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Design, Development and In-Vitro Characterisation of Gelucire Based Floating Beads of Cefixime Trihydrate.

Rinkle Jasuja

Department of Pharmaceutics, Sachdeva college of Pharmacy, Mohali 140401, Punjab

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ABSTRACT

The aim of formulating Cefixime Trihydrate floating beads was to have the sustained release antibiotic which will not only increase patient compliance but also will be helpful for the individual's who cannot take the dose on regular intervals. Cefixime Trihydrate is a thrid generation cephalosporin antibiotic with a high curative effect on many diseases. For this purpose , calcium ions were used as a binder to prepare alginate and alginate gelucire beads by ionotropic gelation method, method was tested by three different grades of Gelucire to know the different properties. Beads were subjected to In-Vitro drug release in 0.1 N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) for remaining hours. In-vitro drug release data were fitting to Higuchi and peppas equation. Next, the properties of the beads, drug penetration into the bead and drug release kinetics were investigated. The results showed that due to the increased concentration of alginate in the formulation, The spherical shape of beads was maintained, resulting in a sustained release. The excess amount of Sodium Alginate and Calcium Chloride was making the beads in irregular shape.

Keywords: **Cefixime Trihydrate, Beads, Gelucire**

INTRODUCTION

Over the past few decades, Oral controlled release (CR) dosage forms have gain utmost importance due to its high therapeutic advantages such as ease of administration, patient compliance and simple method of formulation.

However, along with these aided advantages, several physiological difficulties have been witnessed such as restricting its locating ability to provide the controlled drug delivery within the desired region of gastrointestinal tract (GIT) due to variable gastric difficulties in drug release. Gelucire having low HLB value can be used to reduce the dissolution rate of drugs on the other hand, Gelucire with high HLB value can be used for faster release of drugs. .

In the designation of its name, for example, Gelucire 54/02, 54 indicates melting point while 02 indicates its HLB value. The lipidic materials such as Gelucire are considered as an alternative to other polymers employed in sustained release formulations. Gelucires are mixtures of glyceride-based materials and esters of polyethylene glycol (PEG) which can be used in to manufacture controlled release drug dosage forms.

The nature and ratio of these components can control the hydrophobicity and drug release properties in the drug dosage forms. The major objectives of the study are to improve the solubility and to develop Gelucires based floating bead of Cefixime Trihydrate in terms of increasing the gastric retention time. Apart from that, the formulations also modulate or control the drug release for a sustained action.

Consequently, considering the above objectives, to prepare and to evaluate the floating bead drug delivery system of Cefixime Trihydrate by melt granulation technique.

Methods And Materials

Cefixime trihydrate was a gift from Unnati Pvt. Ltd, different grades of Gelucires was taken from Gattefosse.

Sodium Alginate and Methanol was taken from Fisher Scientific India Pvt. Ltd. Calcium Carbonate and Calcium Chloride was taken from Thomas Baker. Hcl and n-octanol was from SD FINE- Chem ltd, Mumbai.

PREFORMULATION STUDIES

Organoleptic Studies

Table:1 Organoleptic properties

Sr. No.	Properties	Inferences
1.	Colour	Off white to Pale yellow
2.	Odour	Odourless
3.	Form	Crystalline
4.	Taste	Bitter

Melting Point

Melting point of Cefixime Trihydrate was determined by capillary tube method and was found to be quite similar to the reported melting point as shown in table 2

Table: 2 Melting point of cefixime trihydrate

Drug	Reference M.P.	Observed M.P.
Cefixime	218-225°C	220±0.015^{0}C

Uv-spectroscopy

A double beam UV-visible spectrophotometer was used for quantitative analysis of the drug. A 30 µg/ml solution of Cefixime Trihydrate in methanol was scanned in the range of 200-400 nm. The result of UV spectrum of Cefixime is shown in Figure 1

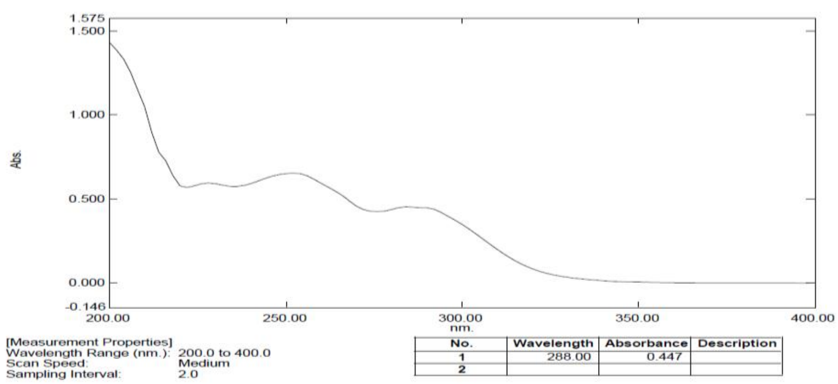

Fig: 1 Uv spectra of Cefiixme trihydarte

Table: 3 Absorption maxima (λ_{max}) of Cefixime in Methanol.

Name of drug	Absorption maxima (λ_{max})	
	Observed	Reference
Cefixime Trihydare	288	290

Preparation of standard curve of Cefixime in methanol

Table :4 Calibration curve of Cefixime in methanol (λ_{max} = 290 nm)

Sr. No.	Concentration (µg/ml)	Absorbance
01.	2	0.235±0.002
02.	4	0.349±0.001
03.	6	0.469±0.002
04.	8	0.589±0.003
05.	10	0.719±0.001
06.	12	0.849±0.002
07.	14	0.976±0.001

