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Studies on formulation development of gastroretentive drug delivery system for pioglitazone hydrochloride

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ABSTRACT

Pioglitazone HCl is used for the management of type-2 diabetes. It is an absorption window limited drug, whose solubility decreases with increase in the pH and has a short half life of 3-7 h. Here an attempt is made to developed the floating matrix tablets, which design in way that after oral administration the GI resistant time is prolonged and thus to give sustained action with increase in the bioavailability of the drug. Pioglitazone HCl showed maximum absorption at wavelength 269 nm in 0.1N HCl. various formulations were developed by using release rate controlling and gel forming polymers like HPMC, Xanthan gum,guar gum & combinations by direct compression method with the incorporation of sodium bicarbonate as gas generating agent. The prepared tablets were characteristics by drug content, floating property, swelling and *in vitro* dissolution test using USP dissolution test apparatus Type – II (paddle method) in dissolution medium of 0.1 N HCl. The *in vitro* dissolution results of all tablets were computed by using dissolution software. The prepared tablets were found to be good hardness, diameter, weight variation, thickness, friability drug content, floating property and *in vitro* drug release. Drug-polymer compatibility studies by FTIR gave conformation about drug purity and showed no interaction between drug and selected polymers. All the formulations had floating lag time below 4 minutes and constantly floated on dissolution medium for more than 12 h. Swelling studies indicated significant water uptake and contributed in drug release. From among all the developed formulations, as F_2 prolonged the drug release (95.86 %) for longer period of time (12 hrs.); they were selected as best formulations. Thus, selected formulations satisfied floating time, swelling index and *in vitro* drug release profile requirements for a floating drug delivery system.Tablets of Pioglitazone HCl prepared with HPMC K4M, HPMC 15M,HPMC K100M,Xanthan gum,Guar gum and Chitosan were found to be acceptable floating property, water uptake and *in vitro* drug release.

Keywords: Pioglitazone Hydrocholoride, Floating Tablet, Extended Release, Releasing Kinetics

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation[7]. Drugs that are easily absorbed from Gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the Drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the Gastrointestinal tract. Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility and secretions have been identified. In the fasting state, the stomach usually contains saliva, mucus, and cellular debris.

The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC). Liquid components easily pass through the partially constricted sphincter Oral controlled release dosage forms (CRDFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is build with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility.

The gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs.

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include: density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture and gender.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- Reduces frequency of dosing with improved patient compliance.
- Produces prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine.
- This site-specific drug delivery reduces undesirable side effects.
- Minimize the counter activity of the body leading to higher drug efficiency.
- Reduces the fluctuation in drug concentration.
- Enhances the pharmacological effects and improves the chemical outcomes.

DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

These drug delivery systems suffer from mainly two adversities:

- The short gastric retention time (GRT).
- Unpredictable short gastric emptying time (GET) .

APPROACHES TO PROLONG GASTRIC RESIDENCE TIME (GRT)[1]

1. Mucoadhesive Or Bioadhesive Systems

An approach to increase gastric residence time of the dosage forms is to bind them to gastric mucosa or epithelial cell surfaces. The mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems.

The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Vander Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic..

2. Expandable Systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

- A small configuration for oral intake,
- An expanded gastroretentive form,
- Small form enabling evacuation following Drug release from the device

These systems consist of at least one erodible polymer (e.g., Hydroxypropyl cellulose, Eudragit) one nonerodible polymer (e.g., polyolefin's,

polyamides, polyurethanes), and a drug that is dispersed with in the polymer matrix.

The importance of the physical characteristics of this type of systems, such as size, shape and flexibility on the resulting gastric emptying was studied in beagle dogs.[28] Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective.

3. Swelling Systems

One way to retain a dosage form in the stomach is increasing the size. Swelling systems are also referred to as plug type systems. Swellable systems are also retained in the stomach due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefits and to avoid unwanted side effects.

The stomach discharges its content through its pylorus into intestine. If the dosage form can attain size larger than that of the pylorus, it can be retained in the stomach for a long time. Of course, it is not possible to swallow dosage form of such a large size. Thus it should attain a large size once it is in the stomach. This large size should be achieved fairly quickly; otherwise the dosage form will be emptied through the pylorus. In addition this enlarged form should not block the pylorus

4. High-Density Systems

High-density systems are intended to lodge in the rugae of the stomach withstanding the peristaltic movements. Systems with a density of 1.3 g/ml or higher are expected to be retained in the lower part of the stomach. Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture.

The formulation of heavy pellets is based on the assumption that the pellets might be positioned in the lower part of the antrum because of their higher density. Devreux et al reported that the pellets with density of at least 1.5 g/ml have significantly higher gastric residence time both in fasted and fed state. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to1.5- 2.4 g/ml.

