate is equivalent to 6.752mg Rosiglitazone

Method Of Preparation[45]

The composition of different formulations of Rosiglitazone Maleate floating tablets is shown in Table. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. The granules (40 mesh) were dried in conventional hot air oven at 45°C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 1 to 3%, as measured by a moisture balance at 105°C. The dried granules were sized through 40/60 mesh, lubricated with magnesium stearate (2% w/w) and purified talc (1 % w/w) and then compressed. [46]

Evaluation Parameters

Precompressional parameters[47]

Bulk density (D_b)

Is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by

$D_b = M / V_0$

Where, M is the mass of powder.

V_0 is the bulk volume of the powder.

Tapped density (D_t) [48]

10 gm of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by

$D_t = M / V_t$

Where, M is the mass of powder.

V_t is the tapped volume of the powder.

Angle of repose (θ) [49]

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation.

$\theta = \text{Tan}^{-1} (h/r)$

Where Ø = Angle of repose,

h = Height of pile,

r = Radius of the base of the pile

Carr's consolidation Index (I) [50]

Carr's index is an indication of the compressibility of a powder. It is expressed in percentage and is given by

$I = D_t - D_b / D_t \times 100$

Where Dt =Tapped density, D_b=Bulk density

Post-Compressional Parameters[51]

Thickness and diameter

Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier callipers. It is measured in mm.

Hardness [52] For each formulation, the hardness of tablets was determined using the Pfizer hardness tester. The value was noted in kg/cm^2.

Weight variation [53]

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighing upto 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

$PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100$

Where PD= Percentage deviation, W_{avg} =Average weight of tablet, $W_{initial}$ =Individual weight of tablet.

Friability (F) [54]

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was then calculated by

$(W_{initial}) - (W_{final})$

$(W_{initial})$

Where, $W_{initial}$ = Initial weight of tablets,

W_{final} = Final weight of tablets.

Floating property[55]

The in vitro buoyancy was determined by the floating lag time. The tablets were placed in 100-mL beaker containing 0.1M HCL. The time required for the tablet to rise to the surface for floating was determined as the

BLT and further floating duration of all tablets was determined by visual observation.

Drug Content [56]

Stock solution I: Twenty tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 100 mg of Rosiglitazone Maleate and transferred to a 100 ml volumetric flask containing few ml of 0.1M HCL and shake for some time and make up the volume up to 100 ml with 0.1M HCL.

stock solution II: Pipette out 10 ml from the I stock solution into another 100 ml volumetric flask and make up the volume with 0.1M (i.e. 100 µg/ml).

Aliquots: From the above solution withdraw 1ml quantity (as per Beer's range 5-30 µg/ml) and the volume was made up to 10 ml with 0.1 M Hcl. The absorbance was measured spectrophotometrically at 318 nm using 0.1 M HCL as blank. [57]

In vitro release studies

The release rate of Rosiglitazone Maleate from floating tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1M HCL, at 37 ± 0.5°C and 50 r/min. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 318 nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot. [58]

Curve Fitting Analysis [59]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows

1. Cumulative % drug released versus time (Zero – order kinetic model)
2. Log cumulative percent drug remaining versus time (First-order kinetic model)
3. Cumulative % drug released versus square route of time (Higuchi model)
4. Log percentage cumulative release versus log time. (Korsemeyer-Peppas model) For Fickian release n=0.45 while for anomalous (non-Fickian) transport, n ranges between 0.45 and 0.89.

Stability Studies[60]

A Study of stability of pharmaceutical product is essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Stability studies are important to prevent the economic repercussions of marketing of an unstable product, since subsequent withdrawal and reformulation may lead to considerable financial loss.[61,62] From the point of view of safety to patient, it is important that the patient receives a uniform dose of the drug throughout the shelf of the product.

