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Floating microspheres: Research article

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ABSTRACT

Gastric emptying is a complex process, one that is highly variable and makes in vivo performance of drug delivery systems uncertain. A controlled drug delivery system with prolonged residence time in the stomach can be great practical importance for drugs with an absorption window in the upper small intestine. The main limitations are attributed to the inter- and intra-subject variability of gastrointestinal (GI) transit time and to the non-uniformity of drug absorption throughout the alimentary canal. Floating drug delivery systems are useful in such applications. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. The present research briefly addresses the physiology of the gastric emptying process with respect to floating drug delivery systems. Floating microsphere were prepared by solvent evapouration method, using hydroxylpropyl methylcellulose (HPMC), ethyl cellulose (EC), Eudragit S 100 polymer in varying ratios. The shape and surface morphology of the microspheres were characterised by differential scanning calorimetry and scanning electron microscopy.

Keywords: Floating Drug Delivery System, Solvent Evapouration, Drug Delivery System, Gastro Intestinal Tract.

INTRODUCTION

Introduction to microspheres

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as a structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000nm). [1]

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). [2] Microspheres are sometimes referred to as micro particles.[3]

Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range they have colloidal properties. The

interfacial properties of microspheres are extremely important, often indicating their activity. [4]

There are various approaches in delivering a therapeutic substance to the target site in a sustained or controlled release fashion. One such approach of using polymeric microspheres as carriers for drugs.

Introduction to floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration.

Moreover it also reduces chances of striking and dose dumping. One another way, it produces prolonged therapeutic effect and therefore reduces dosing frequencies [5]

Effervescent type

[6] stated that swellable polymers e.g., methylcellulose, chitosan and various effervescent compound e.g., sodium bicarbonate, citric acid and tartaric acid are used for the preparation of effervescent dosage.

Floating microsphere of effervescent type liberates carbon dioxide gas due to which the density of the system is reduced and remains in floating condition in stomach for a prolonged period of time, this result in release of drug slowly at a desired rate.

Non-effervescent type

Highly swellable cellulose type hydrocolloids, polysaccharide and matrix forming polymer such as polycarbate, polyacrylate are used to form non effervescent system. This is prepared by thoroughly mixing the drug and gel forming hydrocolloids. When administered, it swells up when comes in contact with gastric fluid and attain a bulk density i.e., less than 1 g/44 mL.

Floating systems was first discovered by DAVIS (1968). These are the low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate which results in increased gastro retention time and reduces fluctuations in plasma drug concentration.

The development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time. [7]

The relatively brief gastric emptying time (GET) 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.

Gastro retentive systems 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 for drugs that are less soluble in a high pH environment. [8]Depending on the proteinoid amino acid composition the size range of the microsphere is 0.1-10mm.

The drug is entrapped within the microspheres by inducing phase transition in the drug solution, The microspheres are stable in acidic and enzymatic environment until the PH reaches the titration point, at this point microsphere undergo spontaneous dissociation and thereby release their contents.[9]

The most important characteristics of microsphere are the micro phase separation morphology which endows it with a controllable variability in degradation rate and also drug release.

MECHANISM OF FLOATING SYSTEMS

There are various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems, mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the

floating dosage forms have been most commonly used.

Floating drug delivery systems (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. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a 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, a novel apparatus for determination of resultant weight has been reported in the literature.

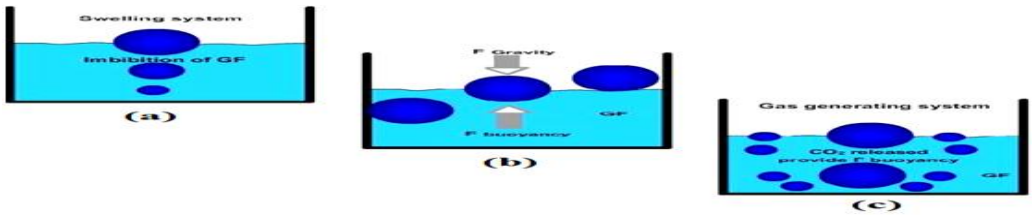


Figure Mechanism of floating systems

The apparatus operates by measuring continuously the force equivalent to F (as a function of time) 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 [10]

(F = F buoyancy - F gravity = (Df - Ds) gv

Where,

F= total vertical force

Df = fluid density

Ds = object density

v = volume and

g = acceleration due to gravity

Advantages of floating microspheres

- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- Improved receptor activation selectivity.
- Extended time over critical (effective) concentration ¾ less inter- and intra-subject variability.
- Better therapeutic effect of short half-life drugs can be achieved. The ¾ gastric retention time is increased because of buoyancy.
- The drug releases in a controlled manner for prolonged period.