5. Superporous Hydrogels

These Swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size ranging between 10nm and 10µm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size >100µm, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores[30]. They swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material.

6. Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

7. Floating Systems:

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability[8].This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine.

After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents.
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder). Stomach Specific FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as ‘hydro dynamically balanced

systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant on the gastric contents with out affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.

Among the different hydrocolloids recommended for floating formulations, cellulose ether polymers are most popular, especially HPMC. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy.

MECHANISM OF FLOATING SYSTEMS

The system is floating on the gastric contents; the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, the apparatus operates by measuring continuously the force equivalent to F that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

F = F buoyancy - F gravity

= (Df - Ds) gv--- (1)

Where, F= total vertical force,

Df = fluid density,

Ds = object density,

v = volume and g = acceleration due to gravity.

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

- Beneficial for drugs absorbed through the stomach.E.g. Ferrous salts, antacids.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid.
- Beneficial for local action in the stomach. E.g. Antacids.
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

2. Site-Specific Drug Delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

3. Absorption Enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

4. Enhanced Bioavailability

The bioavailability of riboflavin CR-FDDS is significantly enhanced in comparison to the administration of non-FDDS CR polymeric formulations. There are several different Processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

MATERIALS AND METHODS

Materials: Pioglitazone HCl was received from Taj pharmaceutical, Hyderabad, HPMC K4M, K15M and K100M which are commercially available grades of hydroxypropyl methylcellulose from SD Fine Chemicals Ltd.,Mumbai, Xanthan Gum from MSN Laboratories, Ltd.India, Guar Gum from S.D. Fine Chem. Ltd, Mumbai, Chitosan from MSN Laboratories, Ltd.India, Magnesium stearate from Ranbaxy pharmaceuticals, Delhi, Sodium bicarbonate and Talc from SD Fine Chemicals Ltd.,Mumbai,Micro Crystalline Cellulose from MSN Laboratories, Ltd.India

Plan of work for different formulations Refer **Table 1**

Methods

Preparation of floating tablets: Pioglitazone hydrochloride and all other ingredients were individually passed through sieve ≠ 60.All the ingredients were mixed thoroughly by triturating up to 15 min.The powder mixture was lubricated with talc.The tablets were prepared by using direct compression method.

PREFORMULATION STUDIES

Bulk Density: It refers to a measurement to describe packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in mg/ml

Procedure:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder in to a measuring cylinder and the initial volume was noted. This initial volume is called bulk volume. The powder was tapped 3 times till a constant volume called bulk density was obtained. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$P_t = m/v_t$

Where m = mass of the blend, v_i = untapped volume

Tapped Density: After determining the poured bulk density, Weighed quantity of API was taken into a graduated cylinder. Volume occupied by DRUG was noted down. Then the cylinder was subjected to 500, 750 & 1250 taps in tap density tester (Electro Lab USP II). According to USP, the blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$P_t = m/v_t$

Tapped bulk density=Mass of powder/Tapped volume of the powder.

Compressibility Index: Weighed API was transferred to 100ml-graduated cylinder and subjected to 500,750&1250 taps in tap density tester (Electro lab). The difference between two taps should be less than 2%. The %of compressibility index calculated using formula

$$\mathbf{CI = v_i - v_t / v_i * 100}$$

Hausner's Ratio: It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is the determined by the ratio of tapped density and bulk density.

$$\mathbf{Hausner's\ ratio = v_i / v_t}$$

Where v_t = Tapped volume , v_i = untapped volume

Angle of repose: Angle that can be obtained between the free surface of a powder heap and horizontal plane. The angle of repose was measured by allowing the powders to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height (about 2 cm). The height of the heap was measured and then circumference of the base of heap was drawn on a graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

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

Where θ= angle of repose , h= height of the heap , r=radius of the base of the heap

Solubility: Freely soluble in water. Soluble in alcohol

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following physicochemical characteristics:

General appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

Hardness test:

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a

spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Friability test: 20 previously weighed tablets were placed in the apparatus. Which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,
Percentage friability = initial weight-final weight /initial weight × 100.

Drug content: 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Pioglitazone Hydrochloride was transferred in to a 100 ml volumetric flask and volume made up with0.1N HCl. Further 1ml of the above solution was diluted to 10 ml with 0.1N HCl and absorbance of the resulting solution was observed at 271 nm.

In vitro Buoyancy studies: The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

RELEASE KINETICS

The analysis of drug release mechanism from a pharmaceutical dosage from is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Korsmeyer-peppa`s-Korsemeyer equation. The results are given in Table 16.

Zero Order Release Kinetics

It defines a linear relationship between the fraction of drug released versus time.

$Q = k_o t$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.
A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics: Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$\ln (1-Q) = - K_1 t$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$Q=K_2 t^{½}$

Where, K2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Power Law: In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Korsmeyer-peppa`s and Korsemeyer equation (Power Law).

