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Preparation and *In-vitro* evaluation of gelucire based gastric floating beads of ofloxacin

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Abstract
Oral controlled release (CR) dosage forms (DFs) 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. Drug bioavailability of oral dosage forms is subjective by various factors. One of the significant factor is a gastric residence time (GRT) of these dosage forms.
Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.

Keywords: Oral controlled release, floating beads, ofloxacin, bioavailability, gastric retention

Introduction
Many drugs given by oral route are subjected to absorption through the GIT, with major absorption from the stomach and intestine. Drugs, which is absorbed from the stomach or show local effect, should spend extreme time in stomach. This is found very hard to happen, in case of the conventional dosage forms such as capsules and tablets, due to the gastric emptying. Gastric emptying of dosage form depends on several factors like temperature and viscosity of the meal, volume and composition of the meal, emotional state of the individual, the pH of the stomach, body posture, etc. Prolonged gastric retention of the drug is required in the following conditions:

- The drug is best absorbed from the stomach. Slow dissolving drugs.
- Drug show local effects within the stomach.
- Gastric fluids facilitate and increase the disintegration and dissolution of the drug.

In order to achieve all these situations, various methods of the controlled drug delivery have been established. One of these types of the methods, which ensure that a particular drug/dosage form remains in the stomach for longer duration of time, is GRDDS.
After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract**.**

❖ Gastro retentive Drug Delivery System (GRDDS)
Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Drug bioavailability of oral dosage forms is subjective by various factors. One of the significant factor is a gastric residence time (GRT) of these dosage forms. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches:

a) Low density form of the dosage form that causes buoyancy in gastric fluid
b) High density dosage form that is retained in the bottom of the stomach
c) Bioadhesion to stomach mucosa
d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients
e) Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

The current study deals with the gastro retentive approaches that has recently become leading methodologies in the field of controlled and site specific drug delivery system.

Factors Controlling Gastric Retention of Dosage Forms
The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents.

Advantages of Gastro retentive delivery systems

- Enhanced bioavailability
- Enhanced first pass biotransformation
- Sustained drug delivery/ reduced frequency of dosing
- Targeted therapy for local ailments in upper GIT
- Reduced fluctuations of drug concentration
- Site specific drug delivery

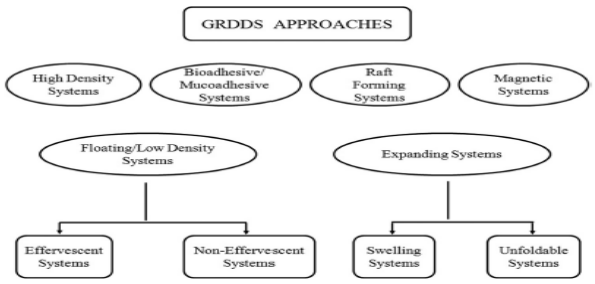

Fig 1: General approaches to gastric retention

Floating Drug Delivery Systems

FDDS are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability.

Experimental Work

Preparation of Floating Beads

Lipid (Gelucire 43/01/ Gelucire 54/02 Gelucire 50/13) was melted at 60°C and the finely powdered drug was gradually added with uniform mixing to form dispersion. The resultant dispersion was dropped via a 23-guage syringe needle (0.65 mm internal diameter) into 100 ml of pre-chilled (4°C) IPA at a rate of 5 ml/min. The distance from the needle tip to the IPA was 5 cm. The content was stirred at 100 rpm using magnetic stirrer for 15 min. The beads were collected after filtration through Whatman filter paper (# 41), washed three times with distilled water and subsequently dried to their constant weight in vacuum dessicator for 24 h to ensure complete removal of solvents. The vehicles such as isopropyl alcohol were used as dispersion medium .

