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FORMULATION AND EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Irfan Ahmed khan*[1] and Rachel Geevarghese[2]

[1]Department of Pharmaceutics, Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar-421 003, India.
[2]Head of Department of Pharmaceutics, Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar-421 003, India.

ABSTRACT

The aim of this research work was to formulate and evaluate the gastro retentive floating microspheres of Cefuroxime Axetil for the prolongation of gastric residence time. The microspheres were prepared by emulsion solvent diffusion-evaporation method. Based on Preliminary trials a 3^2 full factorial design was applied to optimize the formulation. An increasing concentration of Ethylcellulose and fixed concentration HPMC K100M was studied at three different levels arranged in 3^2 full factorial designs. The results of 3^2 full factorial design revealed that the concentration of Ethyl cellulose/ HPMC K100M (X1) and stirring speed (X2) significantly affected the particle size, drug entrapment efficiency, and percentage release after 12 h of microspheres. The best optimized batch of microspheres was compressed into tablet as final dosage form, and evaluated for hardness, friability , drug content, %floating study, %cumulative drug release study, and kinetic of drug release. The result of tablet formulation indicated that they were within pharmacopoeial limit. % cumulative drug release was 96.23% for 12 hours. Drug release data was best fitted into zero order kinetic with highest regression coefficient of 0.998.the drug release mechanism was found non fickian (anomalous transport).Stability study indicated that there was no change in formulation characteristics kept for 3 month at 40°C/75%RH.

Keywords: Cefuroxime Axetil, Ethyl Cellulose, Hydroxy propyl methyl cellulose, floating microspheres.

INTRODUCTION

Oral route of administration has been used the most for both conventional and novel drug delivery system. There are many obvious reasons for this which would include acceptance by the patient, ease of administration and flexibility in formulation. However pharmaceutical product design for oral delivery which are currently available in the market are immediate release or conventional release which maintain the drug concentration within the therapeutic effective range only even when administered several times a day this results in significant fluctuation in the drug level. This is because of several physiological difficulties such as inability to retain and locate the control drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. The ability to maintain the drug delivery system at a particular location for extended period of time has a great application for both local disease treatments as well as for systemic drug bioavailability [1,2]. Dosage form with prolonged gastric residence and controlled drug delivery are called as gastro retentive drug delivery systems. Thus, these dosage forms significantly extend the period of time over which the drug may be released in comparison to other CRDDS. The drugs which are unstable in the intestine and having short biological half life are more suitable for gastroretentive drug delivery system. Cefuroxime Axetil is a second generation cephalosporin antibiotic used in the treatment of upper and lower respiratory tract infection, otitis media, sepsis, urinary tract infection and uncomplicated gonorrhea [3,4]. Cefuroxime axetil is a prodrug developed to increase the oral absorption of the drug by attaching the ester group (axetil) with cefuroxime to increase the lipophilicity of drug. Even though the drug cefuroxime axetil has low oral bioavailability (37-52%) due to intestinal enzyme esterase,

Corresponding Author:- **Irfan Ahmed khan** Email: irfanfateh@gmail.com

Which hydrolyzes the ester group axetil. So the absorption efficiency of the drug get decreased which resulting reduced oral bioavailability. In order to increase the bioavailability of this prodrug, floating microspheres was formulated which avoid the entry of drug in to the intestine where mainly enzyme esterase present. And also the drug has very short half life (1-2 hrs.), so it's prescribed as twice or thrice daily. So this drug formulated as a sustained release microspheres in which ethyl cellulose and Hydroxy propyl methyl cellulose used as polymer [5].

MATERIALS AND METHODS

Cefuroxime axetil was obtained as a gift sample from Comed chemicals Pvt Ltd., Baroda. Ethyl cellulose and HPMC K100M was also obtained as a gift sample from Colorcon Asia pvt ltd. Dichloromethane, Ethanol and Tween-80 purchased from S.D fine chemicals, Mumbai. All other chemicals and reagents used were of analytical grade.

Preparation of Microspheres by solvent evaporation and diffusion method:

Preparation of preliminary trial batches

Weighed amount of Cefuroxime axetil and ethyl cellulose was dissolved in a mixture of dichloromethane and ethanol in the ratio of 1:1. This organic phase was added drop wise to the water containing a surfactant, at the same time the water was stirred at speed of 600 rpm. The drug and polymer were transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and diffusion. Microspheres were collected by filtration and washed with water and desiccated at room temperature for 24 hr [6].

Optimization of microspheres formulation using 3^2 Factorial design (2factors at 3levels)

Based on preliminary trials, a 2-factor 3-level full factorial design was employed to design controlled release microspheres of Cefuroxime Axetil. The two independent formulation variables analyzed during the study were the ratio of drug/Ethyl cellulose/Hydroxy propyl methyl cellulose (*X*1) (1: 1.2: 0.4), (1: 1.6: 0.4), (1: 2.0: 0.4) and Stirring speed (400,600,800). All other independent variables were kept constant) throughout the process. Dependent variables investigated were the %Yield (Y1), particle size(Y2), % Entrapment efficiency (Y3), %Controlled drug release (Y4) and %Floating ability (Y5) [7].

Preparation of floating microspheres by spray drying method

The drug: polymer ratio which gave best results by Emulsion Solvent Evaporation method was also subjected to spray drying. The same organic solvent Composition was used for drug and polymer i.e. Dichloromethane and ethanol. The dispersion was subjected to high-speed homogenization. This dispersion was then atomized in a stream of hot air using 0.7mm nozzle. The atomization lead to the formation of small droplets or the fine mist from which the solvent evaporated instantaneously leading to formation of microspheres in a size range of 1-100µm. Micro particles were separated from the hot air by means of the cyclone separator while the trace of solvent was removed by vacuum drying. Spray drying condition of inlet temperature, pumping flow, and the spray air pressure were set at 70 ◦C, 2ml/min and 3 kg/cm2, respectively [8,9].