$M_t/M_\alpha = K.t^n$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t,k is the kinetic constant and n is the diffusional exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table. A plot between log of M_t/M_α against log of time will be linear if the release obeys Korsmeyer-peppa`s and Korsemeyer equation and the slope of this plot represents "n" value.

EVALUATION OF PREPARED FLOATING TABLETS

The tablets prepared of all formulations were evaluated for quality control parameters, Weight variation, Hardness, Friability, Drug content uniformity, and thickness. All formulations had average tablet weight in the range of 299.26-301.23 mg and thickness was within mean ± 7.5%. The hardness of tablets varied from 4.5-5.5 kp and friability was less than 0.8%, Drug content uniformity of all tablets was in the range of 98.33±1.15-100.63±0.96.

Floating Lag Time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5^{o}C.paddle rotation at 50rpm it is measured using stopwatch.

SWELLING INDEX OF FLOATING TABLETS OF PIOGLITAZONE HCL

Swelling study was performed on optimized batch F_2 for 6 hours. The result of swelling index was shown in the plot of swelling index versus time . It was observed that the swelling of tablets increased up to 4-5 hours after that it gradually decreased because the polymer gradually absorbs water due to its hydrophilicity. The outermost layer of polymer hydrates, swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.Swelling index of pioglitazone HCL floating tablet 91.8%

RESULTS AND DISCUSSION

IN VITRO BUOYANCY STUDIES OF FLOATING TABLETS OF PIOGLITAZONE HCL: All the tablets were prepared by effervescent approach by using sodium bicarbonate as effervescent base. When the floating tablets containing gas generating agent were exposed to 0.1N HCl, hydrochloric acid reacted with sodium bicarbonate in the floating tablet inducing CO_2 formation. The generated gas was entrapped into the matrix of swollen polymer matrix and was well protected by gel formed by hydration of polymers, which led to floating of the dosage forms. The trail batches are evaluated for floating lag time and total floating time. Formulation F_1 containing 20%(60mg) of sodium bicarbonate was floated up to 12hrs .Formulation F_2 containing 20%(60mg) of sodium bicarbonate showed 12hrs floating, formulation F_3 containing 20% (60mg) sodium bicarbonate floated immediately in 240min and floated up to 12hrs.This 4 formulations were conducted by using Xanthan gum &Guar gum. From the trial batches, it was observed that 20% sodium bicarbonate was give good floating lag time, but failed to float for at least 15mins in case of Karaya gum, Carbopal 971p,Carbopal 974p &Carbopal 940. Formulations containing Karaya gum, Carbopal were sank to the bottom swelled and eroded but did not float to the surface. This might be due to less viscosity of the polymer and concentration of the polymer was not sufficient to maintain viscous layer for the entrapment of CO_2.Formulations F_5-F_{11} were conducted using HPMC K4 M, HPMC K15 M, HPMC K100M & formulationsF_{12}-F_{14} were conducted by using Chitosan by keeping 20 %(60mg)concentration of sodium bicarbonate constant. Formulation F_1-F_{14} batches were floated, and remained buoyant for more than 12 hours without disintegration Quality Control Parameters of Pioglitazone HCl floating Tablets Refer **Table 2**

IN VITRO DISSOLUTION TEST:

Dissolution test was carried out using (DBK dissolution test apparatus) rotating basket method (apparatus 1). The stirring rate was 50rpm. 0.1 N hydrochloric acid was used as dissolution medium 900ml and was maintained at 37+-2^{o}C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Pioglitazone Hcl at 222 nm by using a double beam UV spectrophotometer (T60 UV-VISIBLE spectrophotometer). Invitro dissolution studies of all floated formulations of Pioglitazone Hcl were carried out in 0.1 N HCl, by using USP dissolution apparatus Type-II.at 50 rpm. Percentage drug release was calculated at one hour time intervals for 12 hours. Formulation F_1, F_2, F_3 & F_4 containing Drug : Polymer ratio of 1 : 1, 1: 2, 1 : 1&1:2 prepared with sodium bicarbonate,mg stearate,talc, MCC. F1 exhibited 96.81% of drug release within12 hours, formulation F_2 , F_3 &F_4 exhibited 95.86% , 89.65%&76.87% of drug release in 12 hours respectively. Formulation F_5,F_6 was prepared with HPMC K4M in Drug : Polymer ratio of 1:1. F_6 exhibited 69.54% of drug release within 12 hours, Formulation F_7,F_8 was prepared with HPMC K15M in Drug : Polymer ratio of 1:1,1:2. F8 exhibited 74.67% of drug release within 12 hours, Formulation F_9,F_{10} was prepared with HPMC K100M in drug

