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FORMULATION AND EVALUATION OF RECONSTITUTABLE SUSPENSION CONTAINING CEFIXIME TRIHYDRATE LOADED MICROSPHERES

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Keywords:

Cefixime trihydrate; Controlled release, Taste Masking; Microspheres

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ABSTRACT

Cefixime trihydrate is a 3rd generation broad spectrum β- lactam cephalosporin class of antibiotic administered orally in pediatric and adult patients and is extremely bitter in taste. Controlled release and bitter taste masking are the major challenges for better patient compliance particularly in an antibiotic treatment where dose and duration is important. Among the various techniques available for controlled release, microencapsulation is a useful technique as it has significant advantages over the other techniques. Also a polymer used provides protection to active moiety thereby increasing its stability. The oral route of administration is the most important route of administering drugs for systemic effects. Reconstitutable suspensions necessitate water to prior for mixing. Controlled release (CR) suspensions aimed at controlling the rate of release by maintaining desire drug levels in the blood for long duration of time. The most popular dosage forms beings tablets and capsules, but one major drawback of the dosage forms however is the difficulty to swallow for children and the patients who have swallowing disorder. The scenario of drug delivery is rapidly changing; conventional dosage forms are being replaced by new DDS. A reconstitutable suspension can offer several advantages such as maintenance of the chemical stability of the active compounds until reconstitution at the start of treatment. The same suspension can be easily administered to children of different ages by adapting the volume to swallow.

INTRODUCTION

The oral route of administration is the most important method of administering drugs for systemic effects. . It is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process The most popular dosage forms beings tablets and capsules, but one important drawback of the dosage forms however is the difficulty to swallow especially when a dosage form is developed for children. So the major drawback is that there is a problem in swallowing a tablets or capsules when it is given to children. So it is necessity to develop another dosage form for children. One best option of such tablets and capsules is dry suspentions form of that respective drug. The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. [(2)]

Cefixime Trihydrate is an oral 3rd generation cephalosporin antibiotic. It is extremely bitter in taste. It is active against most Gram positive and Gram negative organisms and it is useful in the treatment of uncomplicated urinary tract infections, otitis media, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, uncomplicated gonorrhea.

Microencapsulation of a drug has been suggested to control drug release and to reduce or eliminate gastrointestinal tract irritation · Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules.[(1)]

Advantages of microspheres

- Particle size reduction for enhancing solubility of the poorly soluble drug.
- provide constant and prolonged therapeutic effect.
- provide constant drug concentration in blood there by increasing patent compliance,
- Decrease dose and toxicity.
- Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
- Reduce the dosing frequency and thereby improve the patient compliance
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

- Microsphere morphology allows a controllable variability in degradation and drug release.
- Convert liquid to solid form & to mask the bitter taste.
- Protects the GIT from irritant effects of the drug.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Controlled release delivery biodegradable microspheres are used to control drug release rates
- Thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

The incorporation of microspheres as a dispersed phase in a suspension has been proposed earlier since these systems may spread out more uniformly in the gastrointestinal tract, thereby causing a reduction in local irritation when compared to a single-unit dosage form. The formulation of controlled release suspensions, however, presents a significant challenge to pharmaceutical scientists due to the risk of drug leaching to the suspending medium during storage. A reconstitutable suspension can offer several advantages such as maintenance of the chemical stability of the active compounds until reconstitution at the start of treatment. The same suspension can be easily administered to children of different ages by adapting the volume to swallow.

MATERIALS AND METHODS

List of Raw materials with name of supplier

Sl.No.	NAME OF INGREDIENTS	COMPANY NAME
1	Cefixime trihydrate	SANCE Laboratories Pvt .Ltd.
2	EudrajitRL100	Chemdyes corporation, Rajkot
3	Xanthan gum	Nice chemicals , Cochin
4	Citric acid	Nice chemicals , Cochin
5	Magnesium stearate	Nice chemicals , Cochin
6	Sucrose	Nice chemicals , Cochin
7	Ethanol	Nice chemicals , Cochin
8	Acetone	Nice chemicals , Cochin
9	n-hexane	Nice chemicals , Cochin