Preparation of tablet from microspheres by direct compression

Best batch of optimized formulations (D5) prepared by solvent evaporation diffusion method were directly compressed with super disintegrant Primogel (sodium starch glycolate) and calcium stearate as lubricant and Anti adherent using capsule shape tablet punch and die by Single station tablet punch Machine.

EVALUATION OF MICROSPHERES

Micromeritic Properties [10]

Particle size analysis by Optical microscope:

Particle size of microspheres was determined in terms of average diameter by optical microscopic method using stage and eye piece micrometer.

Flow characteristics

Bulk density:

Bulk density is the ratio of the weight of powder to the volume it occupies. It express in g/ml

Tapped density:

Tapped density is the ratio of Mass of microspheres to the volume of microspheres after tapping.

Angle of Repose:

Angle of repose was determined by using funnel method using the following equation

$\tan \theta = h/r$

Where h and r are the height and radius of the powder respectively.

Hausner's Ratio:

Hausner's Ratio = Tapped Density/ Bulk Density

Compressibility Index:

Compressibility index was determined according to Carr's index:

Carr's index = (Tapped Density – Bulk Density)/ Tapped Density X 100

Physical characterization of Microspheres [11]

Percentage (%) Yield: The prepared microspheres were collected and accurately weighed the weight of prepared

microspheres was divided by total amount of all excipient and drug used in the preparation of microspheres which gives total percentage yield of microspheres

Drug entrapment efficiency: To determine the drug entrapment efficiency, weighed amount of microspheres were thoroughly crushed and dissolved in methanol then filtered it. The filtered solution was analyzed for drug content after suitable dilution by UV spectrophotometry at 281nm.

Floating behavior of microspheres: To assess the floating behavior, weighed amount of microspheres were spread over the surface of a USP24 type-2 paddle (Electrolab, India) dissolution apparatus filled with 900ml of 0.1 N Hydrochloric acid. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floated and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed.

Morphological study using Scanning electron microscopy: Scanning electron microscopy (SEM) was performed to characterize the surface morphology of optimized batch of microspheres of Cefuroxime Axetil. Dried microspheres were coated with gold foil under an argon atmosphere in a gold coating unit and focused under SEM.

***In-vitro* drug release study**: Weighed amount of Cefuroxime Axetil loaded microspheres was placed in USP24 paddle apparatus (Electrolab, India) using 900ml of 0.1N hydrochloric acid as dissolution medium. 0.05% Sodium lauryl sulphate was added to dissolution medium to mimic the surfactant action of bile salts and phospholipids. Samples were withdrawn at a predetermined interval. The withdrawn samples were suitably diluted and analyzed by UV spectrometry at 281 nm.

EVALUATION OF TABLET [13,14]

i. Weight Variation:

Twenty tablets were selected randomly and the average weight was determined. The individual tablet was weighed and was compared with the average weight.

ii. Thickness

Ten tablets were evaluated for thickness using Vernier Caliper (Aerospace).

iii.Disintegration Time

The disintegration time was checked using Disintegration Apparatus (DBK Instruments).

iv. Hardness

Hardness for ten tablets was tested using Monsanto Hardness tester.

v. Friability:

Tablets samples were weighed accurately and placed in friabilator (Roche friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The tablets were then dusted and reweighed. It was calculated using the following equation:

% Friability = (Initial weight – Final Weight)/ Initial Weight X 100.

Uniformity of content: Ten Tablets were weighed and powdered and powder equivalent to 100mg of Cefuroxime Axetil was dissolve in methanol and finally volume make up by 0.1N HCL. The absorbance was measured at 281nm by using 0.1N hydrochloric acid as blank.

vi. *In-vitro* drug release study: Gastro retentive tablet was placed in USP24 paddle apparatus (Electrolab, India) containing 900ml of 0.1N hydrochloric acid, 0.05% Sodium lauryl Sulphate was added to dissolution medium to mimic the stomach containing natural surfactant like bile salts and phospholipids. Samples were withdrawn at a predetermined interval. The withdrawn samples were suitably diluted and analyzed by UV spectrometry at 281 nm.

vii. Kinetic of drug release:

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models.

***viii. In vitro* antibacterial activity [15]**

Antimicrobial activity of Cefuroxime Axetil, formulation D5 tablet was evaluated. Aliquots collected from the *in vitro* release study of formulation D5 were tested against *Escherichia coli* and Staphylococcus Aureus the most commonly found organism in patients with bacterial infections and urinary tract infections. CA (pure drug) at different concentrations in simulated gastric fluid (4, 8, 16 and 32 µg/mL) was also tested against the same strains. Molten agar media was transferred to sterilized petri dishes and allowed to solidify. The plates were swabbed with the culture of the microorganism. Wells equidistant from one another were made in the solidified medium using a sterilized well borer. The 1 mL aliquots collected from the *in vitro* drug release from dissolution of formulation D5 tablet were filtered through a 0.45 µm nylon filter and carefully transferred into the wells. Samples were allowed to diffuse for 2 h at room temperature. The plates were then incubated for 48 h at 37±0.5 °C. The diameter (mm) of zone of growth

inhibition surrounding each agar well was measured using a caliper.

Stability study [16].

Stability study of the microspheres tableted dosage form was carried out at 40^0C/75%RH.for the period of 90 days. Samples were evaluated at the time interval of 0, 1, 2, 3 month.