polymer ratio of 1:1,1:2. F_{11} and F_{12}, containing Drug : Polymer ratio of 1 : 1,1:2 and prepared by using combination of HPMC K4M, HPMC K15M and HPMC K100M ,exhibited74.97 % and 68.75% of drug release in 12 hours respectively. Formulations F_{13},F_{14} were prepared with Chitosan in the ratio of 1:1&1:2, exhibited 42.27%,51.10% of drug release in 12 hours respectively. From the overall dissolution profiles it was observed that as the concentration and of the polymers increased, there is decrease in the drug release rate, where use of less concentration could cause rapid release. From the above results formulations F_2 is found to be satisfactory with dissolution profile results. Hence these formulation was said to be optimized formulations. Invitro dissolution data of pioglitazone hydrochloride floating tablets ($f_1 – f_{14}$) Refer **Table 3.** Dissolution profile of Pioglitazone HCL floating tablets (f1 to f14) Refer **Figure 1,2,3**

RELEASE KINETICS

The results of dissolution data were fitted to various drug release kinetic equations. Regression coefficient (R^2) value was highest for Zero order release equation in formulation F_2. The kinetics of dissolution data with R^2 value obtained from formulation F_1-F_{14} were tabulated in table. Formulation F_2 plots of Zero order, First order, Higuchi and Korsmeyer -peppa`s are depicted. The Zero order drug release graph is plotted time taken on x-axis and the cumulative percentage of drug released on y-axis. The First order drug release graph is plotted between by time taken on x-axis and the log cumulative percentage of drug remaining on y-axis.Higuchi's graph is plotted between the square root of time taken on x-axis and the cumulative percentage of drug released on y-axis. Korsmeyer-Korsmeyer-peppa`s drug release graph is plotted between the log time taken in x-axis and the log cumulative percentage of drug released on y-axis.

Among the various formulations studies, formulations F_2 is considered as ideal formulation which exhibited 95.86% 0f drug release in 12 hours. The R^2 values of Zero order is found to be highest among all other models for these four formulations.

Refer **Table 4** for Coefficient of correlation (r^2) values of different batches of Pioglitazone HCl floating tablets. Refer **Table 5** for Coefficient of correlation (r^2) & Slope values for selective formulations(F_2,F_6,F_8,F_{13}). Refer **Figure 4,5,6,7** for Comparative studies of Zero order,First order, Higuchi's, Korsmeyer-peppa`s kinetics for formulation (F_2,F_6,F_8,F_{13}).

DRUG EXCIPIENT INTERACTION STUDIES FOR OPTIMIZED FORMULATION:

Fourier Transform Infrared spectroscopic studies (FTIR): The FTIR spectra of drug, excipients, drug loaded formulation were recorded. The characteristic peaks of the optimized formulation followed the same trajectory as that of the drug alone with minor differences. Thus there may be no drug-excipient interactions. Refer **Figure 8** for FTIR spectra of Pure Pioglitazone Hcl. Refer **Figure 9** for FTIR spectra of Pioglitazone Hcl, Xanthan Gum. Refer **Figure 10** for FTIR spectra of Optimized formulation

CONCLUSION

This project work was based on formulation and in vitro evaluation of floating matrix tablet for ER of Pilglitazone Hcl. For this purpose Xanthan Gum were incorporated in the formulation and the effect of polymer concentration & viscosity on floating behavior and drug release kinetics was evaluated. F_2 was the most successful batch considering the fact that the R^2 value for zero order plot is highest (0.9924) containing 15% of drug, 30% Xanthan Gum and other excipient. F_2 formulation took 28 sec to become buoyant and float for more than 12 hr, which was sufficient for ER of Pioglitazone Hcl. It has swelling index 91.8%. Above two studies revealed that both are highly dependent on the polymer concentration and viscosity. Anomalous transport were confirmed from these tablets which corresponds to diffusion of water and swelling (polymer arrangement) mechanism or mixed order kinetics have an essential role in drug release. SEM study confirmed that the drug release was mainly due to the erosion of the polymeric matrix with little diffusion through pores initially and in the later part of dissolution study, drug release occurs mainly by diffusion through pore created on the swollen matrix. This result is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the ER release dosage forms.

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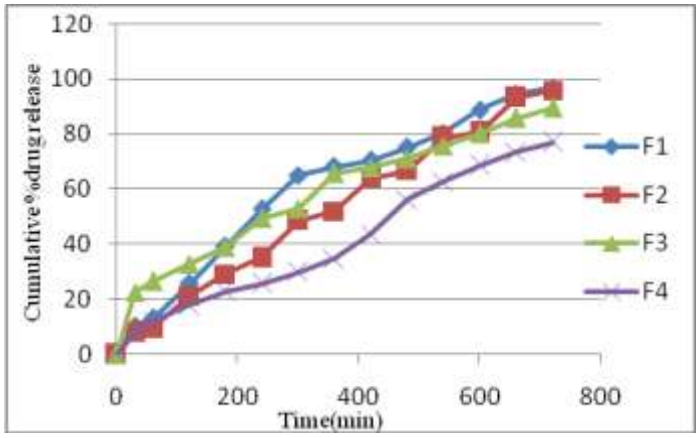