Table 1: Composition of different bead formulations containing Ofloxacin

S.No	Formulation Code	Drug (mg)	Gelucire 43/01 (mg)	Gelucire 54/02 (mg)	Gelucire 50/13 (mg)	Isopropyl alcohol (ml)
1	F1	100	-	100	-	100
2	F2	100	-	500	-	100
3	F3	100	-	1000		100
4	F4	100	-	1500	-	100
5	F5	100	100	-	-	100
6	F6	100	500	-	-	100
7	F7	100	1000	-	-	100
8	F8	100	1500	-	-	100
9	F9	100	-	-	100	100
10	F10	100	-	-	500	100
11	F11	100	-	-	1000	100
12	F12	100	-	-	1500	100

Results and Discussions

1. Pre-formulation

1.1. Organoleptic properties

Table 2: Organoleptic Properties of Ofloxacin

Sr. No.	Properties	Inferences
1.	Colour	Off-white to pale yellow
2.	Form	Crystalline

1.2. Melting Point

Table 3: Melting Point of Ofloxacin

Drug	Observed melting point	Reference melting point
Ofloxacin	266-271°C	270-273°C

1.3. UV Spectroscopy

Determination of absorption maxima in 0.1N HCl

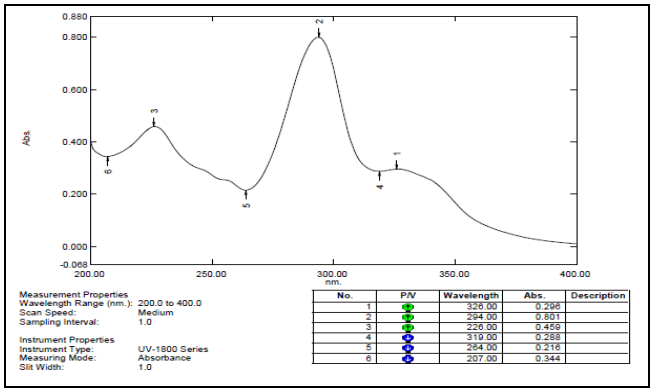

Fig 2: UV Spectrum of Ofloxacin in 0.1N HCl

Preparation of standard curve of Ofloxacin in 0.1N HCl

Table 4: Calibration curve of Ofloxacin in 0.1N HCl (λ_{max}= 294nm)

1	Concentration (µg/ml)	Absorbance (mean±SD)
1	2	0.34 ± 0.001
2	4	0.47±0.001
3	6	0.65±0.001
4	8	0.83±0.002
5	10	0.98±0.007

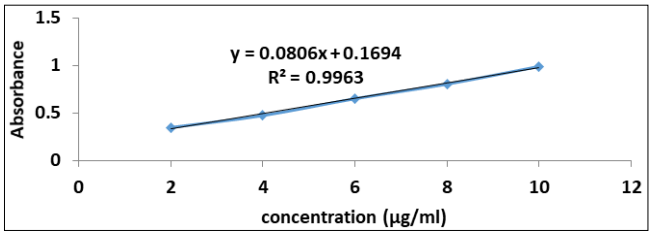

Fig 3: Graph of standard calibration curve of Ofloxacin in 0.1N HCl

Table 5: Result of regression analysis of UV method for estimation of Ofloxacin

Statistical parameters	Results
λ max	294 nm
Regression equation ** Y=mx+C	Y=0.080x+0.169
Slope (b)	0.080
Intercept (C)	0.169
Correlation coefficient (r^2)	0.996

1.4 Solubility Studies of Ofloxacin in various Solvents

Table 6: Solubility studies of Ofloxacin for different solvents

S.No	Solvents	Solubility (mg/ml)
1	Methanol	0.10±0.003
2	Ethanol	0.019±0.0002
3	Water	0.015±0.018
4	pH6.8	0.006±0.0007
5	0.1N NaOH	5.54±0.29
6	0.1NHCL	7.24±0.05