RESULTS AND DISCUSSION

Drug polymer interaction study using FTIR Spectroscopy

Cefuroxime Axetil was characterized by FTIR Spectroscopy.IR Spectrum of pure Cefuroxime Axetil was in concordant with the reference spectrum of Cefuroxime Axetil as per I.P 2007.

Physical mixture of drug and polymer (CA+EC), (CA+HPMC), (CA+EC+HPMC), was characterized by FTIR Spectral analysis for any physical as well as chemical alteration of the drug From the result, it was concluded that there was no interference in the functional group as the principle peak of Cefuroxime Axetil were unaltered in the drug polymer physical mixtures, indicating they were compatible chemically. IR spectra of prepared microspheres and gastroretentive tablet was also performed to check any incompatibility of drug with solvent and process parameter.it was concluded that there was no alteration in the characteristic peak of pure drug of Cefuroxime Axetil.

IR spectra of pure drug shown in figure no. 1.

Functional group region in the FT-IR spectra compared in Table no.7.

Solubility study

Selection of common solvent is very important for microsphere preparation. A mixture of ethanol and dichloromethane in (1:1) ratio was found suitable for the preparation of microsphere. During microspheres preparation ethanol diffused into water and Dichloromethane evaporated. Combination was used since HPMC is not soluble in dichloromethane and non polar solvent dichloromethane evaporates rapidly leading to fast precipitation of polymer solution at the time of mixing resulting in formation of fiber like structure.

Selection of matrix forming polymer

Solvent evaporation diffusion technique was used to prepare the floating microspheres. In preliminary trials an attempt was made to find out good matrix forming polymer for Cefuroxime Axetil with good microspheres characteristics. From the evaluation of Preliminary trials batches it was concluded that the microspheres prepared by using Ethyl cellulose with 0.2% sodium lauryl sulphate shows good microspheres characteristics (%yield, particle size, %Controlled release and floating property). Ethyl cellulose and SLS as a surfactant was selected for the further study to optimize the formulation using using 3^2 full factorial designs.

Table No.19 shows the result of trial batches.

RESULT OF OPTIMISED BATCH

The floating microspheres of Cefuroxime Axetil were prepared and optimized using the 3^2 factorial designs. HPMC K100M was selected in combination with ethyl cellulose to increase the drug release from microspheres. The results of a 3^2 full factorial design revealed that the concentration of polymers (X1) and stirring speed (X2) significantly affected the dependent variables such as drug entrapment efficiency, drug release and particle size of microspheres. Evaluation of formulations, indicated that the formulation D5 (CA:EC: HPMC K100M (1 : 1.6 : 0.4) and stirring speed: 600rpm) fulfilled maximum requisites because of better drug entrapment efficiency, sustained release of the drug optimum particle size, %Yield, and %buoyancy.

The result of the formulations is shown in Table No.21.

Micrometric properties

The result of all nine formulation of optimized batch using 3^2 full factorial design are shown in table no 20, which were evaluated for various parameters such as bulk density tapped density, Hausner's ratio, Carr's compressibility index, and angle of repose.

Hausner's Ratio

The value of Hausner's ratio for formulation D1 to D9 was below 1.25 which indicates good flow property.

Carr's Compressibility Index

The Carr's compressibility index for formulation D1 to D9 was found in the range of 4-12which indicates good flow characteristics.

Angle of Repose

The value of angle of repose for formulation D1 to D9 was found below 30^o which indicates good flow property.

Surface morphology using scanning electron microscope

SEM Photograph of sample revealed that the floating microsphere was smooth and spherical in shape and shows some pores which may be due to escape of volatile solvent during formulation.

Fig No. 2, 3 shows the surface morphology of microspheres.

RESPONSE SURFACE METHADOLOGY

Response surface methodology was used to represent the effect of independent variable, drug to polymer to polymer ratio and stirring speed on dependent variable such as %yield, particle size, %Entrapment

efficiency, %Controlled release and %floating ability of microspheres prepared by using 3^2 full factorial design.

% Yield

Effect of variable X1 & X2 on %yield (Y1) can be explained with response curve. Increase in polymer concentration (X1) results in increased % yield Y1 at same rpm this is because as there is an increase in polymer concentration which result fast formation of microspheres and less loss of material during process. Increase in RPM (X2) did not show any significant increase in response (Y1).

Fig No. 4 shows the %yield Response surface plot

Particle Size

Increase in polymer concentration (X1) results in increased particle size Y2 at same rpm due to availability of increased amount of polymer to form microspheres. Increase in RPM (X2) showed the decrease in response (Y2) this is because at higher level (1) RPM 800 reduced the particle size.

Fig No. 5 shows the Particle size Response surface plot

% Entrapment Efficiency

Increase in polymer concentration (X1) results in increased %Entrapment Y3 at same rpm. This is because as there is an increase in polymer concentration sufficient amount of polymer is present to entrap the drug, thus the entrapment efficiency is increased. Increase in RPM (X2) showed the decrease in response (Y3) because increase in rpm causes decrease in particle size which causes decreases in entrapment efficiency.

Fig No. 6 shows the %Entrapment efficiency Response surface plot

% Controlled Drug Release

Increase in polymer concentration (X1) results in decrease in %drug release Y4 at same rpm. This is because as there is an increase in polymer concentration increases the particle size which increases the path length for the molecule to travel to surface of microsphere for release. Increase in RPM (X2) showed decrease in particle size which causes increase in drug release Y4. Because release of drug from smaller particle is faster than larger particle as the area available is more for drug release.