Figure:1 Dissolution profile of Pioglitazone HCL floating tablets (f1 to f4)

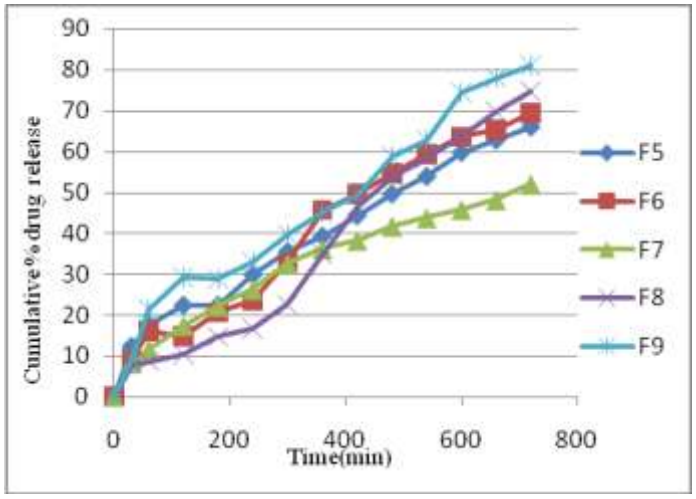

Figure:2 Dissolution profile of Pioglitazone HCL floating tablets (f5 to f9)

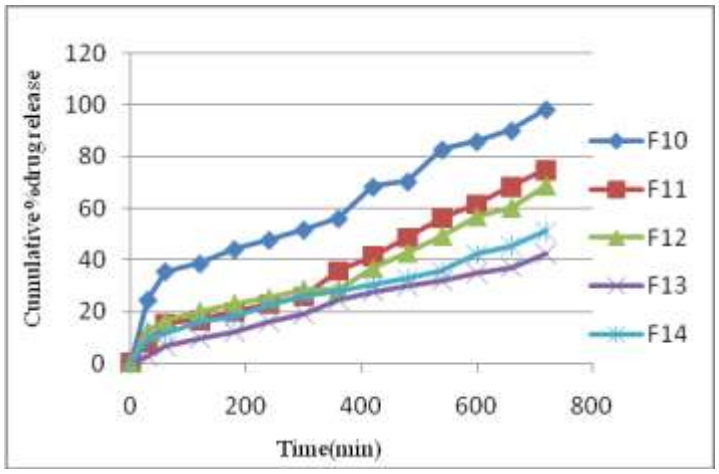

Figure:3 Dissolution profile of Pioglitazone HCL floating tablets (f10 to f14)

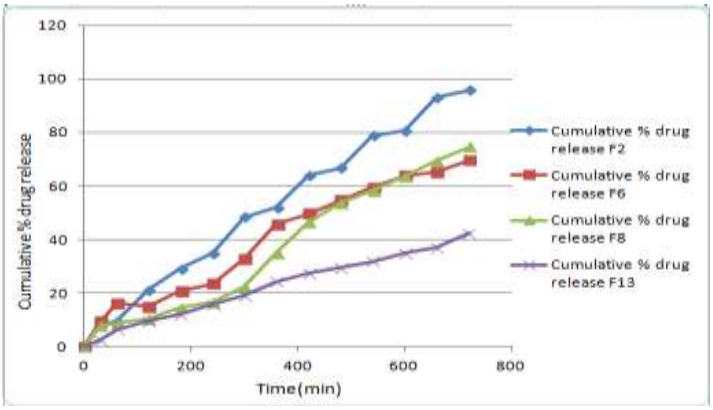

Figure:4 Comparative studies of Zero order kinetics for formulation (F_2,F_6,F_8,F_{13})

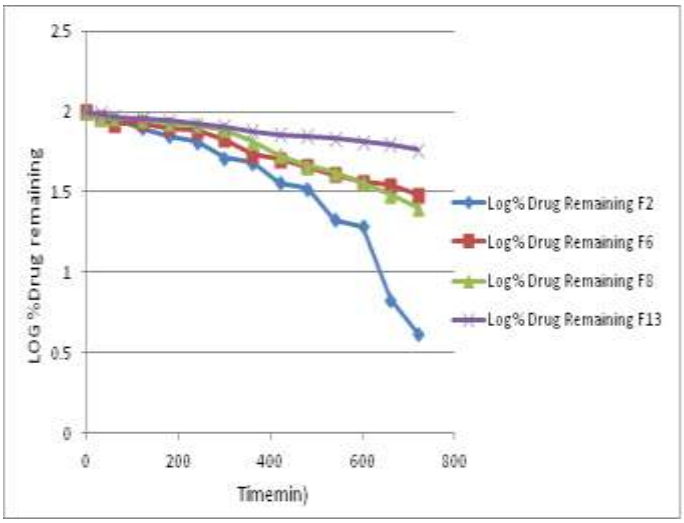

Figure 5. Comparative studies of First order kinetics for formulation (F_2,F_6,F_8,F_{13})