Drug profile

Cefuroxime is second generation cephalosporin. It is resistant to gram-negative β-lctamases; has high activity against organisms producing these enzymes including PPNG and ampicillin resistant H.influenzae, while retaining significant activity on gram-positive cocci and certain anaerobes, but not B.fragilis.[11]

Preparation and method

Selected method: Silvent evapouration method

Procedure and formulation

The microspheres were prepared by (o/w) solvent evaporation method, since Cefuroxime axetil is soluble in water (water soluble drug). Polymers as HPMC and ethyl cellulose were dissolved in 20 ml of dichloromethane in the first three formulations, were as Eudragit RS 100 and Eudragit RL100 were used in the same concentration of next nine formulations. These polymers and drug were mixed vigorously to form a clear solution. Then the above solution was emulsified by adding drop by drop into the aqueous solution containing 250 ml of 0.5% w/v of poly vinyl alcohol which act as an emulsifier.

Dichloromethane was removed at 35^0 c by evaporation. As the solvent was being removed, the emulsifier continued to maintain the oil droplets in their spherical configuration and prevented aggregating until the solvent was completely removed, and the microspheres were hardened as discrete particles. Finally, the hardened microspheres were filtered by using filter paper and dried for 24 hours.

Formulation

Contents	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
E.C	1	1	1	1	1	1	1	1	1	1	1	1
Hpmc	0.5	1.0	1.5	2.0	0	0	0	0	0	0	0	0
Eudragit RS-100	0	0	0	0	0.5	1.0	1.5	2.0	0	0	0	0
Eudragit RL-100	0	0	0	0	0	0	0	0	0.5	1.0	1.5	2.0

Construction of standard graph for cefuroxime axetil preparation of 0.07 N hydrochloric acid

Measure 5.95ml of hydrochloric acid in 1 litre standard volumetric flask and make up the volume using demineralized water.

Calibration of standard curve

Accurately weighed Cefuroxime axetil which is equivalent to 100 mg of cefuroxime in a 100ml standard volumetric flask and dissolved in methanol.The volume was made upto 100ml using 0.07N Hydrochloric acid to obtain a stock solution-1(1000µg/ml).From this stock solution -1,10ml was pippetted out into a 100ml standard volumetric flask and made upto the mark using 0.07N Hydrochloric acid (stock solution-2).

From this stock solution -2,aliquots of 2ml,4ml,6ml,8ml,10ml,and 12ml,were pipetted out into a series of 100ml standard volumetric flasks and the volume was made upto the mark with 0.07N Hydrochloric acid to get drug concentration in the range of 2 to 12µg/ml.The absorbance of the resulting solution was then measured at 278nm using UV double beam spectrophotometer against 0.07N Hydrochloric acid as blank.The standard curve was obtained by plotting concentration(µg/ml)values in X-axis and the absorbance values in Y-axis.

PRE FORMULATION STUDIES

Differential scanning calorimetry

It is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured asa a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment.

Fourier transforms infrared spectroscopy

FT-IR of cefuroxime axitel, floating microspheres was performed using KBr pellet method using infrared spectrometer to determine the possible drug polymer interaction and physical state of the drug in the microspheres.

EVALUATION

Scanning electron microscopy

Scanning electron microscopy (SEM) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with gold film under reduced pressure. This film acts as a conducting medium on which a stream of electron was allowed to flow and then photograph was taken with SEM.

Particle size

It is measured using an optical microscope, and mean particle size is calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer. Different sizes of microspheres and

their distribution in each batch are measured by sieving in a mechanical shaker, using a nest of standard sieves (ASTM) and the shaking period of 15 minutes. Particle size distribution is determined and the mean particle size of microspheres is calculated by using the following formula

Mean particle size = ∑ (mean particle size of the fraction× weight fraction)/∑ (weight fraction)

In Vitro Release of Microspheres

The United States Pharmacopoeia basket-type dissolution rate test apparatus was used for all the in vitro release studies.