Value is expressed as mean ± SD; n = 3

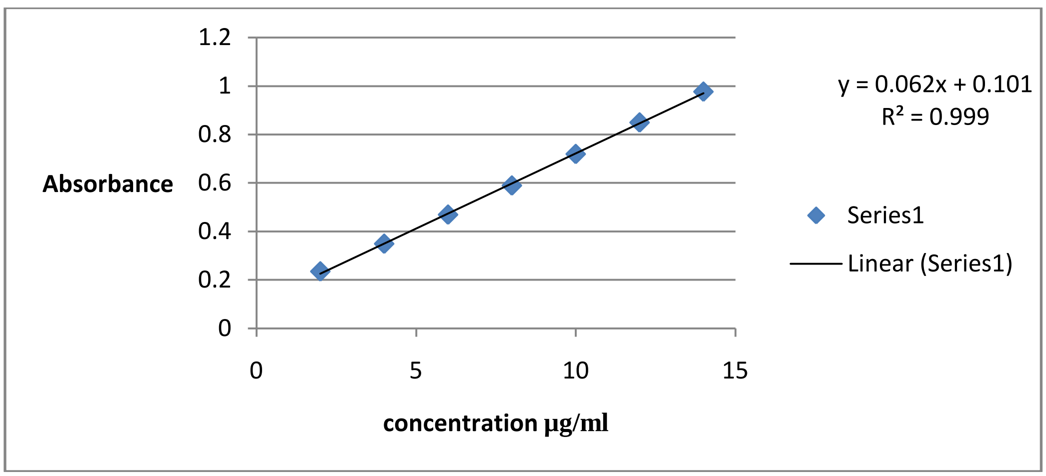

Figure:2 Graph of standard calibration curve of Cefixime Trihydrate in methanol

Table:5 Result of regression analysis of UV method

Statistical parameters	Results
λ max	290 nm
Regression equation (y = mx + c)	y = 0.062x + 0.1019
Slope (b)	0.062
Intercept (C)	0.1019
Correlation coefficient (r^2)	0.9994

Discussion- The calibration curve for Cefixime Trihydrate was obtained by using the 2 to 14 µg/ml concentration of Cefixime Trihydrate in methanol. The absorbance was measured at 290 nm. The calibration curve of Cefixime Trihydrate as shows in graph indicated the regression equation Y=0.062x-0.1019 and R2 value 0.9994, which shows good linearity as shown in fig 2 and table 5

Solubility studies

Solubility of drug in various solvents, were carried out in order to screen for the components to be used for formulation development. Analysis of the drug was carried out on UV Spectrophotometer at 242 nm.

Table: 6 Solubility studies of Cefixime Trihydrate for different solvents

Solvent	Solubility in (mg/ml)	S.D	Solubility as per IP
0.1NHCl	1.611	0.019	Slightly soluble
Water	0.039	0.034	Practically insoluble
DCM	0.007	0.003	Practically insoluble
Ethanol	15.556	1.925	Sparingly soluble
Methanol	117.330	0.169	Freely soluble

Value is expressed as mean ± SD; n = 3

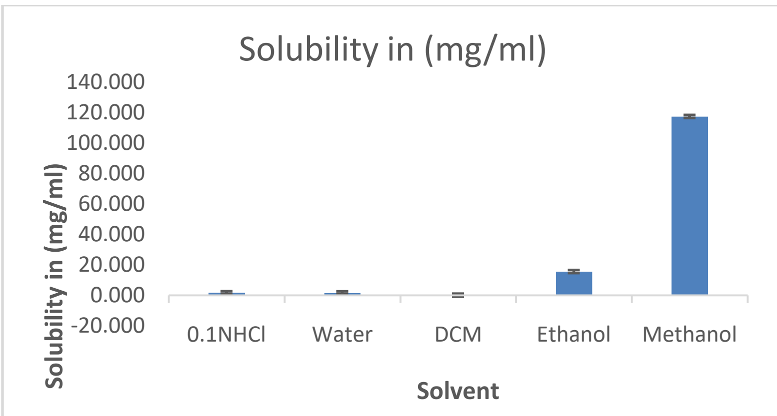

Figure:3 Solubility study of drug in different solvents

Discussion- From the above data, it is clearly seen that Cefixime Trihydrate is highly soluble in Methanol, ethanol, followed by water.

Partition coefficient determination

Partition coefficient of the Cefixime Trihydrate was determined using n-octanol and water. Log P greater than one indicates that the drug is lipophilic in nature, whereas those with partition coefficients less than one are indicative of a hydrophilic drug. This indicated the lipophilicity and purity of drug.

Table: 7 Partition coefficient determination of Cefixime Trihydrate

Partition coefficient of drug	Solvent system	Log P Values	Reference
Cefixime	n-octanol: water	0.002 ± 0.001	-0.4

Value is expressed as mean ± SD; n = 3

Discussion: The partition coefficient of Cefixime in n-octanol: water was found to be 0.002 ± 0.001, this indicates that the drug is hydrophilic in nature which is similar to the literature.

FTIR Studies

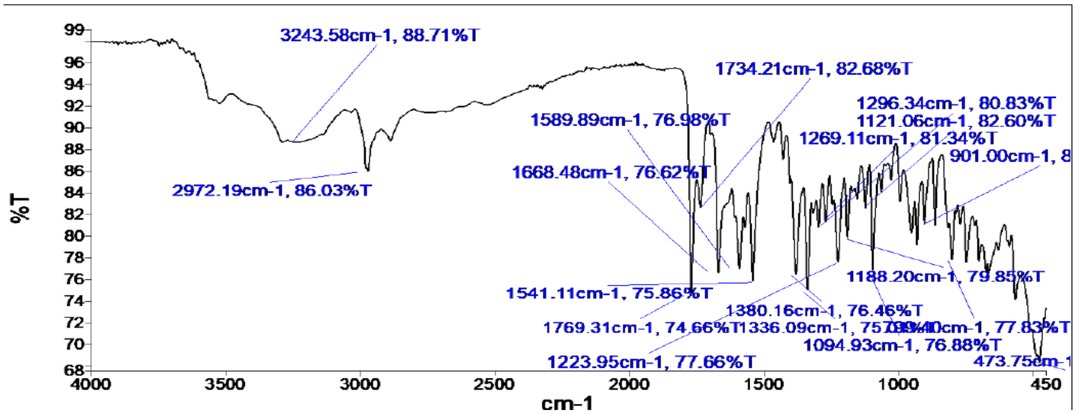

Figure: 4 FTIR spectrum of Cefixime Trihydrate

Table: 8 FTIR interpretation of Cefixime

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C-H stretch	2942.02	2972.19
C O stretch CONH	1669.09	1668.48
C N stretching, aromatic	1337.88	1380.16
C O, stretch, COOH	1771.79	1769.31
C C, stretch	1542.09	1541.11