Method

The optimized formulation F9 was stored at different storage conditions at elevated temperatures such as 25^0C / ± /2^0C / 60% / ± / 5% RH, 30^0C /± / 2^0C / 65% /±/ 5% RH and 40^0 C/ ± / 2^0C / 75% ± / 5% RH for 3 months. The samples were withdrawn at end of 3 months checked for BLT, drug content and in vitro drug release studies.[63]

III. RESULTS AND DISCUSSION

Preformulation Study of Rosiglitazone Maleate Floating Tablets

Melting point determination: Melting point of Rosiglitazone Maleate was found to be in the range 122-123^{0}C.

Solubility: Rosiglitazone Maleate was found to be free soluble in soluble in methanol, 0.1M HCL, sparingly soluble in water and acetone.

Estimation of Rosiglitazone Maleate by UV spectroscopy

Determination of λ_{max}

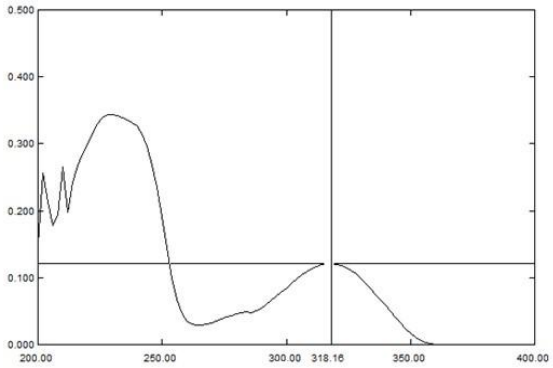

Figure 4.1: UV spectra of Rosiglitazone Maleate at 10 µg/ml concentration

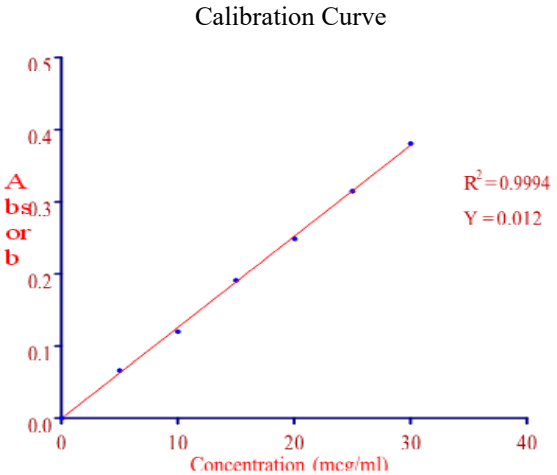

Fig. 4.2 Standard calibration curve of Rosiglitazone Maleate in 0.1M HCL