A weighed quantity of the microspheres was suspended in 900 mL of 0.1 mol HCL of pH 1.2. The dissolution medium was stirred at 100 rpm and maintained at constant temperature (37±0.5 OC). At present time intervals 5 mL aliquots were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium maintaining sink condition throughout the experiment. After suitable dilution, the samples were analyzed for drug quantification at 265 nm using Systronics, Double beam UV-VIS Spectrophotometer.

Buoyancy percentage

Microparticles (0.3g) were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 mol- HCl containing 0.01% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs.

The floating and the settled portion of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.9, 10 %

Buoyancy = Microsphere remained floating × 100
Total mass of microspheres

Floating behavior

100 mg of the floating microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween. The mixture was stirred with paddle at 100 rpm in a magnetic stirrer. The layer of buoyant floating microsphere was taken and separated by filtration at 1, 2, 4 and 6 h. Particles of both types were dried in a desiccator until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Drug Loading and Drug Entrapmen

The drug loading of Cefuroxime floating hollow microspheres for formulations F1 to F4 was found to be26.27%, 23.19%, 20.44%, and 16.72%, for formulations F5 to F8 was found to be 28.65% 25.12%, 21.77%, and17.89%, and for formulations F9 to F12 was found to be 28.30%, 24.2%, 20.85% and17.3%1 for formulations respectively.

The drug entrapment efficiency of Cefuroxime floating hollow microspheres for formulations F1 to F4 was found to be 63.08%,67.26%, 69.52% and71.97 %, for F5 to F8 was found to be 68.77%, 72.85%, 74.05% and77.09%, formulations F9 to F12 was found to be 67.94%, 70.18%, 73.92% and 74.49 % and for formulations respectively.

As the polymer concentration was increased the % drug loading decreased and % entrapment efficiency was increased due to increase in the viscosity of the solution.

This can be attributed to the permeation characteristics of each polymer used, that could facilitate the diffusion of part of entrapped drug to the surrounding medium during preparation of floating hollow microspheres.The values of % drug loading and % entrapment efficiency.

RESULT AND DISCUSSION

Standard curve data of cefuroxime axetil

Table 6.1: Standard curve data of cefuroxime axetil

S.no	Concentration (µg/ml)	Absorbance at 278nm
1	2	0.098
2	4	0.188
3	6	0.266
4	8	0.375
5	10	0.471
6	12	0.563

