INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online atwww.ijpcbs.com

Research Article

FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF ROSIGLITAZONE

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ABSTRACT

The goal in designing floating drug delivery systems (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting the gastric-emptying rate for a prolonged period. The objective of the study is to formulate and evaluate Rosiglitazone floating microspheres by ionotropic gelation method. The Preparation contains nine formulations using different polymers i.e. Xanthan gum and Guargum in different ratios. The prepared batches of Rosiglitazone floating microspheres were evaluated formicromeritic studies like bulk density, tapped density, carr's index (ci), hausner's ratio, angle of repose,and evaluation studies likein vitro buoyancy, swelling index, drug entrapment efficiency and *in-vitro* release studies. All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose the results show that the formulations have very good flow properties. Percentage Drug entrapment efficiency of Rosiglitazone arranged from 56 to 72% for microspheres containing sodium alginate along with guargum as copolymer, 80 to 82% for microspheres containing sodium alginate along with xanthum as copolymer. The formulations F7, F8, and F9 containing Sodium alginate alongwith Xanthumas copolymershowed a maximum release of85.2% at 10^{th} hour, 86.2 % at 12^{th} hour, 71.2% at 12^{th} hour respectively. The satisfactory results were obtained in all prepared formulations and based on the results F8 was the best one when compared to other.

Keywords: FDDS, Drug Entrapment Efficiency, Floating Microspheres.

INTRODUCTION

Floating drug delivery systems (FDDS) or hydro dynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting the gastric-emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release; the residual system is expelled from the stomach. This leads to an increase in the GRT and better control over fluctuations in plasma drug concentration[1].

Floating drug delivery systems either float due to their low density than stomach contents or due to the gaseous phase formed inside the system after they come in contact with the gastric environment. Based on the mechanism of buoyancy, two distinctly different technologies i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS[2].

1. Non-Effervescent FDDS.
2. Effervescent FDDS.

Advantages of FDDS[3, 4]

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.

Disadvantages of FDDS

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

LIMITATIONS [5,6]

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However, this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).
4. The drugs, which are absorbed throughout gastro-intestinal tract, which under go first pass metabolism (nifedipine, propranalol etc.) are not desirable candidate.

Table 1: List of Drugs

S. No.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Griseofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Predmisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	ChlordiazepoxideHCl, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid.
6	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnazirine, Diltiazem, Fluorouracil,

MATERIALS AND METHODS

Rosiglitazone was obtained as a gift sample from Chandra labs Hyderabad, Xanthan Gum, Sodium Alginate, and Guargum from Sd Fine Chemicals Ltd., Mumbai. All other chemicals used were of pharmaceutical grade.

PREPARATION OF FLOATING MICROSPHERES OF ROSIGLITAZONE

Ionotropic gelation method[7]

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as gelispheres. Gelispheres are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionicallycrosslinked moiety. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three dimensional structure.

Polyelectrolyte solution

Drug + polymer solution (water as solvent)
↓$caco_3$
Added drop wise under magnetic stirring by needle
↓
Counter ion solution
[2%Calcium chloride solution w/v] + [2% acetic acid]
↓
Gelispheres

In Ionotropic gelation technique, there has been a growing interest in the use of natural polymers as drug carriers due to their biocompatibility and biodegradability. The natural or semisynthetic polymers i.e. Alginates, Gellan gum, Chitosan, Pectin and Carboxymethyl cellulose are widely use for the encapsulation of drug by this technique Natural polymers used in ionotropic gelation method.These natural polyelectrolytes contain certain anions/cations on their chemical structure, these anions/cations forms meshwork structure by combining with the counter ions and induce gelation by cross linking. In spite of having a property of coating on the drug core these natural polymers also acts as release rate retardant.

FORMULATIONDESIGN

Table 2: Formulation of Rosiglitazone Floating Microspheres

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosiglitazone	1	1	1	1	1	1	1	1	1
Sodium alginate	1	2	3	0.75	1.5	2.25	0.75	1.5	2.25
Guargum	-	-	-	0.25	0.5	0.75	-	-	-
Xanthum	-	-	-	-	-	-	0.25	0.5	0.75
$NaHco_3$	1	2	3	1	2	3	1	2	3
water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

EVALUATIONOFFLOATINGMICROSPHERES[8,9]

Micromeritic Studies

Thepreparedmicrospheresarecharacterizedbytheirmicromeriticproperties, suchasmicrospheresize,tappeddensity,Carr'scompressibilityindex,Hausner's ratio and angle of repose[37].