Discussion: The FTIR spectra of Cefixime were shown in the Figure 4; Table 8. The principal IR absorption peaks of Cefixime at 2972.19cm^{-1} (C-H stretch), 1668.48 cm^{-1} (C O stretch CONH), 1380.16 cm^{-1} (C N stretching, aromatic), 1769.31 cm^{-1} (C O, stretch, COOH), 1541.11 cm^{-1} (C C, stretch), were all observed in the spectra of Cefixime. These observed principal peaks. This observation confirmed the purity and authenticity of the Cefixime trihydrate.

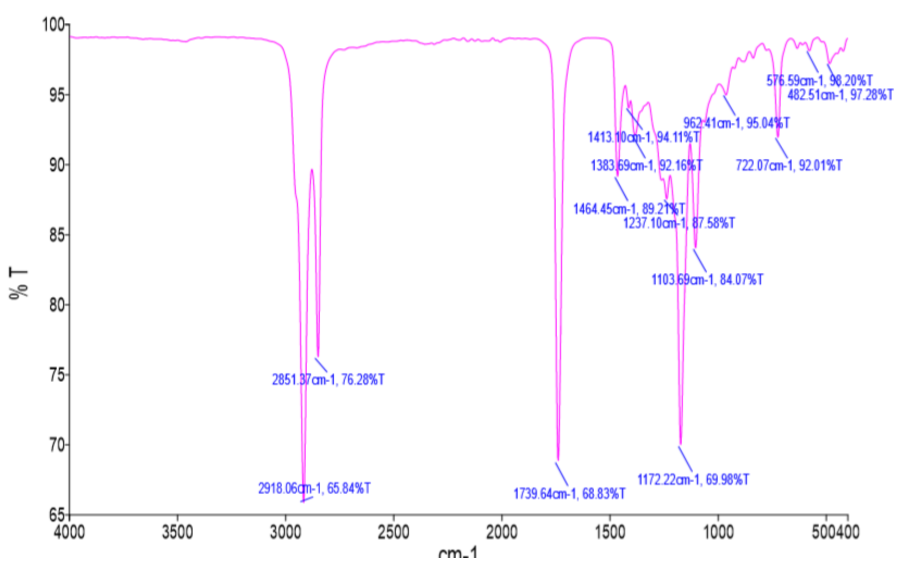

Figure: 5 FTIR Spectrum of Gelucire 43/01

Table:9 Interpretation of FTIR spectrum of Gelucire 43/01

Reported peak (cm^{-1})	Observed peak (cm^{-1})	Functional group
1741	1739.64	C=O stretching of the ester group
1172	1172.22	C–O stretch of alcohols primary
1100	1103.69	C–O stretch of alcohols secondary

Discussion: The FTIR spectra of Gelucire 43/01 were shown in the figure 5; table 9. The principal IR absorption peaks of gelucire 43/01 were observed at 1739.64 cm^{-1} (C=O stretching of the ester group), 1172.22 cm^{-1} (C–O stretch of alcohols primary), 1103.69 cm^{-1} (C–O stretch of alcohols secondary). These observed principal confirmed the purity and authenticity of the Gelucire 43/01.

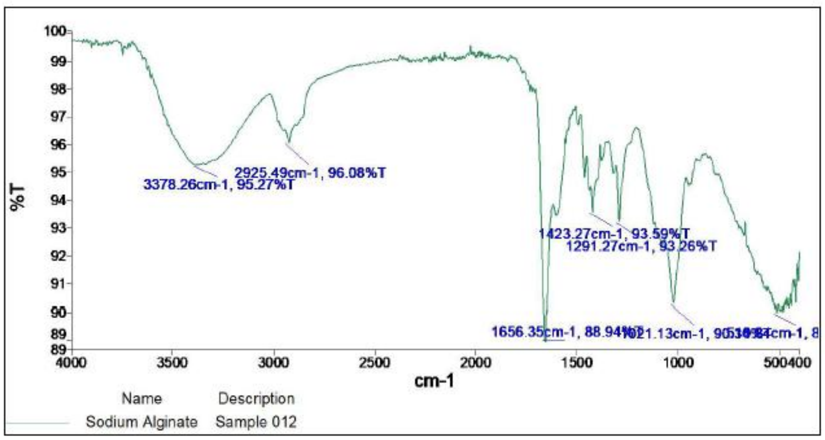

Figure: 6 FTIR Spectrum of Sodium alginate

Table: 10 Interpretation of FTIR spectrum of sodium alginate

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
O-H stretching	3550-3200	3378.26
C-H stretch	3000-2840	2925.49
O-H bending, carboxylic acid	1440-1395	1423
Carboxylate salt	1649	1656.35

Discussion: The FTIR spectra of Sodium Alginate were shown in the Figure 6 Table 10 The principal IR absorption peaks of Sodium Alginate at 3378.26 cm^{-1} (O-H stretch), 2925.49 cm^{-1} (C-H), 1423 cm^{-1} (O-H bending, carboxylic acid), 1656.35 cm^{-1} (Carboxylate salt), were all observed in the spectra of Sodium Alginate. These observed principal peaks. This observation confirmed the purity and authenticity of the Sodium alginate.