Value is expressed as mean ± SD; n = 3

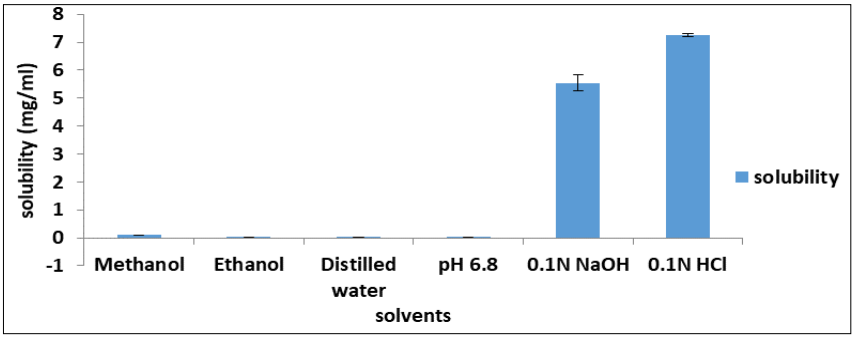

Fig 4: Solubility study of Ofloxacin in different solvents

1.5 Partition coefficient determination

Table 7: Partition coefficient determination of Ofloxacin

Drug	Solvent System	Log P Value	Reported Log P value
Ofloxacin	Water:n-octanol	0.086 ± 0.030	-0.48

1.6 FTIR studies

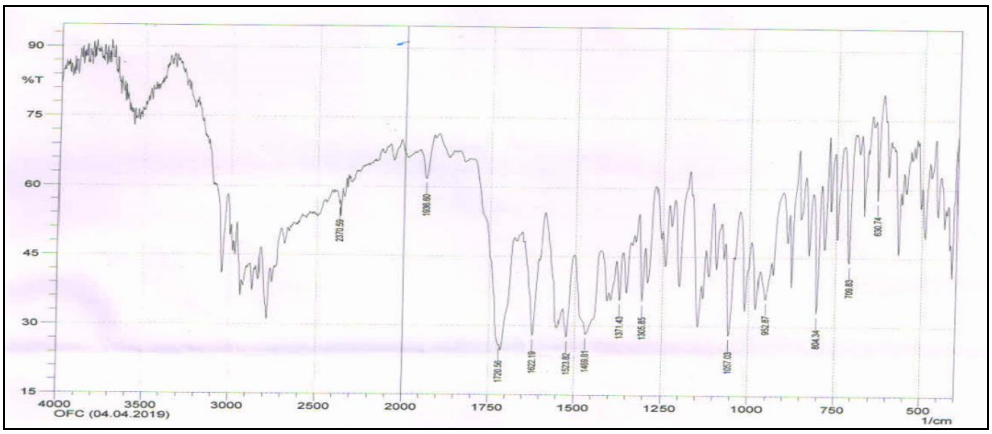

Fig 5: FTIR Spectra of Ofloxacin

Table 8: FTIR interpretation of Ofloxacin

Reference peak (cm^{-1})	Observed peak (cm^{-1})	Characteristic peaks
3300-2500	2370.59	Carboxylic acid OH band
1400	1469.81	Protonation of N_4 in piperazinyl group
1715	1720.56	C=O stretching
1621	1622.19	C=C stretching or carbonyl stretch
1530	1523.82	C=O aromatic stretching
1055	1057.03	C-O-C stretch of ether group