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

$$\text{Bulk density} = \frac{\text{weight of granules}}{\text{Bulk volume of granules}}$$

Bulk density was expressed in g/cc.

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has

reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\text{Tapped density} = \frac{\text{weight of granules}}{\text{Tapped volume of granules}}$$

Carr's Index (CI)

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{(TD-BD) \times 100}{TD}$$

Where TD = Tapped density
BD = Bulk density

Table 3: Flow properties and corresponding Carr's Index values

Excellent	<10
Good	11 – 15
Fair	16 – 20
Possible	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density / Bulk density

Table 4: Flow Properties and Corresponding Hausner's ratio

Excellent	1.00 – 1.11
Good	1.1 – 1.18
Fair	1.19 – 1.25
Possible	1.26 -1.34
Very poor	1.35 -1.45
Very very poor	>1.60

Angle of repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal[4,5].

$$\mathbf{Tan\theta = h/r}$$

Where, h= height of the heap
r= Radius of the heap

Table5: Flow Properties and Corresponding Angle of Repose

ANGLE OF REPOSE	POWDER FLOW
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

STANDARD GRAPH OF ROSIGLITAZONE

Determination of λ max of Rosiglitazone

Standard Stock solution: 100 mg of Rosiglitazonewas dissolved in 100 ml 0.1N HCL to give a concentration of (1000 µg/ml)

Scanning: From the stock solution 10µg/ml was prepared in water and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 248.5 nm and was used for the further analytical studies.

Calibration curve of Rosiglitazone in 0.1N HCl

The standard solutionswerepreparedbyproper dilutionsoftheprimarystocksolutionwithabsolutewater to obtain working standards in the concentrationrangeof 5-25µg/ml of puresampleofRosiglitazone.TheconcentrationofRosiglitazone presentin the microspheres was obtained from the calibrationcurve.

EVALUATION OF MICROSPHERES[10, 11, 12]

In vitro Buoyancy studies

The in vitro buoyancy was determined by floating lag time, and total floating time. The microspheres were placed in a 100ml beaker containing 0.1N HCl. The time required for the microspheres to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the microspheres constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).

$$\%Buoyancy = Q_f / (Q_f + Q_s) X100$$

Where Q_f and Q_s are the weight of the floating and settled microspheres respectively.

Swelling Index Studies

The swelling behavior of a dosage unit wasmeasured by studying its weight gain. The swelling indexof microspheres was determined by placing the microspheres in thebasket of dissolution apparatus using dissolution mediumas 0.1N HCl at 37±0.5°C. After 0.5, 1, 2, 3, 4, 5, and 6h, each dissolution basket containing microspheres waswithdrawn, blotted with tissue paper to remove theexcess water and weighed on the analytical balance(Schimdzu, AX 120). The experiment was performedin triplicate for each time point[13]. Swelling index wascalculated by using the following formula

$$\text{Swelling index} = \frac{\text{(Wet weight of microspheres – Dry weight of microspheres)}}{\text{Dry weight of microspheres.}}$$

Drug Entrapment Efficiency

Microspheresequivalentto8mgofthedrugweretakenforevaluation.Theamountofdrugentrappedwasestimatedb ycrushingthemicrospheresandextracting withaliquotsof0.1NHCl(pH-1.2)repeatedly. Theextract wastransferredtoa100ml volumetricflaskandthevolumewasmadeupusing0.1NHCl(pH-1.2).Thesolution wasfilteredandtheabsorbancewasmeasuredaftersuitabledilution spectrophotometrically(UV1700,Shimadzu,Japan)at248.5nmagainstappropriate blank[14]. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Determination of percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula[15].

$$\text{Percentage yield} = \frac{\text{Practical yield (mg)}}{\text{Theoretical yield}} \times 100$$

***In-vitro*ReleaseStudy**

Thedrugreleasestudywasperformedformicrospherecontainingquantity equivalentto8mgofrosiglitazonebyusingUSPdissolutionapparatusTypeIin900ml of0.1NHCldissolutionmedia(pH-1.2)at100rpmand37^{0}Ctemperature.10mlof samplewaswithdrawnatpredeterminedtimeintervalfor12hoursandsamevolume offreshmediumwasreplacedtomaintainedsinkcondition.Withdrawnsampleswere assayedspectrophotometricallyat248.5nm.Drugreleasewasalsoperformedforpuredrug[16]. Thecumulative%drugreleasewascalculatedusingstandardcalibration curve.