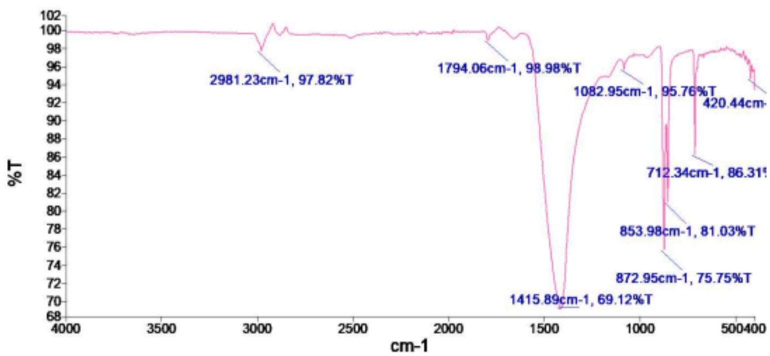

Figure: 7 FTIR Spectrum of Calcium Carbonate

Table: 11 Interpretation of FTIR spectrum of Calcium Carbonate

Peak no.	**X cm^{-1}**	**Y (%T)**
1.	2981.23	97.82
2.	1794.06	98.98
3.	1415.89	69.12
4.	1082.95	95.76
5.	872.95	75.75
6.	853.98	81.03
7.	712.34	86.31
8.	420.44	94.73

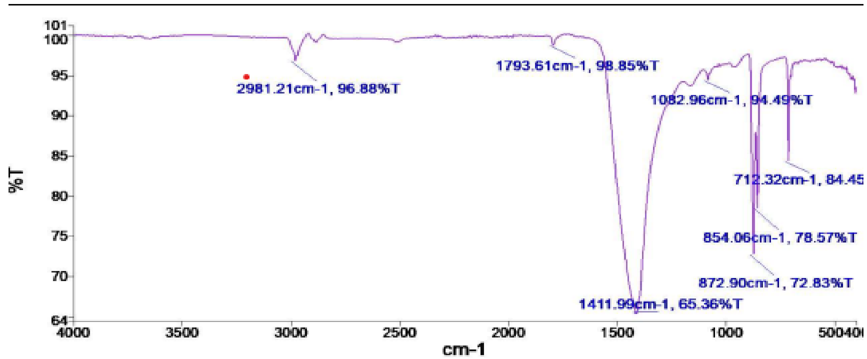

Figure: 8 FTIR Spectrum of Physical mixture

Table : 12 Interpretation of FTIR spectrum of Physical mixture

Peak no.	**X cm^{-1}**	**(%T)**
1	2981.21	96.88
2	1793.61	98.85
3	1411.99	65.36
4	1082.96	94.49
5	872.90	72.83
6	854.06	78.57
7	712.32	84.45

Discussion: FTIR of Pure drug and physical mixture studies were carried out to eliminate the possibility of interaction between drug and excipients used with analytical method of drug estimation. All the spectrum peaks revealed that corresponding peaks of drugs are present in the above spectra along with excipients peaks. Hence no interaction was observed in this mixture.

PREPARATION OF CEFIXIME TRIHYDRATE FLOATING BEADS

Method used- Ionotropic Gelation Method

Preparation of Sodium Alginate mixture- A given amount of sodium alginate was dissolved in distilled water and heated till a mixture was formed. Preparation of Sodium alginate-Gelucire Mixture- Lipid (Gelucire 43/01/ Gelucire 48/13) was melted at 60°C. It was then mixed with prepared Sodium Alginate solution on magnetic stirrer at 100rpm for 15 mins.

Preparation of Drug mixture: The finely powdered drug was mixed with calcium carbonate solution. The entire solution was gradually mixed on magnetic stirrer at 100rpm at temperature 60°C. Formation of Floating Beads- The resultant dispersion was dropped via a 23-guage syringe needle (0.65 mm internal diameter) into 100 ml of calcium chloride solution made with acetic acid at a rate of 5 ml/min. The distance from the needle tip to the calcium chloride was 5 cm.

The beads were collected after filtration through Whatsman filter paper (# 41), washed three times with distilled water and subsequently dried to their constant weight in vacuum desiccator for 24 h to ensure complete removal of solvents. The vehicles such as Calcium chloride were used as dispersion medium.

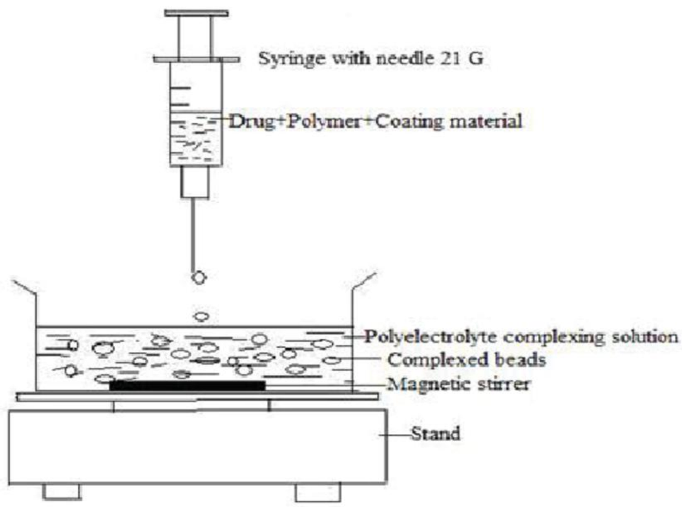

Figure: 9 Schematic presentation of method of preparation of Gelucire beads of Cefixime Trihydrate

Table 13: Composition of different bead formulations containing Cefixime Trihydrate

S no.	Formul-ation Code	Drug (mg)	Gelucire 43/01 (mg)	Gelucire 50/13 (mg)	Gelucire 48/16 (mg)	Calcium Carbonate (mg)	Sodium Alginate (mg)	Calcium Chloride (mg)	Acetic Acid (ml)
1	F1	100	3300	-	-	1500	1000	2000	10
2	F2	100	-	3300	-	1500	1000	2000	10
3	F3	100	-	-	3300	1500	1000	2000	10
4	F4	100	3300	3300	-	1500	1500	2000	10
5	F5	100	3300	-	-	1500	1500	2000	10
6	F6	100	9900	-	-	1500	2000	2000	10
7	F7	100	6600	-	-	1500	3000	2000	10
8	F8	100	6600	-	-	1500	4000	2000	10
9	F9	100	6600	-	-	1500	3000	3000	10
10	F10	100	6600	-	-	1500	3000	4000	10