Calibration curve of cefuroxime axetil

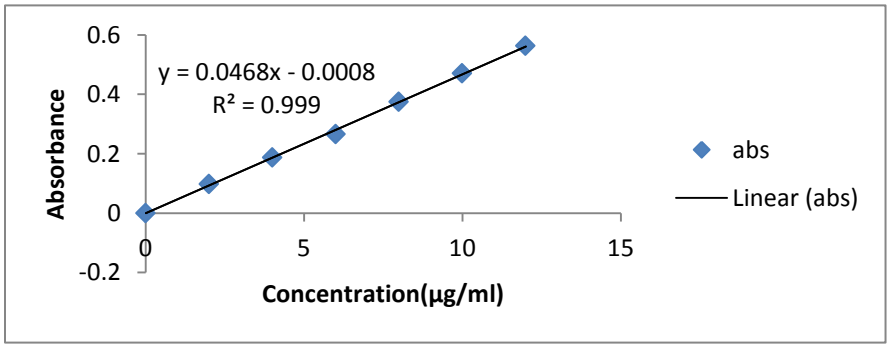
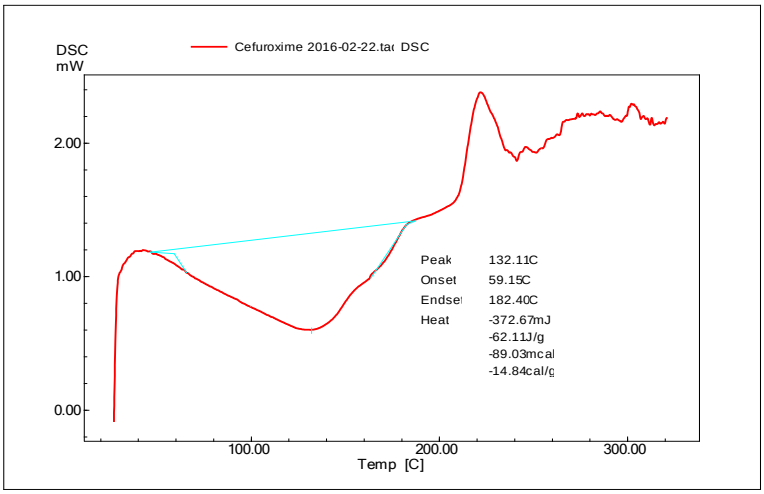
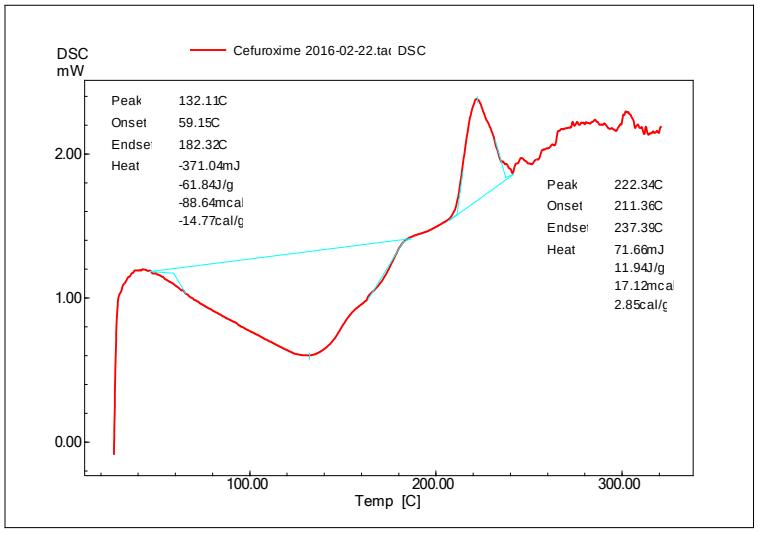


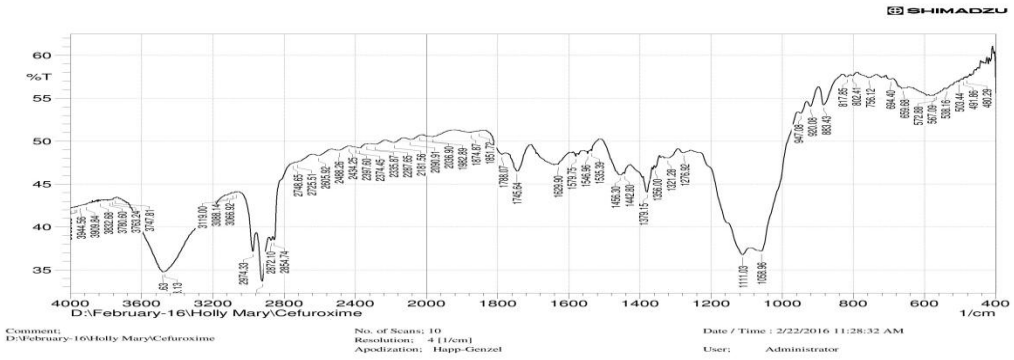
Figure: Calibration curve of cefuroxime axetil