Fig No.7 shows the %Controlled drug release Response surface plot.

% Floating Ability

The surface response plot showed decrease in response Y5 (% floating capacity) as X2 (RPM) was increased from lower level to higher level. While % floating capacity increased with increase in polymer to drug ratio. This is because with increase in polymer there is an increase in particle size which leads to better floating capacity at same RPM. For other two levels same effect was observed. This can be further confirmed by equation which showed negative sign for variable X2 and positive sign for variable X1 which indicated that increase in X2(rpm) gives decrease in response on increase of X1(polymer concentration.) there is an increase in response.

Fig No.8 shows the %floating ability Response surface plot.

Result of Microspheres Prepared By Spray Dryer

Microspheres prepared by spray drying method shows very less practical yield and the cumulative percentage drug release was also fast 100%release occur in less than 8 hours. Because the particle size obtained was very small less than 10µm. Hence it is not considered for the final dosage form.

Table no.11 shows the result of microspheres prepared by spray drying method.

Result of Tablet Formulation

Formulation batch which shows good entrapment efficiency low particle size, and good release profile was selected for compression into tablet for final dosage form using Capsule shape tablet punch and die. From the result it was concluded that the batch D5 had a good balance in all these properties. Hence it was compressed in to capsule shape tablet and evaluated.

Table No.23 shows the result of tablet formulation

Kinetic of Drug Release

In-vitro dissolution data of final dosage form (tablet) was applied to various kinetic models to find the mechanism of drug release. The regression co-efficient determination indicated that the release data was best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism. The diffusion exponent 'n' values of KorsmeyerPeppas model was found to be 0.61 for floating microspheres prepared with HPMC K100 M and EC indicating Non-Fickian (anomalous transport) refers to coupling of fickian diffusion and polymer relaxation.

Fig No. 9 to 13 shows the plot of kinetic of drug release.

The slopes and the regression co-efficient R^2 listed in Table 25.

Antimicrobial activity

Antimicrobial activity of formulation was done (Table 14). Zone of inhibition for gastroretentive preparation and pure drug (standard) was measured. It was found to be comparable to the standard (fig. 14 and 15).

Result of Stability Study

Stability study of the gastro retentive tablet carried out at 40^0C/75%RH.for the period of 90 days. Samples were evaluated at the time interval of 0, 1, 2, 3 month for hardness, drug content, %CDR, %FA, and FTIR

Spectroscopy, etc. The result of stability study reveals that there is no change in physical and chemical properties of the prepared tableted microspheres

Fig No.16 to18 shows FTIR Spectra of tablet at different time interval. Table 27 shows the result of stability study of gastro retentive tablet.

Fig. 1. FTIR Spectra of Cefuroxime Axetil

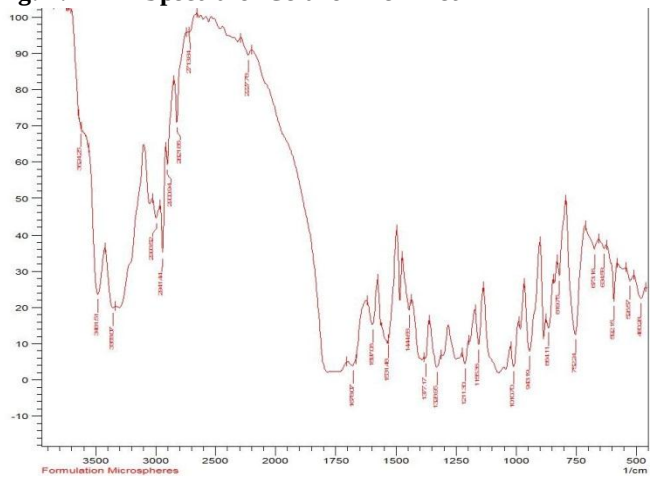

Fig 2. Surface morphology of microsphere of batch D5 using scanning electron microscope.

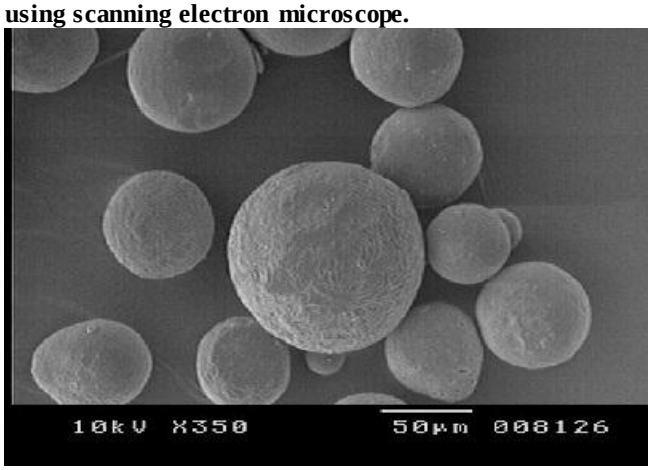

Fig. 3. Surface morphology of microsphere of batch D5 showing pores

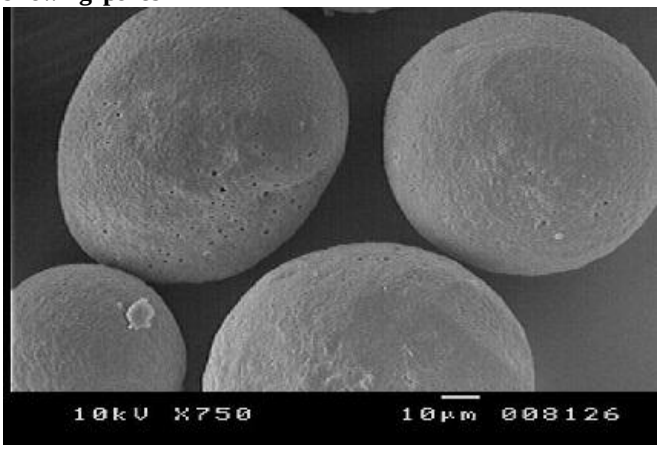

Fig. 4. Response surface plot showing influence of RPM and polymer conc. on the % yield of Microspheres.