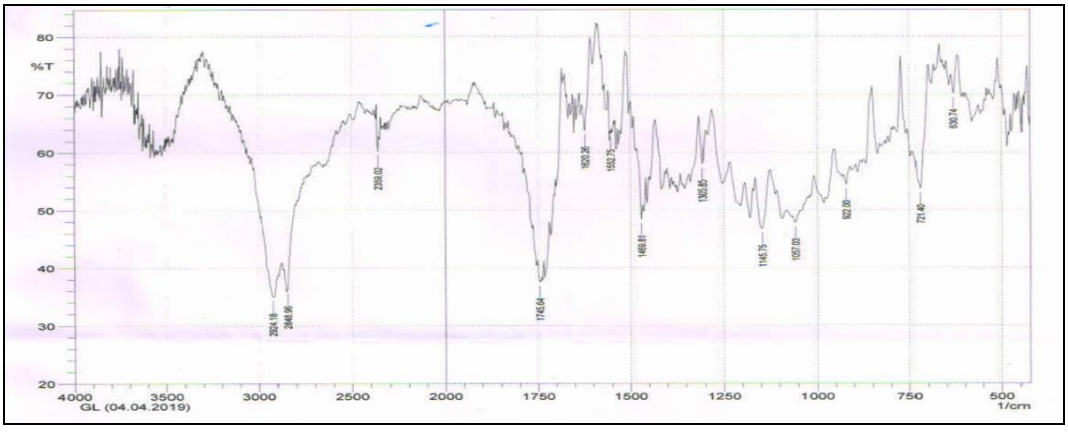

Fig 6: FTIR Spectra of Gelucire 43/01

Table 9: FTIR interpretation of Gelucire 43/01

Reference peak (cm^{-1})	Observed peak (cm^{-1})	Characteristic peaks
1741, 1735	1745.64	C=O stretch of ester group
1,17,21,100	1145.75, 1057.03	C-O stretch of alcohols

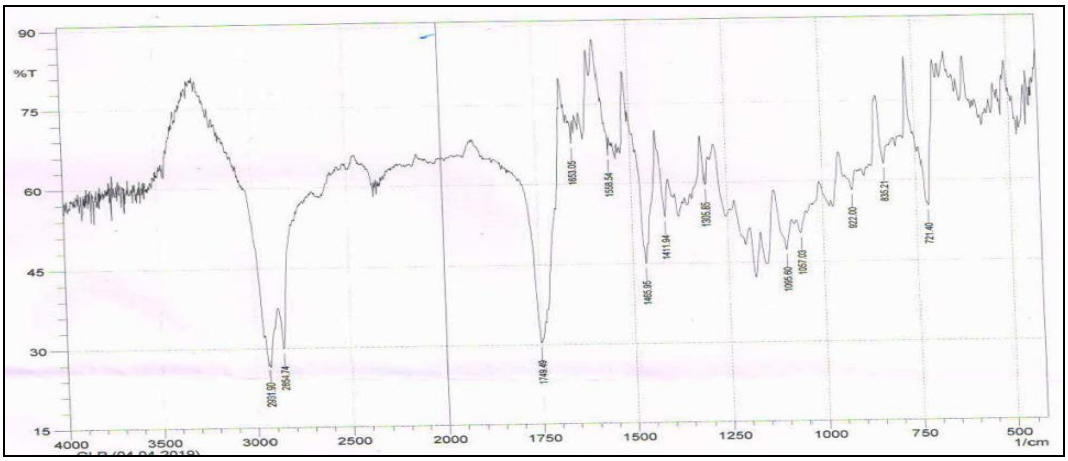

Fig 7: FTIR Spectra of physical mixture

Table 10: FTIR interpretation of physical mixture

Reference peak (cm^{-1})	Observed peak (cm^{-1})	Characteristic peaks
1469.81	1465.95	Protonation of N_4 in piperazinyl group
1720.56	1749.49	C=O stretching
1622.19	1653.05	C=C stretching or carbonyl stretch
1523.82	1558.54	C=O aromatic stretching
1057.03	1057.03	C-O-C stretch of ether group
1745.64	1749.49	C=O stretch of ester group
1145.75	1095.6	C-O stretch of alcohols

FTIR of Pure drug and physical mixture studies were carried out to eliminate the possibility of interaction between drug and excipients. No interaction was observed in this mixture.

2. Preparation of Bead

In the present investigation, a multiparticulate delivery system of Ofloxacin capable of providing controlled release was prepared using Gelucire 43/01. The method of preparation of beads was found to be simple and reproducible.

3. Evaluation of bead

3.1. Appearance of bead

Table 11: Appearance of different Gelucire based bead containing Ofloxacin

S. No	Formulation Code	Appearance
1	F1	Bead Not formed
2	F2	Bead Not formed
3	F3	Irregular shape formed
4	F4	Irregular shape formed
5	F5	Spherical Bead formed
6	F6	Spherical Bead formed
7	F7	Spherical Bead formed
8	F8	Spherical Bead formed
9	F9	Irregular shape formed
10	F10	Irregular shape formed
11	F11	Bead Not formed
12	F12	Irregular shape formed

It was found that Gelucire 43/01 and isopropanol 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 IPA when we used Gelucire 43/01 and IPA was used as surface active agent and cross-linking agent. So these properties might play an important role in uniform bead formation.