Details of dissolution testing:

- Apparatus: ElectrolabUSP TDT 08L
- Dissolution media:0.1 NHCl(pH-1.2)
- Speed: 50 rpm
- Volume of medium: 900 ml
- Aliquots taken at each time interval: 5ml
- Temperature: 37±0.5°C
- Wavelength: 248.5 nm.

RESULTS AND DISCUSSION

Table 6:Calibration curve data for Rosiglitazone in simulated gastric fluidpH 1.2

CONCENTRATION (µg / ml)	ABSORBANCE
0	0
5	0.061
10	0.121
15	0.20
20	0.249
25	0.310
30	0.390

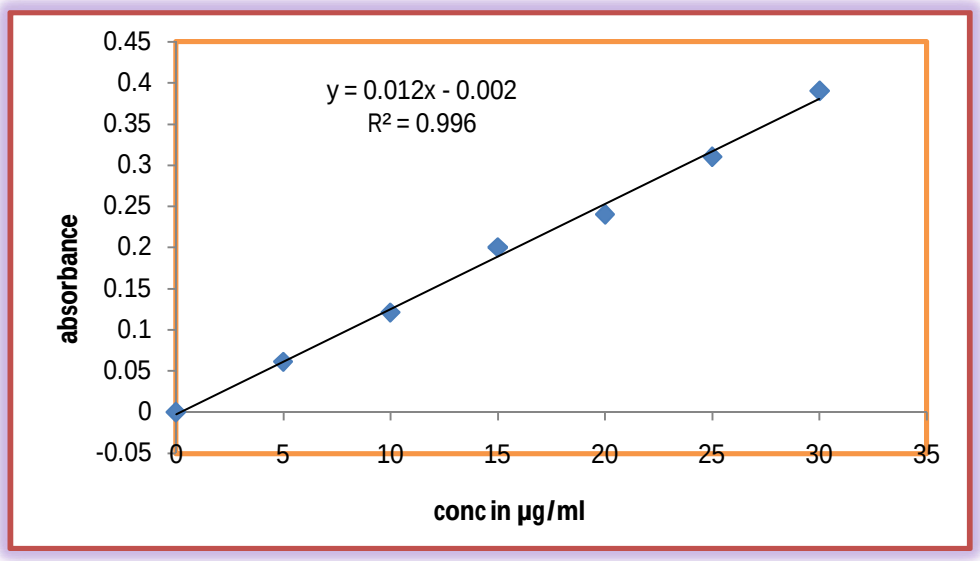

Fig.1: Standard graph of Rosiglitazone in simulated gastric fluidpH 1.2

Table 7:Preformulation Parameters

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)
F1	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06± 0.31
F2	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58± 0.15
F3	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44± 0.11
F4	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36± 0.13
F5	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	28.52± 0.19
F6	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	29.32± 0.19
F7	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09	29.69± 0.19
F8	0.45±0.041	0.52 ± 0.10	15.60±0.21	1.15±0.04	28.06± 0.41
F9	0.44±0.041	0.52± 0.11	15.48±0.54	1.18±0.12	28.52± 0.15

Table 8: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% Yield	Drug Content	% Buoyancy	% Drug entrapment efficiency	%Swelling Index
1	F1	80	79.40	63	62	33.32
2	F2	83	78.66	67	72	35.66
3	F3	85	78.70	75	79	30.91
4	F4	86	79.5	79	56	32.33
5	F5	82	75.07	85	67	35.11
6	F6	80	72.25	89	72	38.18
7	F7	88	75.29	70	80	36.55
8	F8	87	83.5	76	82	37.32
9	F9	80	83.01	84	82	35.66