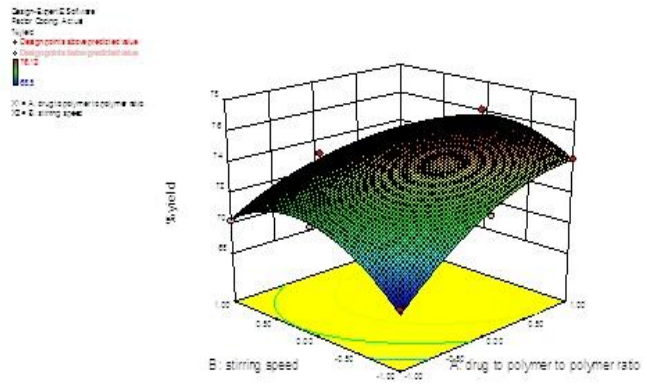

Fig. 5. Response surface plot showing influence of RPM and polymer conc. on the Particle size of Microspheres

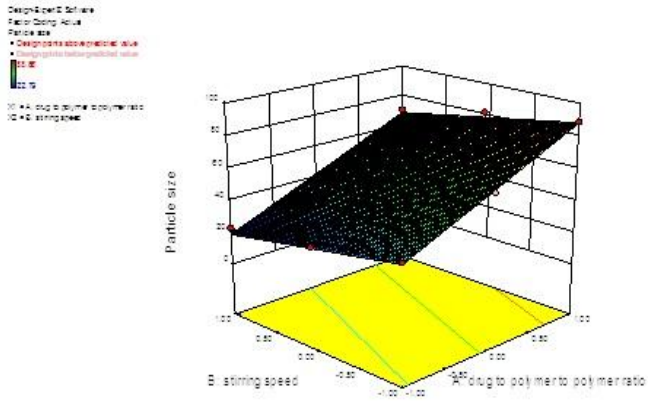

Fig. 6. Response surface plot showing influence of RPM and polymer conc. on the % Entrapment Efficiency of Microspheres

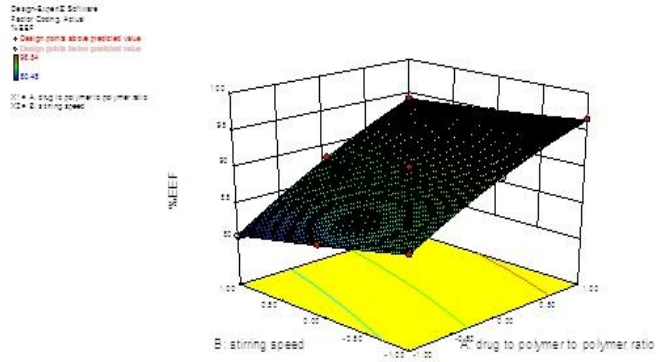

Fig 7. Response surface plot showing influence of RPM and polymer conc. on the % cumulative drug release ofMicrospheres

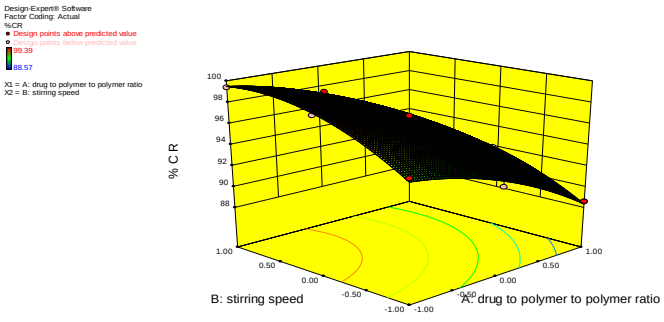

Fig 8. Response surface plot showing influence of RPM and polymer conc. on the % Floating ability of Microspheres

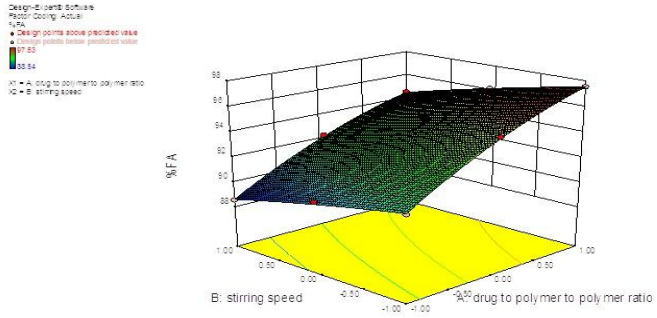

Fig. 9. Plot of cmulative % drug release vs time (zero order) for tablet formulation

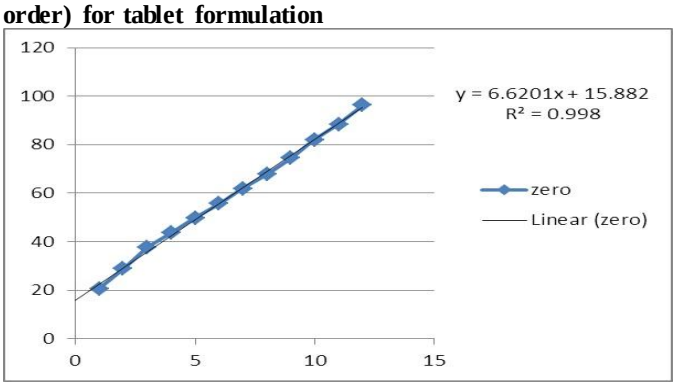

Fig. 10. Plot of log cmulative % drug release vs time (First order) for tablet formulation