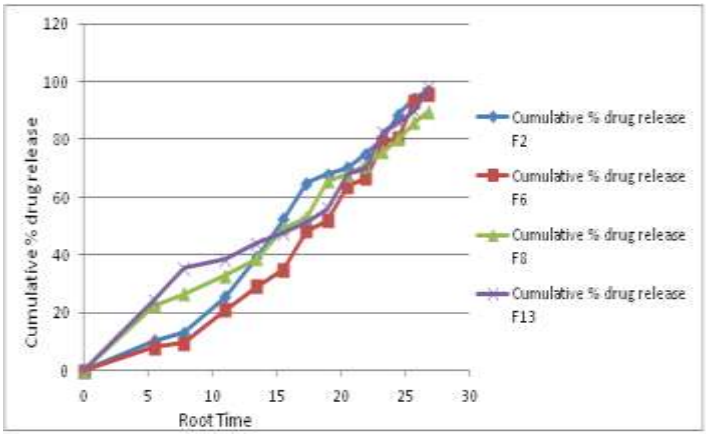

Figure6: Comparative studies of Higuchi's kinetics for formulation (F_2,F_6,F_8,F_{13})

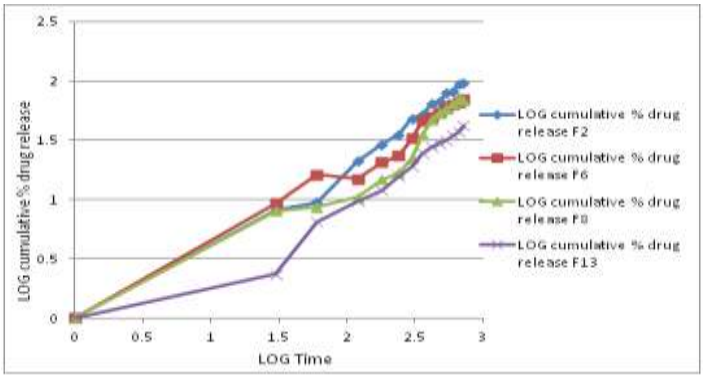

Figure7: Comparative studies of Korsmeyer-peppa`s kinetics for formulation (F_2,F_6,F_8,F_{13})