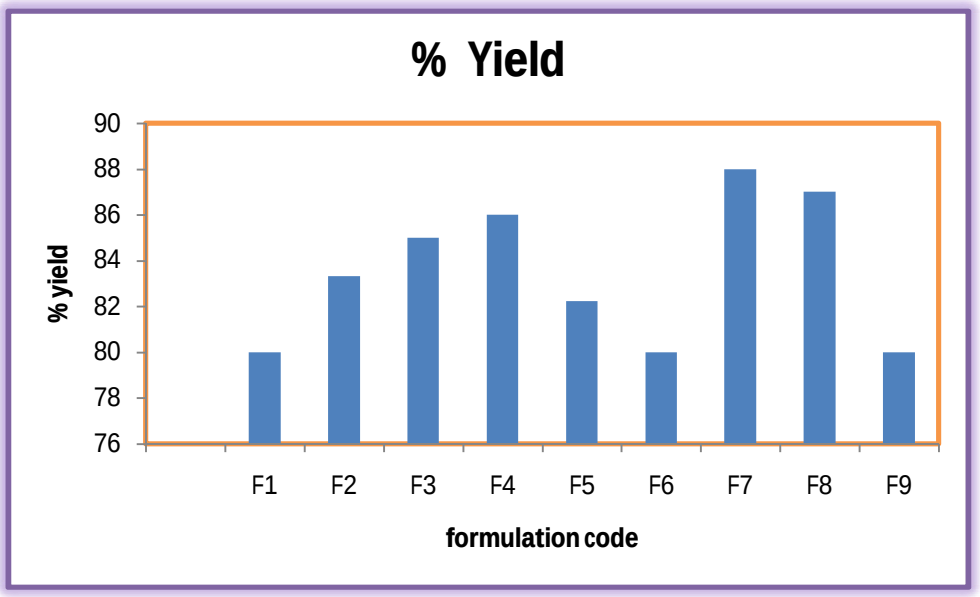

Fig. 2:Graph for % yield vs Formulation code

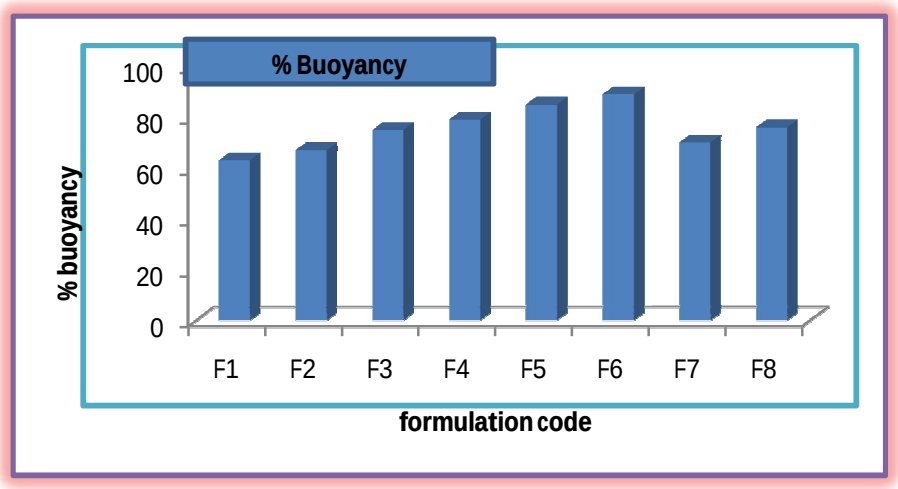

Fig. 3:Graph for % Buoyancy vs Formulation code

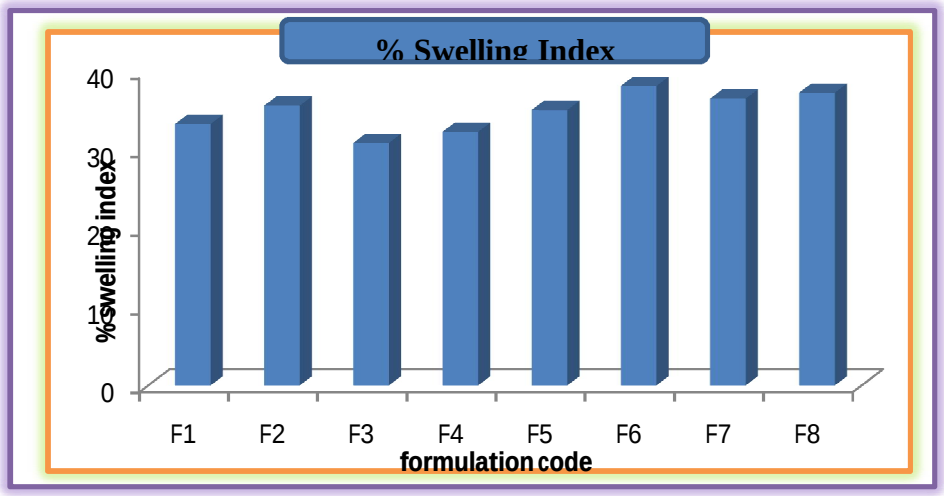

Fig. 4:Graph for % swelling index vs Formulation code

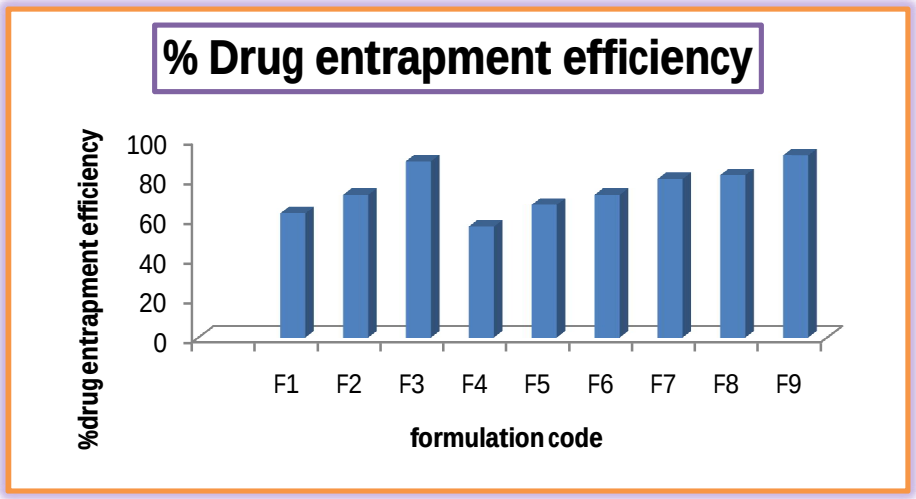

Fig. 5: graph for % drug entrapment efficiency vs Formulation code

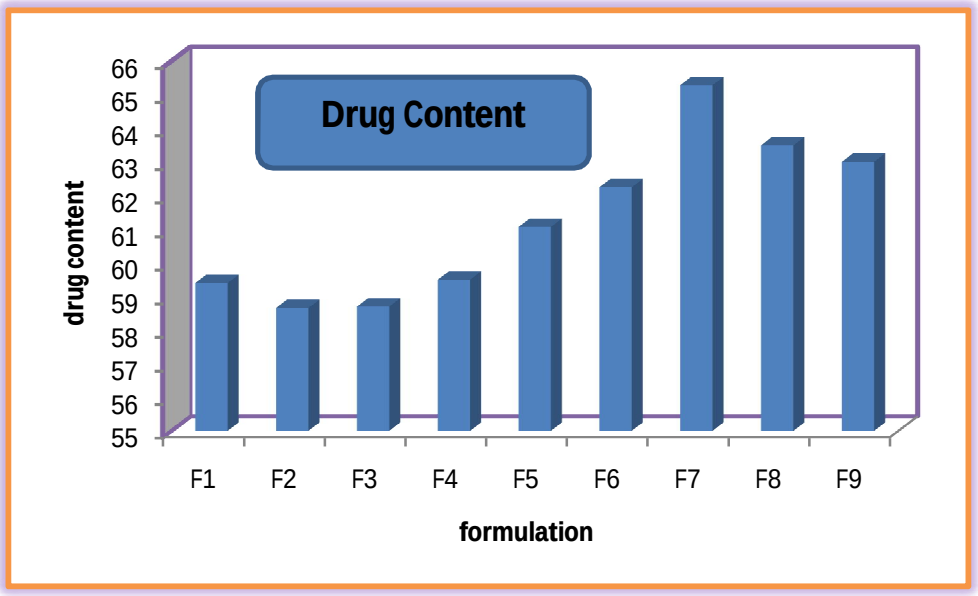

Fig. 6: graph for % drug content vs Formulation code

Table 14:Percentage cumulative drug release for all formulations

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	23	18	16	28.4	23	14	25.3	**16.25**	11.30
2	32	27.2	24	40.3	38	20	37.2	**21.3**	19.6
3	41.5	36	31	49.7	45	26	44.3	**28.6**	25.4
4	57.6	45	42	55.3	50	28	52.4	**30.4**	28.2
5	68.2	53	49	62.4	54	38	57.8	**38.2**	36.3
6	79.7	67	54	68.3	63	42	65.2	**44.3**	40.4
7	86.4	72	58.7	76.9	69	48	70.8	**51.6**	46.8
8	-	84	70.4	83.2	78	54	79.2	**57.2**	59.3
10	-	-	-	86.9	83	63	85.2	**78.3**	62.4
12	-	-	-	-	-	76	-	**86.2**	71.2