3.2. Percentage yield

Table 12: Percentage yield of different Gelucire based bead containing Ofloxacin

S.No.	Formulation Code	Percentage Yield
1	F5	70±1.5
2	F6	77.5±0.76
3	F7	80.78±0.59
4	F8	89.25±0.28

Percentage yield was found in a range of 70±1.5 to 89.25±0.28.

3.3. Percentage Drug Entrapment

Table 13: Percentage Drug Entrapment of different Gelucire based bead containing Ofloxacin

S.No.	Formulation Code	Percentage drug entrapment
1	F5	47.79±1.90
2	F6	69.68±0.57
3	F7	73.43±0.781
4	F8	87.95±0.75

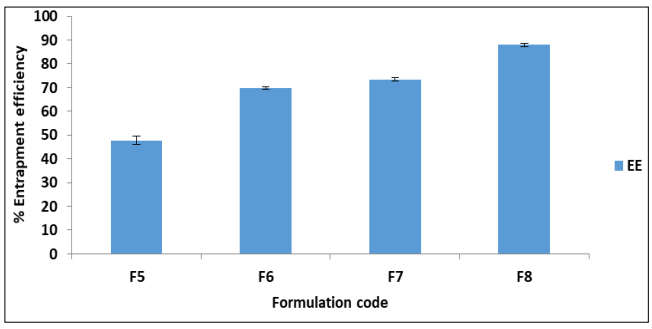

Fig 8: Percentage drug entrapment of Ofloxacin loaded Gelucire floating beads

It was found that Percentage drug entrapment of all formulation was found to be in a range 47.79±1.90 to 87.95±0.75. These results explain that there is a significant effect on percent entrapment efficiency of beads with lipid concentration.

3.4. Particle Size analysis

Table 14: Particle size of different Gelucire based bead containing Ofloxacin

S.no.	Formulation Code	Particle Size (µm)
1	F5	2.42±0.13
2	F6	3.00±0.08
3	F7	3.04±0.05
4	F8	3.24±0.05

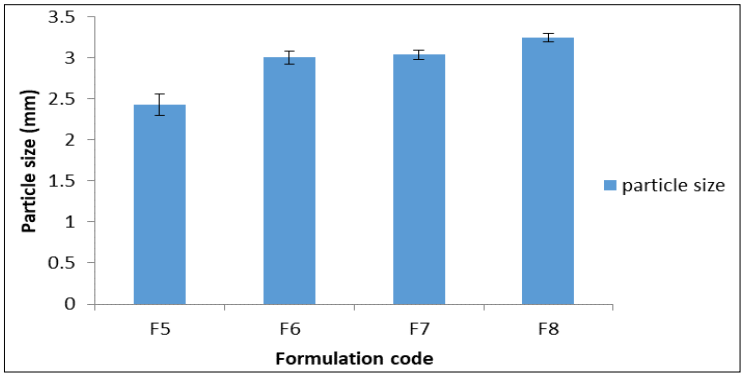

Fig 9: Particle Size of Ofloxacin loaded Gelucire floating beads

Particle size of all beads found to be in the range from 2.42±0.13 to 3.24±0.05µm. 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.

3.5. *In vitro* Floating study

Table 15: Percentage floating of different Gelucire based bead containing Ofloxacin

S. No.	Formulation Code	Percentage Floating
1	F5	90% floating
2	F6	80% floating
3	F7	100 % floating
4	F8	100 % floating

The results show that all formulations remain floating up to 8 h, reflects excellent floating ability of beads. On the basis of above parameters, F8 formulation was selected for further drug release studies.