Differential scanning calorimetry

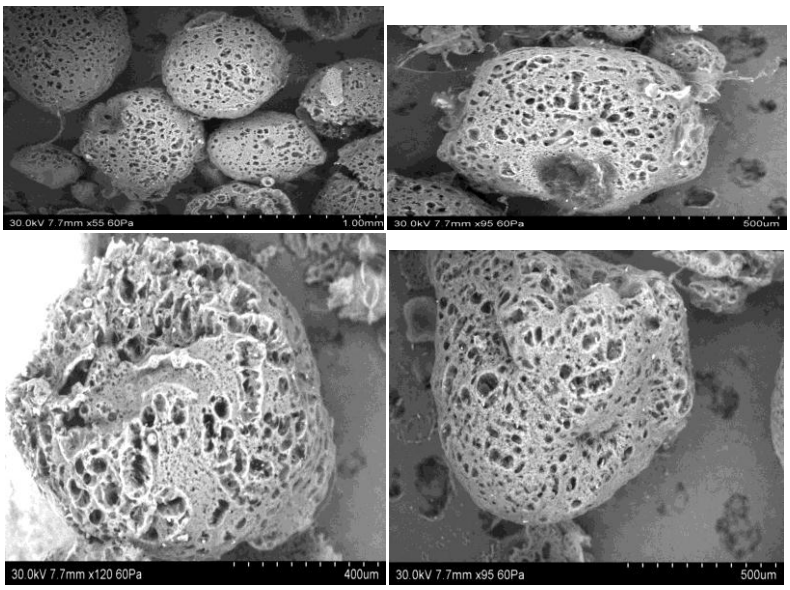




Fourier transforms infrared spectroscopy



Scanning electron microscopy



Particle size

Average Particle Size of Cefuroxime axetil Floating microspheres

Table 6.2: Particle size

Formulation code	Average Particle size(µm)
F1	130
F2	180
F3	220
F4	225
F5	100
F6	110
F7	120
F8	170
F9	70
F10	95
F11	100
F12	150

In vitro release data of Cefuroxime axetil

Cumulative % drug release (F1-F4)

Table 6.3 Cumulative % drug release (F1-F4)

TIME (hr)	F1	F2	F3	F4
0	0	0	0	0
0.5	16.78	21.55	28.94	34.26
1	27.96	34.99	40.89	48.37
1.5	36.62	44.72	51.80	60.32
2	43.64	48.70	56.84	69.62
4	50.97	58.95	65.92	75.25
6	54.82	60.45	71.85	83.45
8	59.47	66.35	74.76	85.55
10	64.28	73.55	80.76	88.98
12	68.06	78.24	84.18	92.67
14	73.10	82.08	90.05	99.34
16	77.83	89.77	92.10	101.10

Cumulative % drug release (F5-F8)

Table 6.4 Cumulative % drug release (F5-F8)

Time (hr)	F5	F6	F7	F8
0	0	0	0	0
0.5	12.65	20.55	30.56	37.36
1	21.54	35.76	44.49	52.21
1.5	30.72	41.64	53.23	61.45
2	39.74	46.84	58.14	67.78
4	45.65	52.95	60.52	69.85

6	50.72	63.25	75.15	80.35
8	56.67	64.50	76.80	89.55
10	68.28	75.65	80.36	89.48
12	74.06	80.24	89.18	94.67
14	79.40	85.25	90.05	95.34
16	84.39	90.77	99.10	106.50

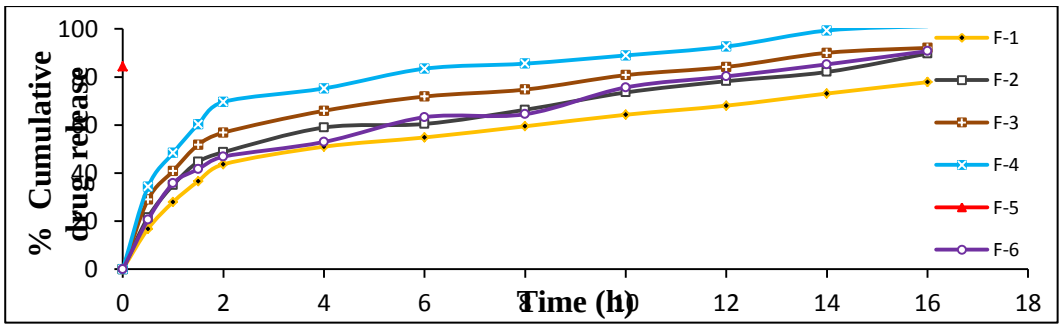


Figure: Cumulative % drug release (F5-F8)

Cumulative % drug release (F9-F12)

Table 6.5 Cumulative % drug release (F9-F12)

Time (hr)	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0
0.5	15.35	24.34	36.26	40.45
1	23.54	37.76	44.56	54.61
1.5	30.62	41.54	55.23	66.45
2	39.74	48.84	55.14	69.98
4	46.65	58.85	64.52	70.85
6	55.23	67.35	78.15	87.35
8	61.12	70.50	81.20	90.15
10	71.28	82.65	89.46	96.58
12	79.66	90.24	98.09	104.67
14	82.40	91.25	102.05	114.34
16	89.99	96.77	106.10	114.07