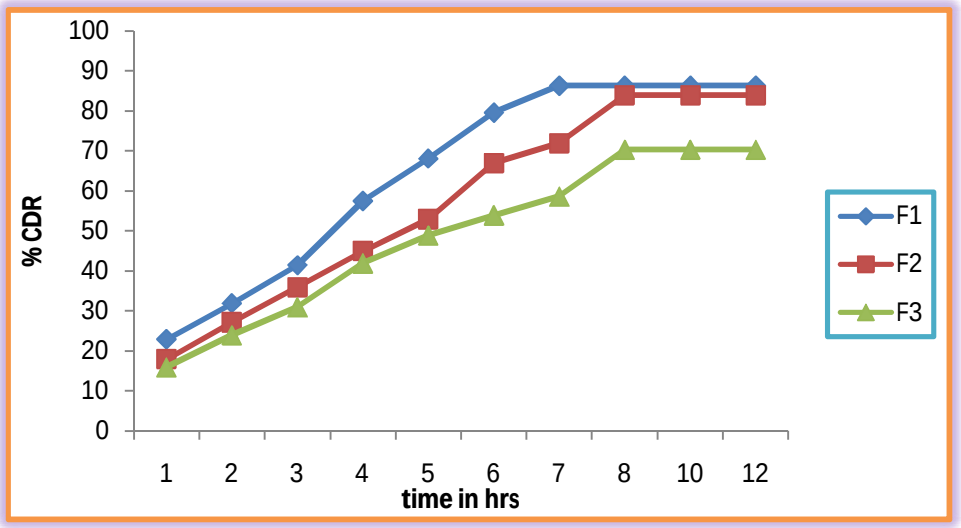

Fig. 7: Dissolution graph for formulation F1-F3 (Drug: Sodium alginate)

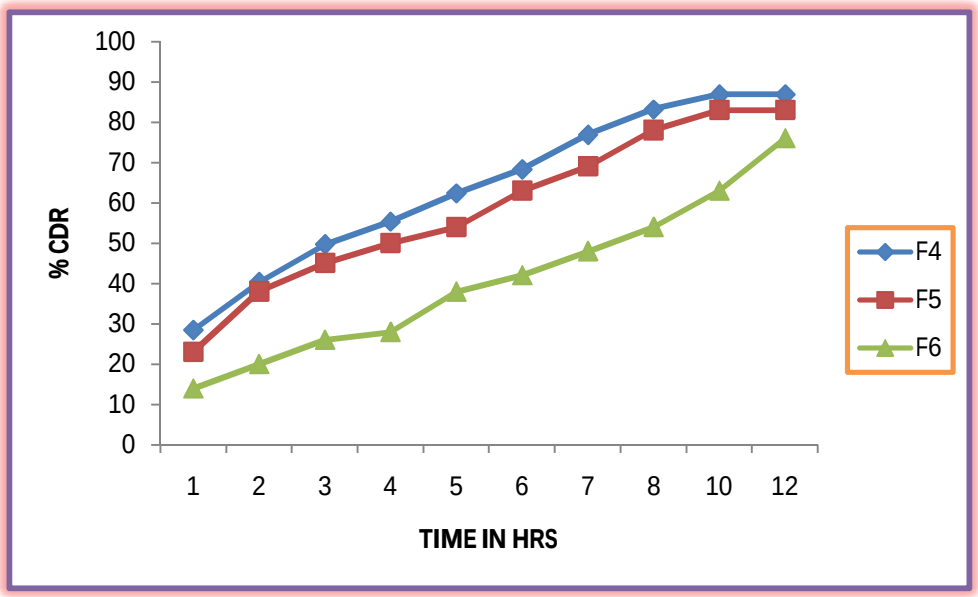

Fig. 8: Dissolution graph for formulation F4 –F6 (Drug: Sodium alginate + Guargum)