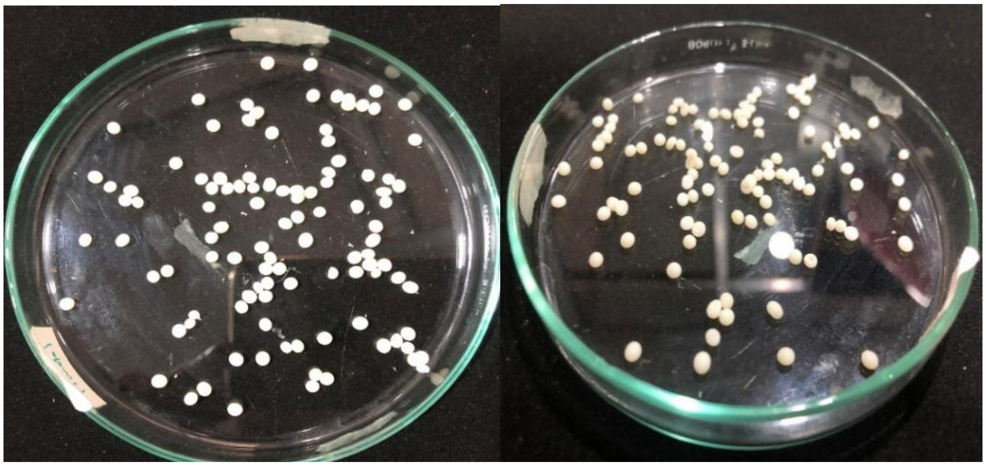

Figure 10: Cefixime Trihydare floating beads

EVALUATION OF FLOATING BEADS

Appearance of Bead

Table 14: Appearance of different Gelucire based bead containing Cefixime Trihydrate

S. No	Formulation Code	Appearance
1	F1	Irregular shape formed
2	F2	Gel formed
3	F3	Beads Not formed
4	F4	Beads Not formed
5	F5	Spherical Beads formed
6	F6	Beads Not formed
7	F7	Irregular shape formed
8	F8	Spherical Bead formed
9	F9	Spherical Bead formed
10	F10	Spherical Bead formed

Discussion- From the above table 14 and figure 10 , it was found that Gelucire 43/01 and Calcium Chloride has formed spherical shape beads. Beads were not formed when the high ratio of lipid as well as low ratio of lipid was used. Uniform and compact beads were formed with Calcium Chloride. Calcium chloride was used as surface active agent and cross-linking agent. So, might be these properties play an important role in uniform beads formation. In the formulation F1-F4, F6-F7, where the shape was not spherical because the amount of Sodium Alginate used played an important role. More Sodium Alginate will increase the cross-linking with calcium chloride, which will decrease the rate of drug and allow the drug to remain entrap in the wall. The spherical shape was lost and beads became disc or irregular shape.

Percentage Yield

Table15 : Percentage yield of different Gelucire beads containing Cefixime

	Formulation Code	Percentage Yield
1	F5	72.27±1.52
2	F8	87.06±2.51
3	F9	87.30±2.08
4	F10	77.91±2.51

Value is expressed as mean ± SD; n = 3

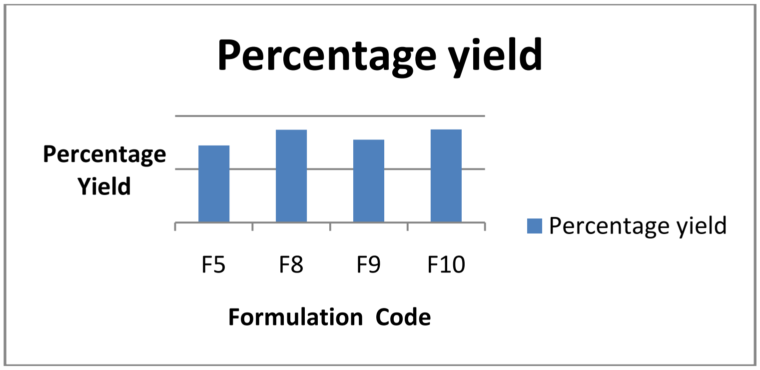

Figure 11: Percentage yield of Cefixime loaded Gelucire floating beads

Discussion- Percentage yield was calculated of the formulation which was found successful in bead formation with floating ability in gastric medium. The yield thus calculated was found in a range of 72.27±1.52 to 87.30±1.52 with the maximum yield possessed by F9 formulation, which was 87.30±1.52.

Percentage Drug Entrapment

Percentage Drug Entrapment of all formulation was given in a table 16

Table16 Percentage Drug Entrapment of different Gelucire based bead containing Cefixime Trihydrate

	Formulation Code	Percentage drug entrapment
1	F5	72.76±0.045
2	F8	79.86±0.043
3	F9	84.33±0.033
4	F10	82.88±0.033

Value is expressed as mean ± SD; n = 3

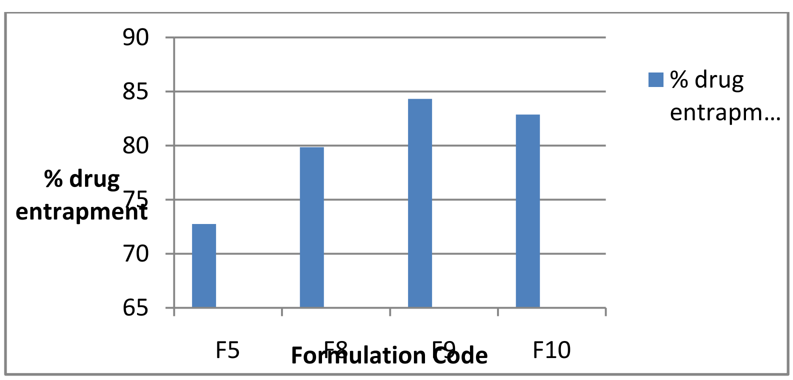

Figure:12 Percentage drug entrapment of Cefixime loaded Gelucire floating beads

Discussion- From the above table, it was found that Percentage drug entrapment of all formulation was found to be in a range 72.76±0.045 to 84.33±0.033. These results explain that there is a significant effect on percent entrapment efficiency of beads was observed with lipid concentration.