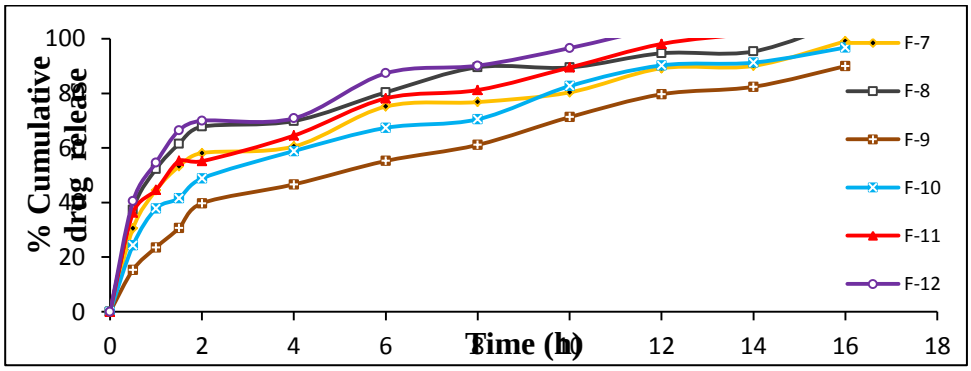


Figure: Cumulative % drug release (F9-F12)

In-vitro Buoyancy study

In-vitro buoyancy studies reveal that in spite of stirring the dissolution medium for 12hours about 77.95±2.06% – 91.13±1.07% of all formulations still continued to float without any apparent gelatin.

The floating behavior of the formulation showed in the fig 5.13 & 5.14 and the %buoyancy of all microspheres

Results of buoyancy (%) for Cefuroxime axetil floating microspheres

Table 6.6 Formulation code and % buoyancy

Formulation code	% Buoyancy
F1	80.91±1.09
F2	85.67±2.07
F3	87.36±1.21
F4	91.13±1.07
F5	78.89±1.65
F6	83.53±2.00
F7	86.31±2.09
F8	89.67±1.80
F9	77.95±2.06
F10	80.9±1.05
F11	85.54±1.52
F12	87.39±2.03

The microspheres prepared by using higher polymer concentrations shows lager particle size. So the microspheres having higher polymer concentrations were more buoyant than with lower polymer concentration.

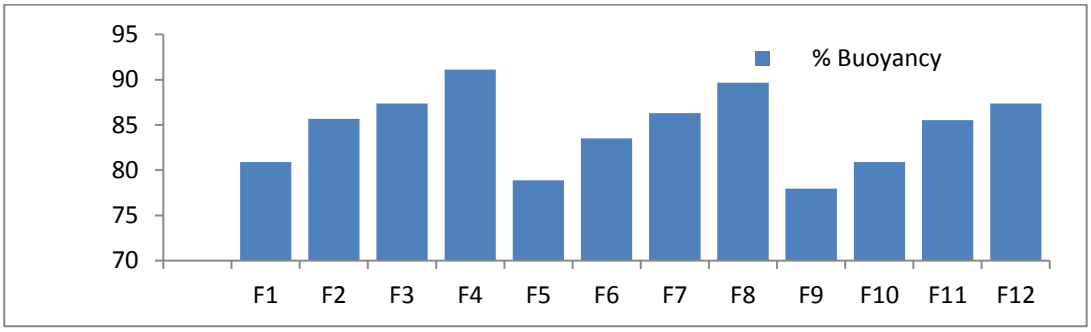


Figure: Comparison of percentage buoyancy of Cefuroxime axetil floating Microspheres