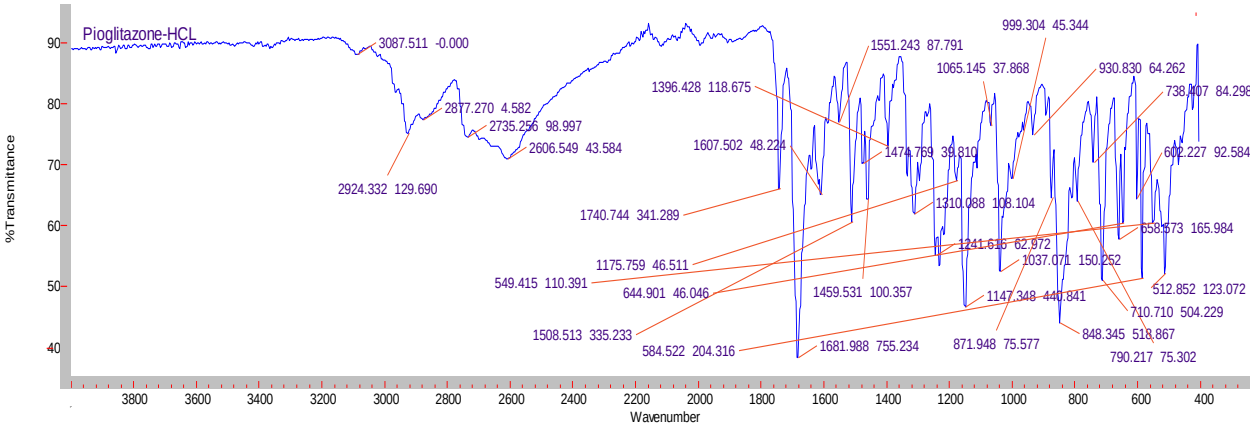

Figure no.8: FTIR spectra of Pure Pioglitazone Hcl

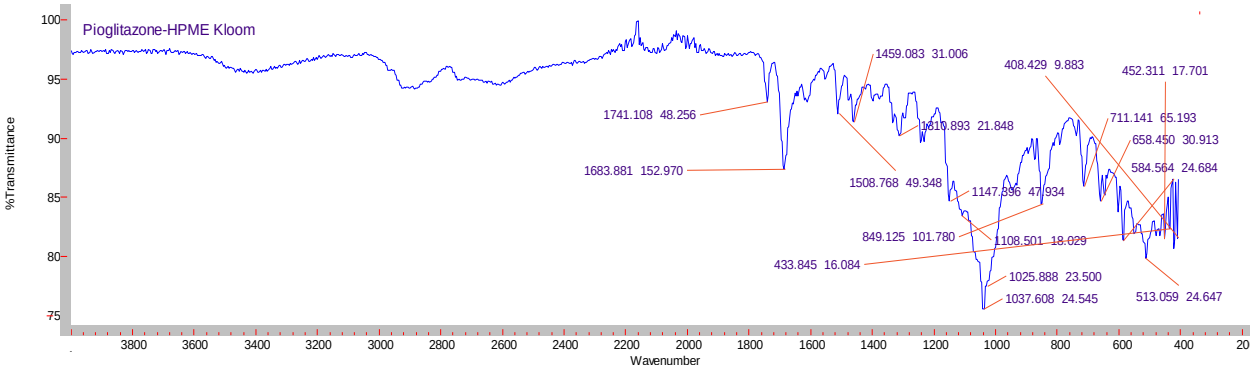

Figure no.9: FTIR spectra of Pioglitazone Hcl, Xanthan Gum

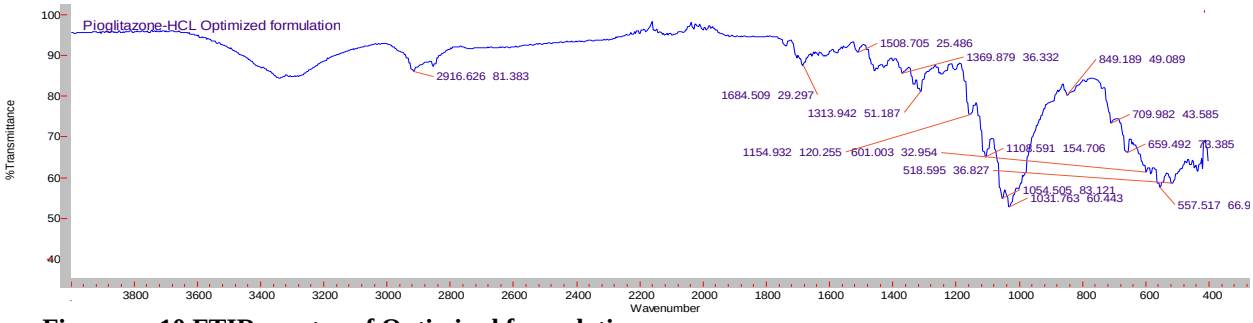

Figure no.10 FTIR spectra of Optimised formulation

Table 1: Plan of work for different formulations

Formulation No.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
PioglitazonHCl (mg)	45	45	45	45	45	45	45	45	45	45	45	45	45	45
Xanthan Gum	45	90	-	-	-	-	-	-	-	-	-	-	-	-
Guar Gum(mg)	-	-	45	90	-	-	-	-	-	-	-	-	-	-
HPMC K4M(mg)	-	-	-	-	45	90	-	-	-	-	45	-	-	-
HPMC K15M(mg)	-	-	-	-	-	-	45	90	-	-	45	45	-	-
HPMC K100M(mg)	-	-	-	-	-	-	-	-	45	90	-	45	-	-
Chitosan(mg)	-	-	-	-	-	-	-	-	-	-	-	-	45	90
$NaHCO_3$ (mg)	60	60	60	60	60	60	60	60	60	60	60	60	60	60
MCC (mg)	142	97	142	97	142	97	97	97	142	97	142	97	142	97
Mag.Stearate(mg)	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc(mg)	4	4	4	4	4	4	4	4	4	4	4	4	4	4
TabletWt.(mg)	300	300	300	300	300	300	300	300	300	300	300	300	300	300

TABLE 2: Quality Control Parameters of Pioglitazone HCl floating Tablets

Formulation No.	Avg. Weight	Friability	Hardness (kg/cm^2)	% Drug content (mg)	Buoyancy Lag time (sec)	Total floating Time(hrs)
F_1	300	0.72	5.0	99.34	180	>12hrs
F_2	300	0.72	5.0	99.87	28	>12hrs
F_3	300	0.70	5.0	98.46	240	>12hrs
F_4	299	0.70	4.5	98.34	120	>12hrs
F_5	299	0.70	4.5	98.76	45	>12hrs
F_6	300	0.72	5.5	99.65	15	>12hrs
F_7	301	0.72	5.5	100.12	25	>12hrs
F_8	300	0.70	4.5	99.01	40	>12hrs
F_9	300	0.72	5.0	99.73	20	>12hrs
F_{10}	300	0.72	5.0	99.84	35	>12hrs
F_{11}	300	0.70	5.0	99.86	35	>12hrs
F_{12}	300	0.72	5.0	99.68	40	>12hrs
F_{13}	301	0.70	5.5	100.23	60	>12hrs
F_{14}	300	0.72	5.5	99.58	90	>12hrs

TABLE 3: INVITRO Dissolution Data of PIOGLITAZONE HydrochloRide FLOATING TABLETS (F_1 – F_{14}) formulations.