Particle Size

Table17 Particle size of different Gelucire based bead containing Cefixime Trihydrate

	Formulation Code	Particle Size (µm)
1	F5	3.27±0.45
3	F8	3.42±0.83
4	F9	3.69±0.18
5	F10	3.81±0.74

Value is expressed as mean ± SD; n = 3

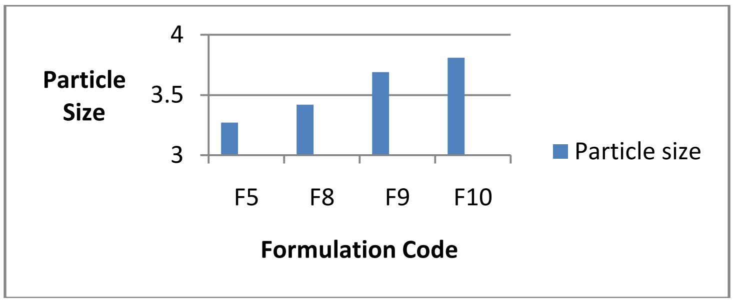

Figure:13 Particle Size of Cefixime loaded Gelucire floating beads

Discussion- Particle size of all beads found to be in the range from 3.27±0.45 to 3.81±0.74 µm. From the result it was found that on increasing lipid concentration particle size slightly increase. The formed beads were sufficiently hard and spherical in shape.

FTIR spectral analysis

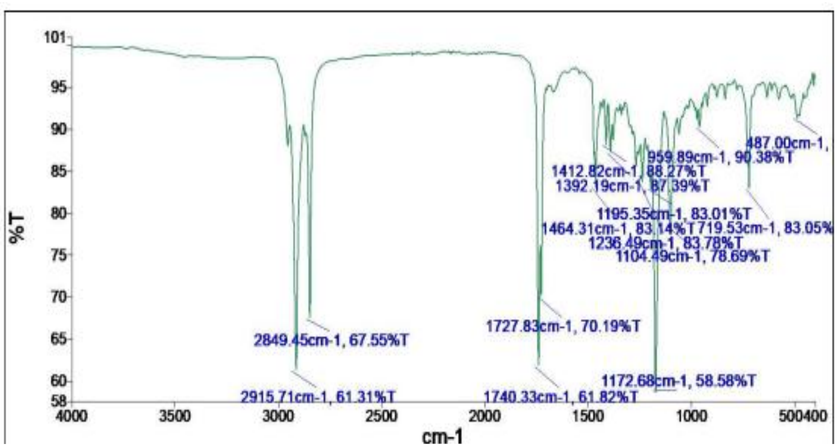

Figure:14 FTIR of formulation (F9)

As seen from figure14 the spectrum of formulation (F9), peaks were obtained at 2915.71 cm^{-1} (aliphatic C–H vibrations), 1740.33 cm^{-1} (N–H stretching), 1172.68 cm^{-1} (C=S stretching).

The absence and low peak intensity of drug shows entrapment of drug in developed formulation. Overall, there was no alteration in the characteristic peaks of drug and Gelucires suggesting that there was no interaction between the drug and Gelucire.

In vitro Floating study

Table 18: Percentage floating of different Gelucire based bead containing Cefixime

S.No.	Formulation Code	Percentage Floating
1	F5	95% floating
2	F8	100% floating
3	F9	100% floating
4	F10	100% floating

Discussion- The results show that all formulations remain floating up to 8 h, reflects excellent floating ability of beads Apart from hydrophobicity, density of Gelucire 43/01 (true density 0.0856 g/cm^3) also plays an important role in floating ability of beads.
On the basis of result of above parameters formulation F9 was selected for further in-vitro drug release study.

Micromeretic properties

Table 19: Flow properties

Formulation Code	Angle of Repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's ratio
F5	25.751 ± 1.14	0.521 ± 0.003	0.560 ± 0.002	6.828 ± 0.822	1.073± 0.009
F8	22.454± 1.91	0.516 ± 0.014	0.605 ± 0.035	13.786± 1.135	1.160± 0.015
F9	28.649± 0.71	0.482 ± 0.013	0.581 ± 0.004	17.084± 2.737	1.207± 0.041
F10	27.669± 0.71	0.482 ± 0.013	0.581 ± 0.004	17.084± 2.737	1.207± 0.041

Value is expressed as mean ± SD; n = 3

Result: From the above table, it is concluded that the powder formed has good flow properties.

Swelling Index
Results of water uptake study showed that the order of swelling in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved up to 12 hrs. The complete swelling was achieved by the end of 12 hrs. The % of swelling of F9 was higher due to increase in the concentration of gelucire which also gives the firm structure to the Beads.

Table 20 Swelling Index

S.No.	Formulation Code	Swelling Index
1	F5	68.42±0.80%
2	F8	76.40±0.63%
3	F9	86.23±0.23%
4	F10	78.40±0.20%

In-vitro Drug release study

The in-vitro drug release of Formulation F9 and Pure drug was given in a table 21

Table21: Percentage drug release of Formulation F9 and Pure drug

Time (hrs)	% Drug release of pure drug	% Drug release of F9 formulation
0	0	0
0.25	1.50±0.830	1.28±0.271
0.5	5.84±0.543	5.57±0.271
1	7.47±0.543	11.00±0.269
2	11.54±0.543	15.07±0.156
3	18.05±0.543	28.09±0.156
4	21.85±0.543	37.05±0.271
6	30.26±0.543	47.27±0.156
8	37.72±0.543	55.68±0.271
12	40.30±0.543	62.19±0.271
18	41.52±0.543	69.74±0.271
24	48.58±0.543	79.73±0.271