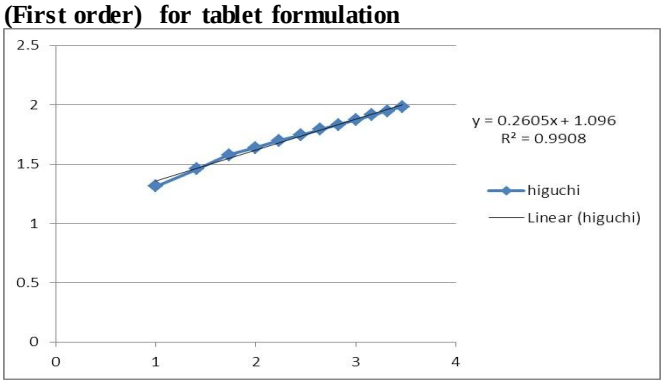

Fig. 11. Plot of cmulative % drug release vs square root of time (Higuchi matrix) for tablet formulation

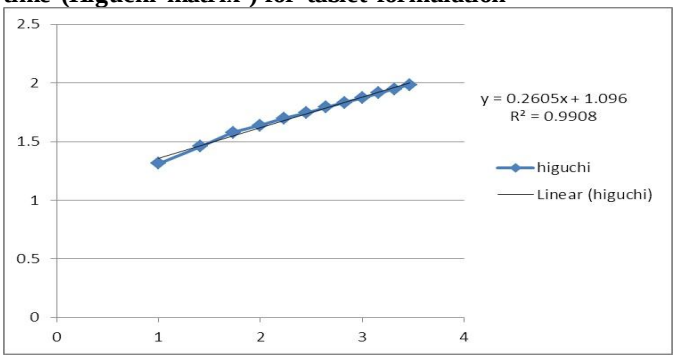

Fig. 12. Plot of log cmulative % drug release vs log time (peppas model) for tablet formulation

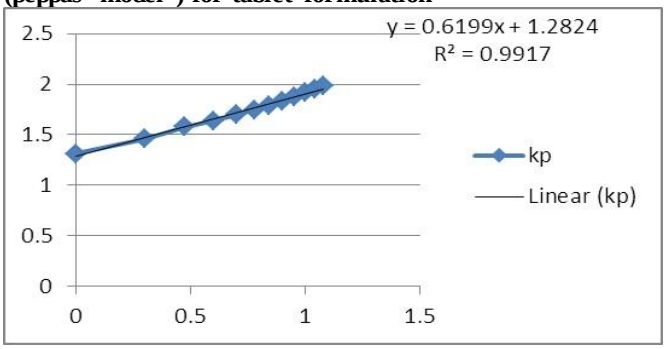

Fig 13. Plot of cube root of cmulative % drug release vs time (Hixson Crowell model) for tablet formulation