Compatibility studies
TIR spectroscopy

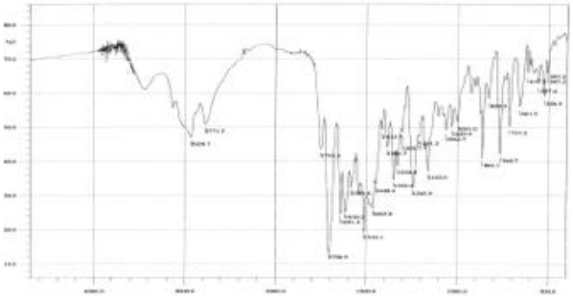

Fig. 4.3: IR spectra of Rosiglitazone Maleate

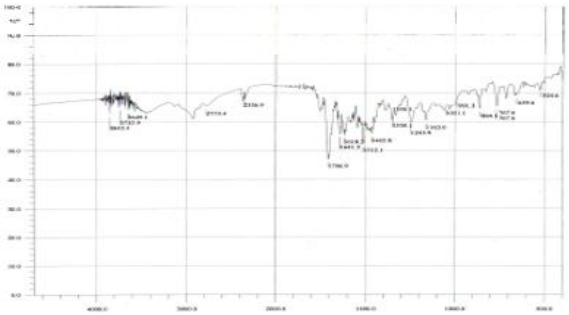

Fig.4.4: IR spectra of ROSIGLITAZONE MALEATE + HPMC K15M

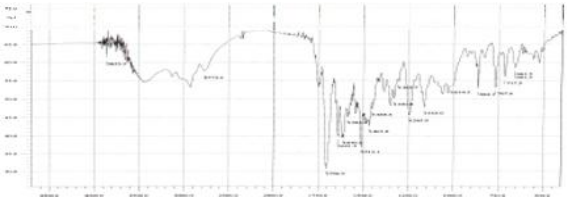

Fig. 4.5: IR specra of Rosiglitazone Maleate + Xanthan gum

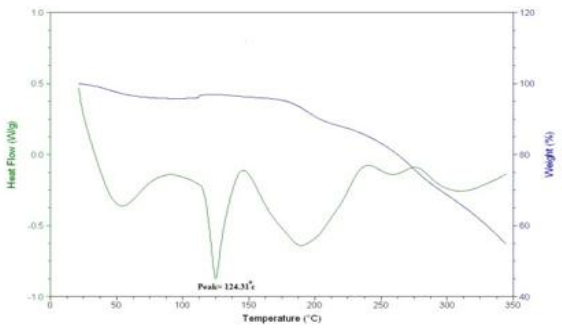

Fig. 4.6: DSC of Rosiglitazone Maleate + HPMC K15 M + Xanthan gum

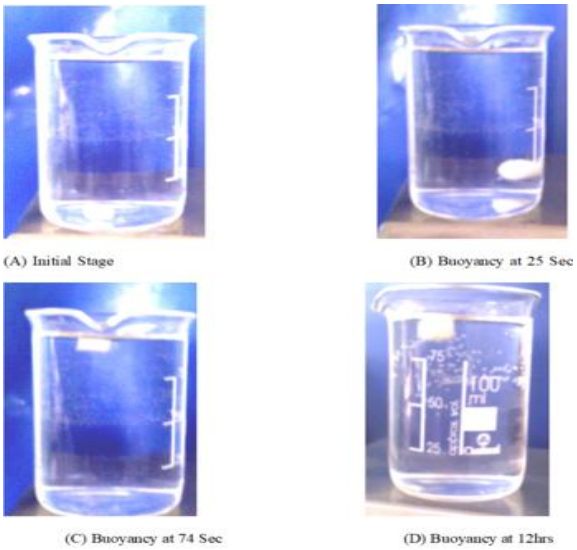

Fig.4.7: Floating tablet buoyancy time study of formulation F9

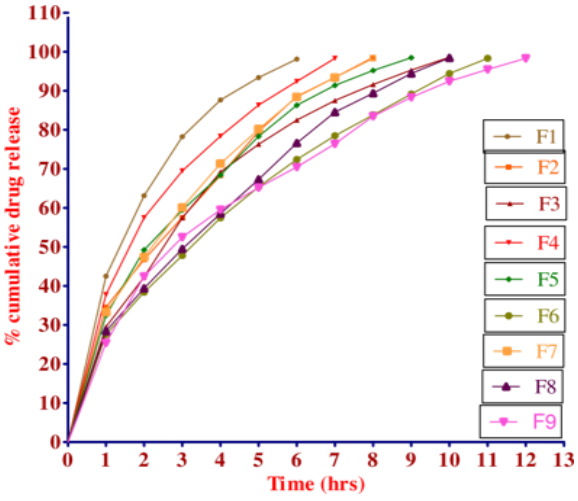

Fig. 4.8: In Vitro drug release profile of Rosiglitazone Maleate floating tablet formulation F1 to F9

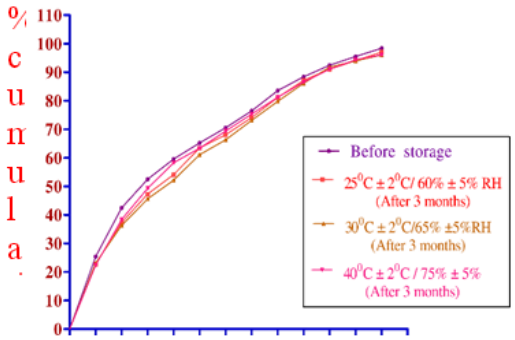

Fig. 4.9: Comparison of stability studies by In vitro drug release profile of formulation of F9

Discussion

Gatroretentive systems have potential to remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.