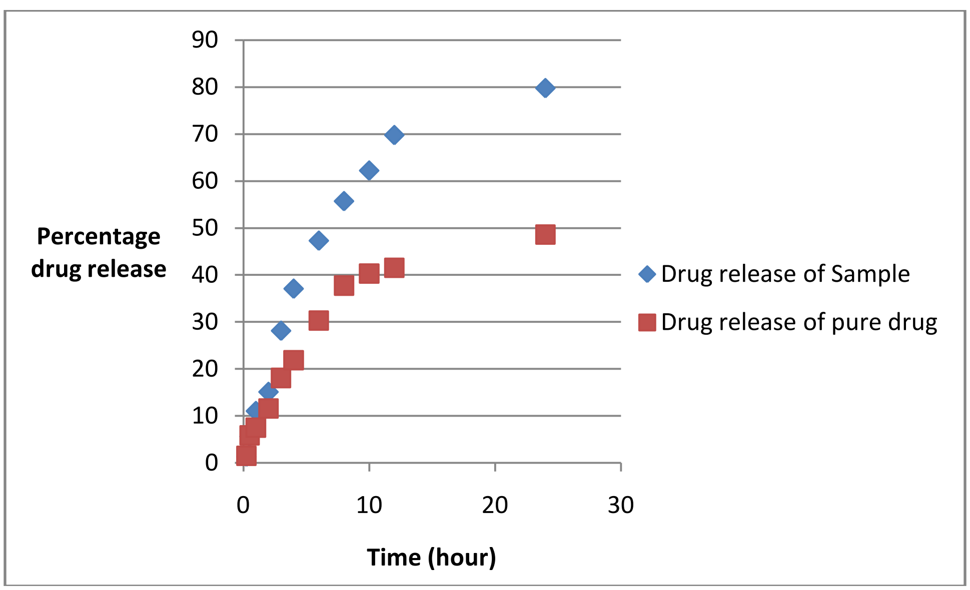

Figure:15 In-Vitro Drug release of Cefixime loaded Gelucire 43/01 floating bead and pure drug.

Discussion: The in-vitro release of drug from the lipid based floating bead was found to be higher as compare to pure drug that showed the effect of lipid matrix of Gelucire in drug release property. The fast effect, namely the amount of encapsulated compound released at short times, is normally related to the drug embedded into or near the beads surface. Drug was dispersed into the molten Gelucire 43/01 as a micronized powder and the resulting beads were formed by a dispersion of drug particles through the waxy matrix. Table 21 indicated that in vitro release of pure drug show 49% released within 24 hr. Formulations displayed a biphasic sustained release pattern and an initial burst release of Cefixime trihydrate was obtained from F9. Furthermore, the release profiles of Cefixime trihydrate from beads made from Gelucire 43/01 showed that Gelucire 43/01 employed yielded a sustained cefixime trihydrate release. From the in-vitro drug release study it was found that F9 formulation showed lower drug release as compare to pure drug..

In-vitro drug release kinetic

To understand the mechanism by which the drug was released from the Cefixime Trihydrate floating beads F9 formulation, various release kinetics model including zero order, first order, Higuchi and Korsmeyer-Peppas model were applied as shown in Figure16-19