TIME(min)	CUMULATIVE percent drug dissolved			
	F_1	F_2	F_3	F_4
0	0	0	0	0
30	10.5	8.09	22.68	7.65
60	13.11	9.51	26.68	11.86
120	25.6	21.14	32.89	17.86
180	39.2	29.1	38.89	22.96
240	52.6	35.1	49.34	25.72
300	65	48.48	53.03	29.87
360	68	52	65.65	34.78
420	70.36	64	67.86	43.65
480	75.05	66.75	71.1	56.23
540	80.48	78.82	75.75	62.78
600	88.76	80.62	80.27	68.67
660	94.34	93.24	85.89	73.54
720	96.81	95.86	89.65	76.87

TIME(min)	CUMULATIVE percent drug dissolved				
	F_5	F_6	F_7	F_8	F_9
0	0	0	0	0	0
30	12.34	9.31	8.13	8	9.44
60	17.72	16.13	11.51	8.62	21.44
120	22.41	14.82	17.37	10.48	29.17
180	22.41	20.68	22.13	14.68	28.75
240	29.86	23.51	26.2	16.75	33.03
300	35.54	32.89	32.55	22.48	39.58
360	39.28	45.76	36.2	34.89	45.1
420	44.27	49.67	38.2	46.56	49.37
480	49.61	54.64	41.72	53.76	58.62
540	53.88	59.48	43.72	58.24	62.68
600	59.73	63.72	45.79	63.76	74.34
660	62.75	65.36	48.13	69.54	77.93
720	65.96	69.54	52	74.67	80.96

TIME(min)	CUMULATIVE percent drug dissolved				
	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
0	0	0	0	0	0
30	24.34	8	12.34	2.34	9.65
60	35.44	15.37	16.2	6.48	11.24
120	38.48	16.68	20.06	9.65	16
180	44	19.72	23.1	12	18.06
240	47.58	22.89	25.17	15.79	22.41
300	51.58	25.86	28.55	19.03	25.79
360	55.93	35.78	28.27	24.34	28
420	68.27	41.45	36.65	27.58	30.27
480	70.27	48.76	42.69	29.72	32.55
540	82.68	56.23	49.28	31.86	35.86
600	85.86	61.76	56.74	34.82	42.34
660	90.06	68.46	60.17	36.96	45.37
720	98.24	74.97	68.75	42.27	51.1

Table4: Coefficient of correlation (r^2) values of different batches of Pioglitazone HCl floating tablets

Formulation	Zero order	First order	Higuchi's	Korsmeyer-peppa`s
F_1	0.9674	0.9818	0.9515	0.9774
F_2	0.9924	0.9749	0.9344	0.986
F_3	0.9296	0.9674	0.9782	0.9505
F_4	0.9703	0.9738	0.9661	0.9908
F_5	0.9327	0.9599	0.975	0.9554
F_6	0.945	0.9277	0.8826	0.8754
F_7	0.9671	0.9845	0.9862	0.9955
F_8	0.9069	0.8633	0.79	0.8191

F_9	0.9001	0.9437	0.9765	0.9315
F_{10}	0.8315	0.9035	0.9513	0.9471
F_{11}	0.9389	0.9391	0.9285	0.9249
F_{12}	0.8667	0.9002	0.9688	0.9732
F_{13}	0.9906	0.9901	0.9386	0.9762
F_{14}	0.9284	0.9528	0.9931	0.9789

Table 5 : **Coefficient of correlation (r^2) & Slope values for selective formulations(F_2,F_6,F_8,F_{13})**

S. No	Name of the Parameter		F_2	F_6	F_8	F_{13}
1	Zero Order	R^2	0.9924	0.945	0.9069	0.9906
		Slope	0.1464	0.1065	0.0926	0.0631
2	First Order	R^2	0.9749	0.9277	0.8633	0.9901
		Slope	-0.001	0.0006	-0.0005	-0.0003
3	Higuchi	R^2	0.94	0.8992	0.8099	0.9496
		Slope	3.1548	2.2951	1.9309	1.3664
4	Korsmeyer-peppa`s	R^2	0.986	0.8754	0.8191	0.9762
		n	0.4252	0.5842	0.6281	0.8622
5	Rate of release K_0 (mg/min)		0.1464	0.1065	0.0926	0.0631

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