The aim of the study was to formulate and characterize the floating tablets of Rosiglitazone Maleate by wet granulation technique with HPMC K15M, Xanthan gum, as polymers, sodium bicarbonate and tartaric acid as gas generating agent and DCP as diluent and finally to carry out the stability studies for optimized formulation. The tablets were prepared by using generally approved excipients which are compatible with Rosiglitazone Maleate. [64]

Selection Of Drug

In the present study a dosage form containing Rosiglitazone Maleate, sodium bicarbonate, tartaric acid, DCP and different polymers (HPMC K15M and Xanthan gum) were prepared as floating tablets and evaluated. Moreover, rosiglitazone maleate has a very short half-life (3-4hrs) and solubility decreases increasing physiological pH, which makes Rosiglitazone Maleate as suitable candidate for formulation into floating dosage form in order to prolong the GRT.

Drug-polymer interaction study

The drug-polymer interaction study was carried out using FTIR i.e. by KBr pellet method and DSC.

FTIR

FTIR drug-polymers interaction studies are shown in figure 4 to 8 and reported in table 7. It was found that Rosiglitazone Maleate was compatible with polymers used in the formulation.

There were no extra peaks observed. Thus, the chosen polymers for the formulations were found to be compatible with the Rosiglitazone Maleate and have no physical interaction.

DSC

DSC enables the quantitative detection of all the process in which energy required or produced (i.e. endothermic or exothermic phase transformations). The thermo grams of Rosiglitazone Maleate and physical mixture of Rosiglitazone Maleate with HPMC K15M and Xanthan gum are presented in figure 9 and 10. The Rosiglitazone Maleate showed melting peak at 125.04°C. Peak of Rosiglitazone Maleate 125.04°C was presented at the same position i.e. near to 124.31^{0}C in the physical mixture of Rosiglitazone Maleate with both HPMC K15M and Xanthan gum. This confirmed the no interaction between Rosiglitazone Maleate and polymers.[65]

Preformulation Parameters

Determination of λ_{max} of Rosiglitazone Maleate

On the basis of preliminary identification test it was concluded that the Rosiglitazone Maleate complied the preliminary identification. By scanning the drug in U.V spectrophotometer in 200-400 nm range, a sharp peak was observed at 318.16 nm using 0.1M HCL as solvent. It was concluded that the drug has max of 318.16nm (318 nm as per I.P) as showed in figure 3.

Preparation of standard calibration curve of Rosiglitazone Maleate

From the standard curve of Rosiglitazone Maleate it was observed that the drug obeys Beer's law in the range5-30 g/ml and the equation was generated it was showed figure 3.1 and table 6. Absorbance = 0.012 Conc + 0, was used to calculate the drug content and % CDR of the dosage form.

Evaluation Parameters[66]

Pre- compressional parameters

Flow properties play an important role in pharmaceuticals especially in tablet formulation. The bulk density of the granules for formulations was in the range of 0.442 to 0.578 gm/cc; the tapped density

was in the range of 0.521 to 0.578 gm/cc, which indicate powder was not bulky. The angle of repose of the drug powder was in the range of 20.1^0 to 23.9^0, which indicate good flow of the granules, the Carr's index was found to be in the range of 13.82 to 17.80 indicating compressibility of the tablet granules is good as reported in table 8.

Post-Compressional parameters

Weight variation

Prepared tablets were evaluated for weight variation and percentage deviation from the average weight are reported in table 9 and was found to be within the prescribed official limits.