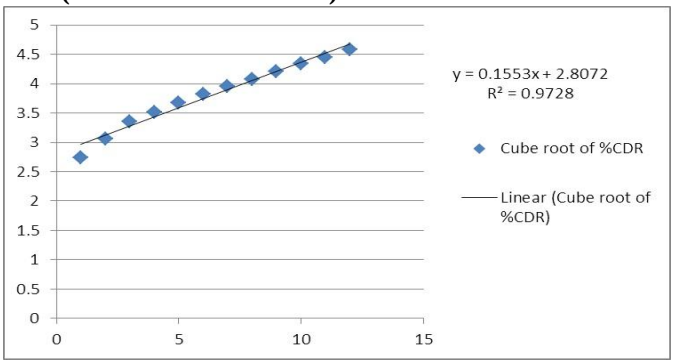

Fig 14. Antimicrobial activity Cefuroxime Axetil formulation on *S.aureus*

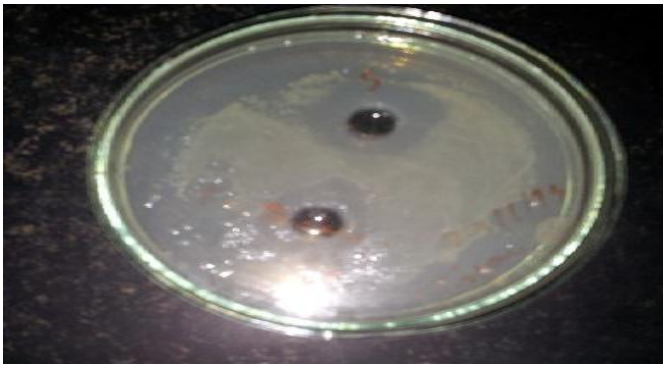

Fig 15. Antimicrobial activity cefuroxime axetil formulation on E.coli

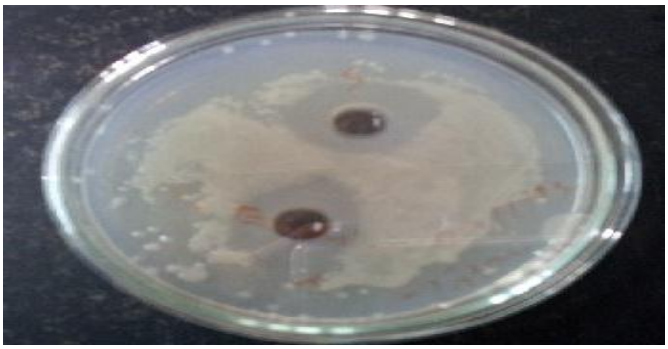

Fig 16. FTIR Spectra of final formulation (tablet) at 1st Month

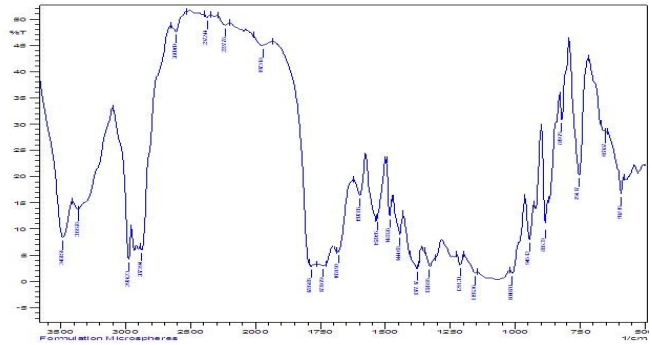

Fig 17. FTIR Spectra of final formulation (tablet) at 2nd Month

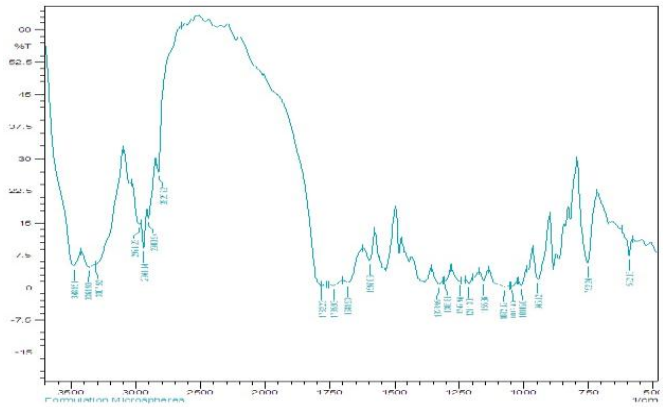

Fig 18. FTIR Spectra of final formulation (tablet) at 3rd Month

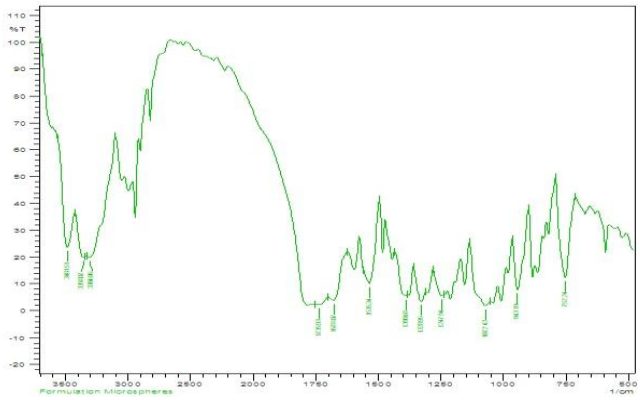

Table 1. Preparation of Preliminary Trial Batches

Formulation code	A1	A2	A3	B1	B2	B3	C1	C2	C3
Drug to polymer ratio in (mg)	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
Internal phase(organic solvent) in ml	16	16	16	16	16	16	16	16	16
External phase(aqueous phase) in ml	100	100	100	100	100	100	100	100	100
Surfactant (Tween 80)	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.2%	0.2%	0.2%
stirring speed in rpm	600	600	600	600	600	600	600	600	600
Stirring time in min	45	45	45	45	45	45	45	45	45

For the formulation batches A1-A3 Eudragit RS 100 and 0.01% Tween was used.
For the formulation batches B1-B3 Ethyl Cellulose and 0.01% Tween was used.
For the formulation batches C1-C3 Ethyl Cellulose and 0.2% Sodium lauryl sulphate was used.

Table 2. Dependent and Independent Variables of Factorial Design

Independent variables	Dependent variables
X1=Drug : Polymer : Polymer (mg)	Y1 = % Yield
X2 =Stirring Speed in rpm	Y2 = Microsphere size
	Y3 = % Entrapment efficiency
	Y4 = % drug release after 12 hrs.
	Y5 = % Floating capacity

Table 3. Coded Value of Independent Variables

Variable levels	Low (-1)	Medium(0)	High (+1)
CA+EC+HPMC (X1) (Drug : Polymer)	250+300+100 (1 : 1.2 : 0.4)	250+400+100 (1 : 1.6 : 0.4)	250+500+100 (1 : 2.0 : 0.4)
Stirring Speed (X2)	400	600	800

Table 4. Formulation of Microspheres of Cefuroxime Axetil Using 3^2 Factorial Design: D1-D9

Sr No.	Formulation code	Drug (Cefuroxime Axetil) mg	Polymers (mg)		Stirring speed (rpm)
			Ethyl cellulose	HPMC K 100 M	
1	D1	250	300	100	400
2	D2	250	300	100	600
3	D3	250	300	100	800
4	D4	250	400	100	400
5	D5	250	400	100	600
6	D6	250	400	100	800
7	D7	250	500	100	400
8	D8	250	500	100	600
9	D9	250	500	100	800

For all the formulation batches 0.2% w/v SLS was used.
For all the formulation batches inner phase was dichloromethane + ethanol 16 ml (1:1)
For all the formulation batches stirring time was 45 minute.