In vitro buoyancy of Cefuroxime axetil floating microspheres

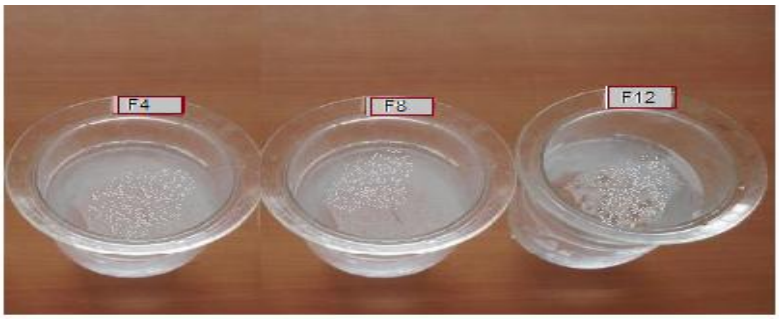


Figure: *In vitro* buoyancy of Cefuroxime axetil floating microspheres

Drug loading and Drug Entrapment of Cefuroxime axetil floating microspheres

Table 6.7 Drug loading and drug entrapment

Formulation code	Actual drug content(mg)	Theoretical drug content(mg)	Total weight of microspheres (mg)	% Drug Entrapment efficiency	% Drug loading
F1	13.139±0.05	20.83	50	63.08±0.25	26.27±0.10
F2	11.59±0.04	17.24	50	67.26±0.23	23.19±0.08
F3	10.22±0.01	14.70	50	69.52±0.06	20.44±0.02
F4	8.36±0.015	11.62	50	71.97±0.13	16.72±0.03
F5	14.326±0.02	20.83	50	68.77±0.09	28.65±0.04
F6	12.56±0.01	17.24	50	72.85±0.05	25.12±0.02
F7	10.88±0.015	14.70	50	74.05±0.10	21.77±0.03
F8	8.936±0.025	11.62	50	77.09±0.216	17.89±0.05
F9	14.15±0.04	20.83	50	67.94±0.19	28.30±0.08
F10	12.10±0.01	17.24	50	70.18±0.05	24.2±0.02
F11	10.426±0.015	14.70	50	73.92±0.10	20.85±0.03
F12	8.656±0.02	11.62	50	74.49±0.17	17.31±0.04

SUMMARY

The goal of any drug delivery system is to provide therapeutic amount of drug to the proper site in the body and also to achieve and maintain desired drug concentration. The specific site are targeted, combined with delivery at an optimal rate would not only improve the efficacy of a drug but would also reduce the possibility of unwanted toxic side effects, thus improving the therapeutic index. Microspheres possess several advantages over other targeted drug delivery systems like larger drug loading capacity, greater and controlled release over extend period of time. In the present study an attempt was made to formulate Cefuroxime axetil as micro particulate drug delivery system in order to localize drug at absorption site, enhances bioavailability, reduce dose, thereby improving patient compliance through sustained release. Cefuroxime axetil microspheres were formulated by using Hydroxy propyl methyl cellulose, Ethyl cellulose, Eudrgit RS 100, Eudragit RL 100 polymers. Solvent evaporation method was used for the preparation of cefuroxime axetil microspheres. Prior to formulation, preformulation studies were carried out in order to establish compatibility with drug and polymer by Infrared spectroscopy. Preformulation studies reveal that the drug cefuroxime axetil and polymers hydroxyl propyl methyl cellulose, ethyl cellulose, eudragit rs 100 and eudragit el 100 were satisfactorily compatible, without significance changes in the chemical nature of the drug.

CONCLUSION

It has been observed that the floating microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of detection of bimolecular interactions and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for targeting. In the present study a satisfactory attempt was made to formulate and evaluate Cefuroxime axetil microspheres with sustained release. Cefuroxime axetil microspheres were prepared using ethyl cellulose, hpmc and eudragit RL and RS100. Microspheres were evaluated for particle size, entrapment efficiency and drug load, in vitro drug release studies, scanning electron microscopy, differential scanning calorimetry, fourier transform infrared spectroscopy. In vitro data obtained for floating microspheres of cefuroxime axetil showed good incorporation efficiency, and prolonged drug release. Results from fourier transform infrared spectroscopy showed that cefuroxime axetil is stable in the matrices developed without undergoing any chemical changes. Differential scanning calorimetry studies indicated no chemical interaction between drug and polymers during

encapsulation process. In the present study gastro-retentive floating tablets of cefuroxime axetil were successfully prepared by solvent evaporation method using polymer HPMC and eudragit RS & RL 100. From the study it is observed that formulation F5-F8 was best in terms of drug release.

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