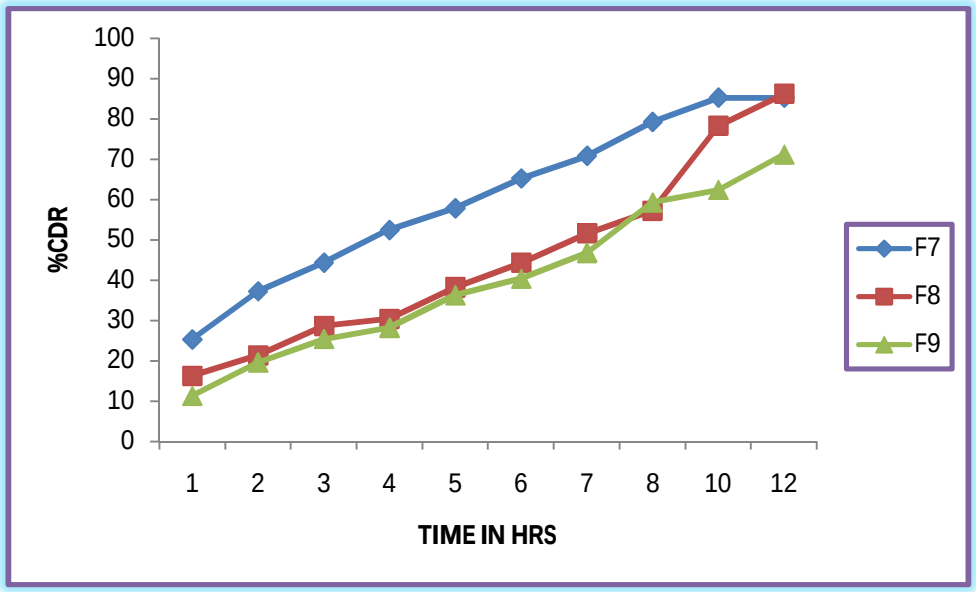

Fig. 9: Dissolution graph for formulation F7 –F9 (Drug: Sodium alginate + Xanthum

DISCUSSION

PREFORMULATION PARAMETERS

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have very good flow properties.

PERCENTAGE YIELD

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle andwastage of the drug-polymer solution, adhesion ofpolymer solution tothe magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of80 to 86% for microspheres containing sodium alginate along with Guargum as copolymer, 80 to 88% for microspheres containing sodium alginate along with Xanthum as copolymer.

DRUG ENTRAPMENT EFFICIENCY

Percentage Drug entrapment efficiency of Rosiglitazonearanged from 56 to 72% for microspheres containing sodium alginate along with guargum as copolymer, 80 to 82% for microspheres containing sodium alginate along with xanthum as copolymer and . The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency.

***IN-VITRO* DRUG RELEASE STUDIES**

Dissolution studies of all the formulations were carriedout using dissolutionapparatusUSPtype I. The dissolution studies were conducted by using dissolution media, pH 1.2.The results of the in-vitro dissolution studiesof formulations are shown in table.

The formulations F_4, F_5, F_6 containing Sodium alginate alongwith Guargumas copolymer showed a maximum release of 86.9% at 10th hour, 83% at 10th hour, 76% at 12th hour respectively.

The formulations F7, F8, and F9 containing Sodium alginate alongwith Xanthumas copolymershowed a maximum release of85.2% at 10th hour, 86.2 % at 12th hour, 71.2% at 12th hour respectively.

Thisshowsthat more sustained release was observed withthe increase in percentage of polymers.As the polymer to drug ratio was increased the extent of drug releasedecreased.A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion pathlength which the drug molecules have to traverse. The release of the drug has beencontrolled byswellingcontrol release mechanism. Additionally, the larger particlesizeathigher polymerconcentration also restricted the total surface area resulting inslower release.

SUMMARY AND CONCLUSION

The objective of the study is to formulate and evaluate Rosiglitazone floating microspheres by ionotropic gelation method. The Preparation contains nine formulations using different polymers i.e. Xanthan gum and Guargum in different ratios. The prepared batches of Rosiglitazone floating microspheres were evaluated formicromeritic studies like bulk density, tapped density, carr's index (ci), hausner's ratio, angle of repose,and evaluation studies likein vitro buoyancy, swelling index, drug entrapment efficiency and *in-vitro*releasestudies.

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The satisfactory results were obtained in all prepared formulations and based on the results F8 (Sodium alginate+ Xanthum gum)was the best one when compared to other.

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