Friability

The friability of the formulations as found to be between 0.359 - 0.678% are reported in table 9 and as that of which was found to be within the official requirement (i.e. not more than 1%).

Tablet thickness and hardness

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (7 mm) and the weight of the tablet (150 mg). The thickness of the batch from F1-F9 was found to be 2.80-2.83 mm and hardness was found to be 3.9-4.3 Kg/cm^2 as reported in table 9 which have good mechanical strength.

Drug content

The drug content estimation data for all the formulations were shown in table 10 found to be within the limit.

In Vitro buoyancy studies [67]

Buoyancy Studies were performed using 0.1M HCL solution pH at 37; the tablets floated and remained buoyant without disintegration. Table 11 showed the results of Buoyancy study and figure 12 showed buoyancy character of prepared tablet. Duration of floating for prepared tablet of each batch remained buoyant up to 12 hrs.

In Vitro dissolution study

In- vitro dissolution studies were performed for all the formulations using USP type II tablet dissolution tester employing basket type at 50 rpm using 900 ml of 0.1M HCL as dissolution medium. As showed in table 12 and figure 13.

The formulation F1 containing Drug: HPMC (1:5) shown cumulative percentage release of 98.14% at 6^{th} hr. But the objective of the formulation is to develop Rosiglitazone Maleate tablet which sustain the release upto 12 hrs. Formulation F2 containing Drug: HPMC (1:6) showed 98.55% cumulative release at the end of 8^{th} hrs. Formulation F3 containing Drug: HPMC (1:7) was increased showed 98.6% cumulative release at the end of 10^{th} hr.

In the formulation F4, F5, F6 attempt was made to achieve the objective by incorporating Xanthan gum instead of HPMC. The formulation F4 containing Drug: Xanthan gum (1:5) shown cumulative percentage release of 98.34% at 7^{th} hr.F5 formulation containing Drug: Xanthan gum (1:6) was increased to sustain the release upto 12 hr, showed 98.47% cumulative release at the end of 9^{th} hrs. F6 formulation containing Drug: Xanthan gum (1:7) was increased to sustain the release upto 12 hr, showed 98.3% cumulative release at the end of 11^{th} hrs.

An attempt was made to optimize the release by using mixture of HPMC and

Xanthan gum in different ratio. Formulation F7 containing combination of HPMC: Xanthan gum (2:1) showed cumulative percentage release of 98.3% at 8^{th} hrs. Formulation F8 HPMC: Xanthan gum (1:1) showed 98.3% cumulative release at the end of 10^{th} hrs. Formulation F9 containing HPMC: Xanthan gum (1:2) showed 98.38% cumulative release at the end of 12^{th} hrs. Formulation F9 was found to achieve the objective.

Curve fitting analysis

The dissolution data of all batches fitted to zero order, first order, Higuchi, Korsemeyer-Peppas equations (table 13 to 16 and fig 5.13 to 5.16). Observed that formulation F1 and F3 follows first order release kinetics, remaining all formulations F2, F4, F5, F6, F7, F8, and F9 follows zero order kinetics, korsemeyer-Peppas model indicates drug release from the tablets were non fickian diffusion and controlled by both diffusion and erosion. Higuchi model confirms diffusion as showed in table 17.

Stability studies

The stability studies were performed on optimized formulation F9 at 25°C ± 2°C / 60% ± 5% RH , 30°C ± 2°C / 65% ± 5% RH , 40°C ± 2°C / 75% ± 5% RH

and analyzed for BLT, drug content and invitro dissolution studies in 0.1M HCL. As showed in table 18 to 20 and figure 18 to 20 no significant difference was observed for above parameters and the optimized formulation F9 shows good stability. Therefore, main objective of study was achieved.