3.6. *In-vitro* Drug release study

Table 16: Percentage drug release of Formulation F8 and Pure drug

Time (h)	% Drug release of pure drug	% Drug release of F8 formulation
0	0	0
0.25	33.48±0.17	8.21±0.02
0.5	58.42±0.45	12.82±0.11
1	80.17±0.25	23.58±0.28
2	96.75±1.94	31.91±0.34
3	99±1.12	39.78±0.17
4		47.17±0.23
5		55.42±0.06
6		60.93±0.56
7		64.8±0.19
8		69.6±0.17
9		74.92±0.40
10		76.23±0.34
12		80.06±0.28

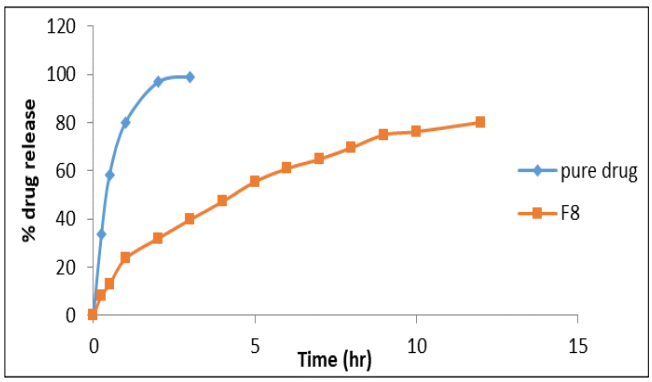

Fig 10: *In-Vitro* Drug release of Ofloxacin loaded Gelucire 43/01 floating bead and pure drug.

The in-vitro release of drug from the lipid based floating bead was found to be lower as compare to pure drug that showed the effect of lipid matrix of Gelucire in drug release property.

Formulations displayed a biphasic sustained release pattern and an initial burst release viz. 12.82 % of Ofloxacin was obtained from F8 in 15mins. From the in-vitro drug release

study it was found that F8 formulation showed lower drug release as compare to pure drug.

3.7. In-vitro drug release kinetic

In-vitro drug release kinetic study data of formulation F8 is given below.