Table 5. Parameters For The Preparation of Microspheres by Spray Drying Method

Parameter	Condition
Nozzle size	0.7mm
Inlet Temperature	70^oC
Outlet Temperature	40^oC
Feed flow rate	2ml/min
Spray air pressure	$3kg/cm^2$

Table 6. Preparation of Gastro retentive Tablet

Sr .No	Ingredient	Formula for one tablet (700mg)
1	Microspheres	660mg
2	Sodium starch glycolate	28mg
3	Calcium stearate	12mg

Table 7. Drug Polymer Compatibility Study Using FTIR-Spectroscopy

FunctionalGroup	C-S Stretch	C-N stretch	C=0 Carbonyl	N-H of amide	C-C Stretch
Referencestandard(limit)	705-570	1090-1020	1760-1670	3500-3300	1300-700
Drug (CA)	592.15	943.19	1678.07	3481.51	752.14
Drug +EC	592.15	943.19	1683.86	3481.51	752.14
Drug +HPMC K100 M	592.15	752.14	1681.93	3481.51	752.14
drug +EC+HPMC	592.15	945.12	1681.93	1681.93	752.24
Microspheres	592.15	754.17,	1681.93	3481.51	754.17
Tablet	592.15	754.17	1681.93	3481.51	754.17

Table 8. Results of Preliminary Trial Batches

Evaluation parameter	Formulations								
Batch Code	**A1**	**A2**	**A3**	**B1**	**B2**	**B3**	**C1**	**C2**	**C3**
% Yield	60.32	63.54	65.89	71.29	73.2	75.35	76.89	79.23	81.54
Particle Size in µm	201.34	225.13	245.23	195.83	220.83	237.5	125.30	162.5	187.5
% EEF	82.35	85.42	87.54	92.59	95.23	97.12	92.64	96.54	97.31
% CDR	72.21	70.12	67.22	83.2	79.54	76.52	87.35	85.23	83.13
% FA	90.12	92.2	93.54	94.25	96.23	97.52	92.12	93.4	95.24

Table 9. Micromeritic Properties of Optimized Batch

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	Caar's index (%)	Angle of repose(θ)
D1	0.133	0.139	1.04	4.31	28.49
D2	0.125	0.135	1.08	7.40	29.74

D3	0.122	0.131	1.07	6.87	29.35
D4	0.148	0.154	1.04	3.89	28.07
D5	0.135	0.150	1.11	10	26.56
D6	0.128	0.145	1.12	11.7	24.67
D7	0.151	0.165	1.09	8.48	24.30
D8	0.144	0.161	1.11	11.80	26.56
D9	0.140	0.157	1.12	10.82	27.29

Table 10. Results of Optimized Batches

Evaluation Parameter	**Formulations**								
Batch Code	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**
% YIELD	68.5	71.6	70.2	72.30	75.30	73.13	74.2	76.12	72.7
Particle Size in µm	39.8	29.7	22.79	61.66	50.20	38.20	88.66	81.54	70.56
% EEF	85.85	83.5	80.45	91.92	90.07	88.37	96.54	95.07	94.24
% CDR	95.12	98.4	99.39	92.21	96.79	97.43	88.57	91.14	92.32
% FA	91.31	90.9	88.54	95.18	93.58	92.24	97.53	96.12	94.52

Table 11. Result of Microspheres Prepared by Spray Drying Method (D5 Batch)

Evaluation parameter	**Batch D5**
% yield	25.34%
Particle size in µm	6.25
% EEF	90.23
% FA	95.34%
% CDR	100 (<8 hours)

Table 12. Result of Gastro Retentive Tablet

Evaluation parameter	**Result**
1. Weight Variation	1.75%
2. Thickness	5.0mm
3. Disintegration time	115sec
4. Hardness	4.4kg/cm^2
5. Drug content	98.90%
6. Friability	0.56%
7.%CDR	96.23% (12hours)
8.%FA	93.12%

Table 13. Kinetic of Drug Release Data of Gastro Retentive Tablet

Time in hours	**Square root of time**	**Log of time**	**% CDR**	**Log of % CDR**	**Cube root of % CDR**
1	1	0	20.57	1.3132	2.7457
2	1.4142	0.301	28.79	1.4592	3.0648
3	1.732	0.4771	37.67	1.5759	3.3522
4	2	0.602	43.56	1.639	3.5185
5	2.236	0.6989	49.85	1.6976	3.6803
6	2.4494	0.7781	55.65	1.7454	3.8178
7	2.6457	0.845	61.97	1.7921	3.9572
8	2.8284	0.903	67.84	1.8314	4.0784
9	3	0.9542	74.54	1.8723	4.2085
10	3.162	1	81.95	1.9135	4.3435
11	3.3166	1.0413	88.34	1.9461	4.4536
12	3.4641	1.0791	96.23	1.9833	4.5825

Table 14. Result of Kinetic of Drug Release

Batch	Zero order	First order	Higuchi	Korsmeyerpeppas	n-value of kp	Hixson-Crowell
Tablet (D5)	0.998	0.9419	0.9908	0.9917	0.6199	0.9728

Table 15. Results of Antimicrobial Study

Microorganism	Zone of inhibition (mm)	Interpretation
Escherichia coli ATCC 25922	24	Susceptible
Staphylococcus aureus ATCC 25923	28	Susceptible

Table 16. Results of Stability Study Of Gastro retentive Tablet

Time in month	Hardness	Drug content	% CDR	% FA	Colour and Appearance
0	4.4kg/cm^2	98.90%	96.23%	92.64%	Off white
1	4.3kg/ cm^2	98.56%	96.13%	92.45%	Off white
2	4.3kg/ cm^2	98.34%	96.03%	91.89%	Off white
3	4.3kg/ cm^2	98.21%	95.87%	91.56%	Off white

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