IV. SUMMARY AND CONCLUSION

Rosiglitazone Maleate, has a half-life of (3-4 hrs) and it reaches a peak plasma concentration after 1h. It is highly soluble in 0.1M HCL (11.803 mg/ml) and solubility decreases with increasing pH over the physiological range, which makes Rosiglitazone Maleate as a suitable candidate for FDDS in order to prolong the gastric residence time.

For the formulation of floating tablets, hydrophilic swellable (HPMC K15M), natural gum (Xanthan gum) was used as matrix forming agent. Other excipients used are $NaHCO_3$ and tartaric acid as gas generating agent and other excipients includes magnesium stearate as lubricant, talc as glident, DCP as diluent and PVP K 30 as a binder. FTIR and DSC confirmed the absence of any drug polymers interactions.

Rosiglitazone Maleate floating tablets were compressed using 7 mm circular flat-headed punch and die on Elit Jemkay 16-station rotary punching machine. Wet granulation method was employed to formulate the Rosiglitazone Maleate floating tablets.

In pre formulation study, estimation of Rosiglitazone Maleate was carried out by Shimadzu UV spectrophotometer at max 318 nm using 0.1M HCL as solvent, which had a good reproducibility and this method was used in entire study.

The prepared floating Rosiglitazone Maleate tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, BLT and floating duration. All formulations were found to be within acceptable limits and formulation F9 showed drug release up to 12hrs was selected as optimized one for stability studies.

The formulation was found to be stable because there was no significant change has been observed in the various evaluated parameters.

All formulations were subjected for four different models viz. Zero order, first order, Higuchi and Peppas model and all the formulations followed Peppas model. Diffusion exponent for all formulation was found to be in range of 0.45-0.89 which indicates the mechanism of release of Rosiglitazone Maleate was anomalous (non-Fickian) transport. It was revealed that polymers ratio has significant influence on drug release.

Conclusion

The concept of formulating floating tablets containing RZM offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, floating tablets of Rosiglitazone Maleate were prepared successfully by wet granulation method using the different concentration and combination of polymers like HPMC K15M, and Xanthan gum, sodium bicarbonate and tartaric acid as gas generating agent, and other excipients such as magnesium stearate as lubricant, talc as glident, DCP as diluent and PVP K 30 as a binder. All the pre-compressional parameters like angle of repose, bulk density, Carr's index were studied. The compressed tablets were subjected to drug content, hardness, friability, weight variation, in vitro dissolution studies, floating properties and stability studies.

Based on the above studies, following conclusions can be drawn.

The drug and excipients compatibility was studied by FTIR and DSC which revealed there was no chemical or physical interaction. Floating tablets of Rosiglitazone Maleate prepared using hydrophilic swellable polymer (HPMC K15M), natural gum (Xanthan gum), sodium bicarbonate, tartaric acid, Mg stearate, talc and DCP by wet granulation method, were found to be good without chipping, capping and sticking. The drug content was uniform in all the tablet formulations indicating uniform distribution of drug within the matrices. From in vitro buoyancy studies it was concluded that all formulations exhibited satisfactory floatation ability and remained buoyant for more than 12hrs. Invitro studies conclude that as concentration of HPMC K15M is increased in formulation F1, F2, F3 showed an increase in release time upto 6, 8, 10 hrs respectively. With Xanthan gum in formulation F4, F5, F6 release was found to be increased up to 7, 9, 11 hrs respectively. With combination of HPMC K 15 M and Xanthan gum in formulation F7, F8, F9 release was found to be increased up to 8,10,12 hrs respectively. By sustaining release up to 12 hrs F9 was found to be best

formulation. All formulations showed 'n' value in range of 0.45 -0.89 for Peppas plot indicating that the drug release was by anomalous transport (non-fickian diffusion).

The stability studies carried out for 90 days showed that the optimized formulation (F9) was stable and intact without any interaction. Final optimized formulation (F9) was found to be complying with all the properties of tablets and the formulations were satisfactory.

Disclosure statement

The authors declare no potential conflicts of interest.

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