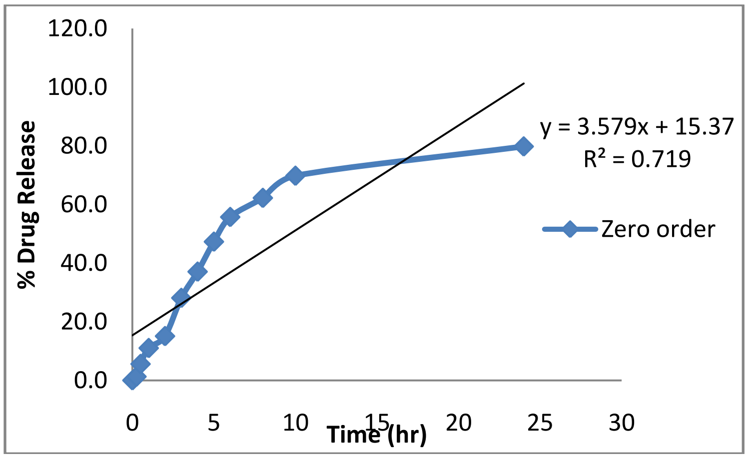

Figure:16 Zero order release kinetics of optimized F9 formulation

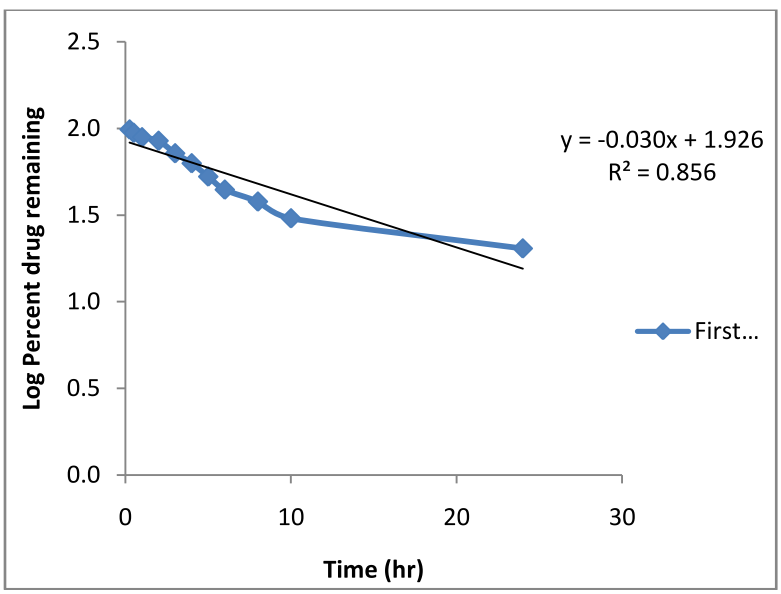

Figure:17 First order release kinetics of optimized F9 formulation

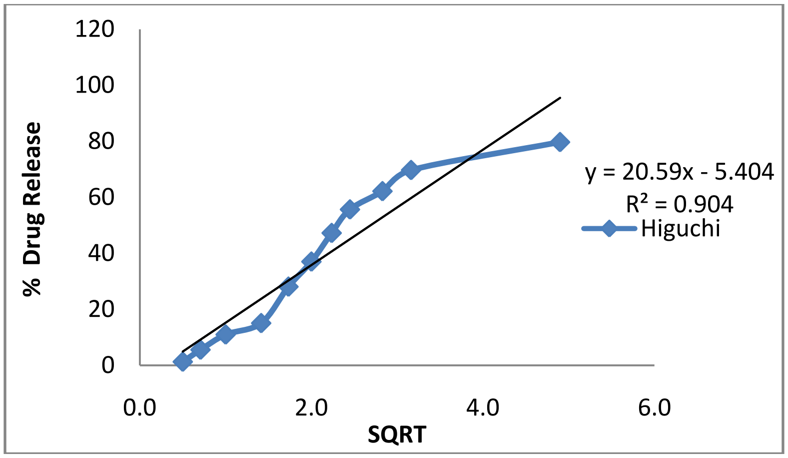

Figure 18: Higuchi order release kinetics of optimized F9 formulation

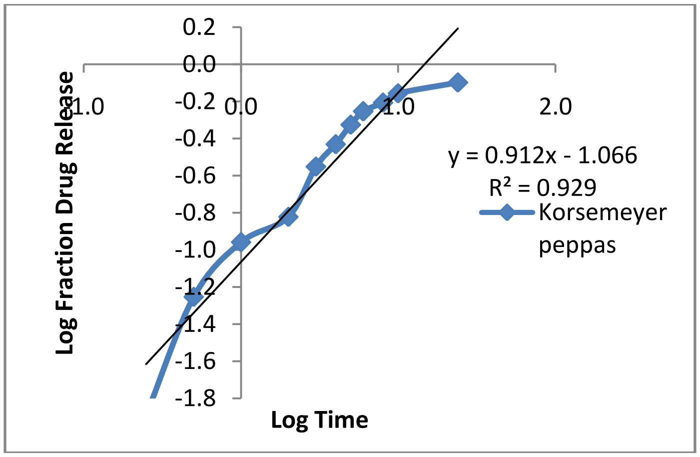

Figure 19: Korsmeyer peppas release kinetics of optimized F9 formulation

Discussion- Mathematical models are commonly used to predict the release mechanism and compare release profile. For all the optimized formulations, the % drug release vs time (zero order), log percent drug remaining vs time (first order), log per cent drug release vs square root of time (Higuchi plot), and log of log % drug release vs. log time (Korsmeyer and Peppas Exponential Equation) were plotted.

Table:22 Kinetic equation parameter of formulation F9

Formulation name	Zero order		First order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F9	3.580	0.719	-0.031	0.857	20.593	0.904	0.912	0.930

Discussion- In each case, R^2 value was calculated from the graph and reported in table 22 and figure 16 to figure19. considering the determination coefficients, K. Peppas model was found (r^2=0.930) to fit the release data best. This demonstrates that Cefixime Trihydrate molecules loaded in the bead and there was no interaction between the drug and formulation material. It could be concluded from the results that the drug was released from bead by a sustain mechanism.

SUMMARY AND CONCLUSION

Gastric floating drug delivery system (GFDDS) is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. Gelucires are a family of relatively inexpensive materials, comprising mixtures of mono-, di-, and triglycerides and also poly (ethylene glycol) esters of fatty acid. Gelucires are available with a range of properties depending on their hydrophilic lipophilic balance (HLB; 1–18) and melting point (33–65°C) range.

On physicochemical evaluation, melting point of Cefixme Trihydrate was found to be 220°C. On UV spectrophotometer analysis absorption maxima was found to be 288 nm in methanol. Drug was freely soluble in methanol, sparingly soluble in ethanol and practically soluble in water. The partition coefficient of Cefixime Trihydrate in n-octanol: water was found to be 0.002, this indicated that the drug is hydrophilic in nature. On FTIR spectroscopy analysis there was no incompatibility between drug and lipid.

An attempt is made to prepare bead of Cefixime Trihydrate using various grades of gelucire such as Gelucire 48/01, Gelucire50/13 and Gelucire 43/01. Among which gelucire 43/01 gave spherical bead. The method of preparation of beads was found to be simple and reproducible. Percentage yield was found in a range of 72.27±1.52 to 87.30±1.52. Percentage drug entrapment of drug was obtained in all formulations with successful bead formation in a range of 72.76±0.045 to 84.33±0.033.

Due to higher drug-lipid ratio beads the size of bead slightly increased produce. The Micromeretics properties shows the good flow of formed beads as ranges vary from 25.751 ± 1.14 to 28.649± 0.71, 0.521 ± 0.003 to 0.482 ± 0.013, 0.560 ± 0.002 to 0.581 ± 0.004, 6.828 ± 0.822 to 17.084± 2.737 and 1.073± 0.009 to 1.207± 0.041 for Angle of repose , Bulk Density , Tapped Density, Carr's Index and Hausner's Ratio respectively. The average size of bead range was between 3.27±0.45 to 3.81±0.74 µm. The in vitro data indicated that pure drug showed 48% release within 24 hr. The drug release from the bead prepared in formulation F9 achieved 79.73±0.271% in 24 hr.

According to model fitting methods the highest regression coefficient (R^2) value was 0.912 through Peppas order model. Hence from all aspects; we concluded that the release of drug Cefixime Trihydrate can be controlled by proper designing of the formulation and selection of a suitable method of preparation.

It is concluded that the method of preparation of beads was found to be simple, reproducible, provides good yield and entrapment efficiency. The *in vitro* data obtained for floating beads of Cefixime Trihydrate showed excellent buoyancy ability. Prepared formulation showed better sustained release behavior when compared with its pure Cefixime Trihydrate.

Thus, Gelucire 43/01 can be considered as an effective carrier for the design of a gastroretentive multiparticulate drug delivery system.

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