Zero order

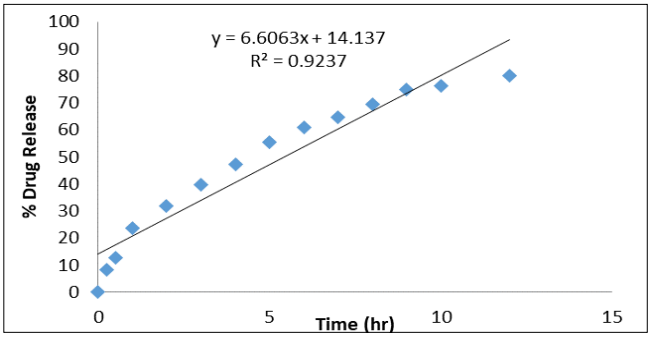

Fig 11: Zero order graph of formulation F8

First Order

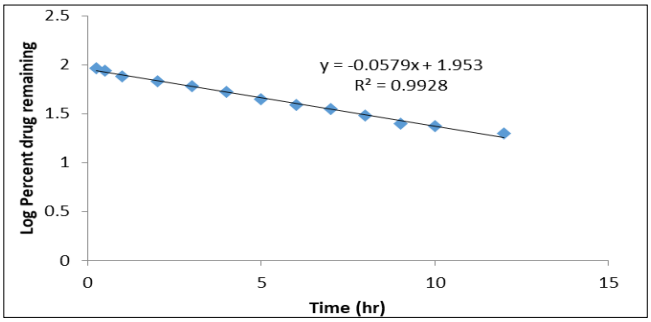

Fig 12: First order graph of formulation F8

Higuchi

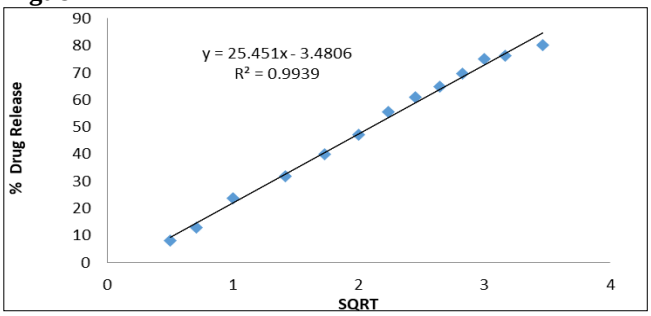

Fig 13: Higuchi order graph of formulation F8

Korsmeyer peppas

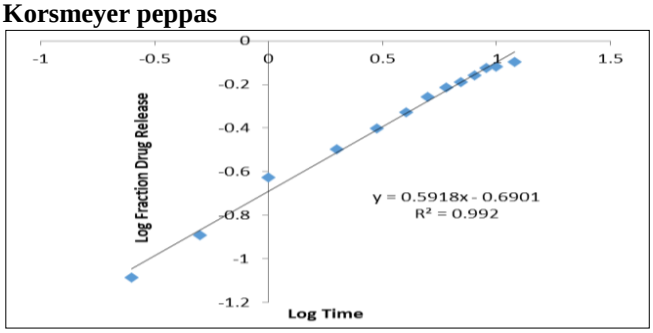

Fig 14: Korsmeyer peppas order graph of formulation F8

Table 17: Kinetic equation parameter of formulation F8

Formulation name	Zero order		First order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F8	0.923	6.606	0.992	-0.057	**0.993**	25.45	0.992	0.591

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 fraction drug release vs. log time (Korsmeyer and Peppas Exponential Equation) were plotted.

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 Ofloxacin was found to be 266-271^{0}C. On UV spectrophotometer analysis absorption maxima was found to be 294 nm in 0.1N HCL. Drug was freely soluble in 0.1N HCL & 0.1N NaOH and less soluble in pH 6.8. The partition coefficient of Ofloxacin in n-octanol: water was found to be 0.086±0.030 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 294nm using various grades of gelucire such as Gelucire 50/13, Gelucire 48/01, 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 70±1.5 to 89.25±0.28. Percentage drug entrapment of drug was obtained in all formulations in a range of 47.79±1.90 to 87.95±0.75. Due to higher Drug-lipid ratio beads the size of bead slightly increased produce. The average size of bead range was between 2.42±0.13 to 3.24±0.05µm. The in vitro data indicated that pure drug was 99% release with in 3hrs. The drug release from the bead prepared in formulation F8 achieved 60.93±0.56% in 6hrs and 80.06±0.28% in 12hrs.

According to model fitting methods the highest regression coefficient (R^2) value was 0.993 through Higuchi order model. Hence from all aspects; we concluded that the release of drug ofloxacin 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 ofloxacin showed excellent buoyancy ability. Prepared formulation showed better controlled release behavior when compared with its pure ofloxacin. Thus, Gelucire 43/01 can be considered as an effective carrier for the design of a

gastroretentive multiparticulate drug delivery system with broad-spectrum antibiotic drugs i.e. Ofloxacin.

References

1. Badoni A, Ojha G, Gnanarajan P. Kothiyal. Review on Gastro Retentive Drug Delivery System. The Pharm. Innov. 2012; 1(8):32-42.
2. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review. AAPS Pharm Sci Tech. 2005; 6(3):E372-E390.
3. Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. Trop J Pharm Res. 2008; 7(3):1055-1066.
4. Timmermans J, Moes AJ. How well do floating dosage forms float. Int J Pharm. 1990; 62:207-16.
5. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm. 2001; 220:13-21.
6. Wilson CG, Washington N. The stomach: its role in oral drug delivery. In: Rubinstein MH, ed. Physiological Pharmacetical: Biological Barriers to Drug Absorption. Chichester, UK: Ellis Horwood, 1989, 47-70.
7. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J. Control. Release. 2003; 90:143-162.
8. Bhowmik D, Chiranjib B, Chandira M, Jayakar B. Floating Drug Delivery System-A Review, Der Pharm. Lett. 2009; 1:199-218.
9. Borase BC. Floating systems for oral controlled release drug delivery. Int. J. Appl. Pharm. 2012; 4(2):1-13.
10. Awar. Gastro retentive dosage forms: A review with special emphasis on floating drug delivery systems, Drug delivery. 2011; 18(2):97-110.
11. Bhardwaj V, Nirmala SL, Harikumar. Floating drug delivery system: A Review. Pharmacophore. 2013; 4(1):26-38.
12. Chojecka A, Wiercinska O, Rodowald ER, Kanclerski K, Jakimiak B. Susceptibility of selected strains used for evaluation of biocidal efficiency of disinfectants and antibiotic-resistant strains to didecyldimethylammonium chloride in 2-propanol. Med Dosw Mikrobiol. 2015; 67(1):47-53.
13. Ceresana updates report on the global solvent market, Trade Publ. 2012; 17:24.
14. Ngai IM, Van Arsdale A, Govindappagari S, Judge NE, Neto NK, Bernstein J *et al*. Skin Preparation for Prevention of Surgical Site Infection after Cesarean Delivery: A Randomized Controlled Trial. Obstet Gynecol. 2015; 126(6):1251-1257.
15. Sodium Isopropyl Xanthate, SIPX, Xanthate. 3D Chem. com., 2012.
16. Society for Experimental Biology and Medicine. Proceedings of the Society for Experimental Biology and Medicine. 1992; 19:85.
17. Solanki R, Parikh SJ, Goyal S. Formulation and evaluation of floatable in situ gel of ofloxacin. Asian J Pharm. 2018; 12(2):S722-S727.
18. Gulkari VD, Bakhle SS, Yelane LS. Development and evaluation of ofloxacin floating tablets using natural polymer: Sterculia foetida linn. Gum. Int J Pharm Pharm Sci. 2016; 8(5):356-360.
19. Hussain MA, Mahender B, Anjum M. Formulation and Evaluation of effervescent floating matrix tablets of Ofloxacin. Int. J. Drug Dev. & Res. 2014; 6(1):188-198.
20. Babu JR, Vidyadhara S, Basha A. Formulation and *in vitro* evaluation of ofloxacin as floating drug delivery system. Der Pharmacia Lettre. 2013; 5(5):82-92.
21. Reddy ND, Reddy CP, Sunil R, Rao MY. Development of floating matrix tablets of Ofloxacin and Ornidazole in combined dosage form: in vitro and in vivo evaluation in healthy human volunteers. Int. J Drg. Del. 2012; 4(4):462-469.
22. Ritesh Kumar, Pawan Kumar Gautam, Amrish Chandra, Formulation and Evaluation of Multiple Unit Floating Beads of Antiulcer Drug. Asian J Pharm. 2018; 12(2):S680-690.
23. Sharma M, Kohli S, Dinda A. *In-vitro* and *in-vivo* evaluation of repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer. Saudi Pharmaceutical Journal, 2015, 1-11.
24. Adebisi AO, Laity PR, Conway BR. Formulation and evaluation of floating Mucoadhesive alginate beads for targeting Helicobacter pylori. J Pharm and Pharmcol. 2015; 67(4):511-524.
25. Adel S, Kasabgy NAE. Design of innovated lipid-based floating beads loaded with an antispasmodic drug: *in-vitro* and *in-vivo* evaluation. J Liposome Res., 2014, 1-14.
26. Smriti M, Singh S, Pandey J, Kondalkar AK, Tagde P. Formulation and evaluation of floating microbeads of ciprofloxacin HCl by emulsion gelation method. Scholars Research Library Der Pharmacia Lettre. 2013; 5(2):63-68.
27. Krishna RT, Development of Multiparticulate-Floating System for Pulsatile Release of Montelukast Sodium, Pharmaceutical Sciences. 2012; (2):328-338.
28. Yao H. Preparation and evaluation of a novel gastric floating alginate/poloxamer inner-porous beads using foam solution, Int. J Pharm. 2011; 422:211-219.
29. Nimase PK, Gali V, Ghule PJ. Preparation and evaluation of multiple-unit floating drug delivery system of clarithromycin. Int J Pharm Res Dev. 2010; 2(9):139-45.
30. Satishbabu BK, Sandeep VR, Ravi RB, Shrutinag R. Formulation and Evaluation of Floating Drug Delivery System of Famotidine. Indian J Pharm Sci. 2010; 72(6):738-744.