List of Equipment with company name

SL. No	INSTURMENTS	COMPANY NAME
1	UV-Spectrophotometer	Shimadzu 2401/PC Japan
2	Dissolution testing apparatus	Shimadzu 2401/PC Japan
3	Magnetic stirrer	REMI, Cochin
4	Digital weighing balances	Shimadzu AUX220
5	Digital pH Meter	Microtonics, Model M-19
6	Brook field viscometer	Startech lab, Hyderabad
7	FTIR	Jascu 4100
8	Mechanical stirrer	KEMI,Kerala
9	SEM	JEOL JSM6390
10	Melting point	Macro Scientific Works

FORMULATION OF CEFIXIME TRIHYDRATE MICROSPHERES

Cefixime Trihydrate microspheres were prepared based on solvent evaporation technique. Different batches of CT microspheres, F1 to F9 were prepared by varying the concentration of Eudragit RL100 . Different amounts of Eudragit RL100 was dissolved in 25 ml acetone separately by using a magnetic stirrer. Pure cefixime trihydrate (1g previously dissolved in 10 ml methanol) and magnesium stearate [100mg] were dispersed in the polymer solution. The resulting dispersion was then poured into 1000ml beaker, containing the mixture of 270 ml liquid paraffin light and 30ml n-hexane, while stirring. A mechanical stirrer with a blade [4 cm diameter] was used. Stirring (at 500-700 rpm) was continued for 3h, until acetone evaporated completely. After evaporation of acetone, the microspheres formed were filtered using Whatman no.1 filter paper. The residue was washed with 4-5 times in 50 ml petroleum ether (400 C-600 C) each. Microspheres were dried at room temperature for 24h.

Name of ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	1g	1g	1g	1g	1g	1g	1g	1g	1g
Polymer	0.5g	1g	1.5g	2g	2.5g	3g	3.5g	4g	4.5g
Acetone	25ml	25ml	25ml	25ml	25ml	25ml	25ml	25ml	25ml
Magnesium stearate	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Methanol	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml
Liquid paraffin	270ml	270ml	270ml	270ml	270ml	270ml	270ml	270ml	270ml
n-hexane	30ml	30ml	30ml	30ml	30ml	30ml	30ml	30ml	30ml
Petroleum ether	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

Micromeritic properties:

Prepared microspheres were tested for various micromeritic properties including angle of repose, bulk density, tapped density and hausner's ratio .

A. Repose angle :

Repose angle was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using following formula:

$\tan \theta = h/r$, OR

$\theta = \tan^{-1} h/r$

Where, θ is Angle of repose; h = height of cone and r = radius of cone.

B.Bulk density

Bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk density was calculated using the equation;

$\rho b = M / Vb$

Where, Vb is bulk volume, M is the weight of the powder.

C.Tapped Density

Tapped Density was determined by pouring blend and tapped into a graduated measuring cylinder for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured using the equation;

$\rho t = M / Vt$

D. Hausner's ratio

= Tapped density/Bulk density

Percentage Yield of Microsphere Formation:

The prepared microspheres were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of all nonvolatile components. The percentage yield of microspheres was calculated as follows.

% Process yield = Total weight of microspheres x 100 /Total weight of drug, polymer.

Entrapment Efficiency

About 100 mg of microspheres were completely dissolved in 500 ml of phosphate buffer

solutions (pH 7.4), and stirred for 1h. Then, 2 ml of solution was filtered and the concentration of drug was determined spectrophotometrically by UV at 233nm(.10.11)

%Drug Entrapment= Calculated drug concentration x 100 /Theoretical drug concentration

Determination of drug content:

Drug content of microspheres was determined by UV-Visible spectrophotometer (Shimadzu UV 1700). The weighed amounts (100 mg) of drug-loaded polymer microspheres were powdered and suspended in 100 ml methanol: water (1:99 v/v) solvent system. The resultant dispersion was kept for 20 min for complete mixing with continuous agitation and filtered through a 0.45 μm membrane filter. The drug content was determined.

SEM analysis

The surface morphology of the microsphere was examined by means of scanning electron microscope.

***In vitro* drug release studies**

The dissolution studies were carried out using USP apparatus 1(rotating basket) at 60 rpm and 37±0.5°C. The microspheres equivalent to 100 mg of drug were filled in to basket separately. The dissolution medium phosphate buffer pH 7.4 was selected 5ml of sample solution was withdrawn at predetermined time intervals, filtered through a Whitman filter paper, diluted suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Samples were analyzed at 233nm.

Formulation of the dry mixtures for reconstitutable suspensions

Dry powder for Reconstitution was prepared as dosage form for microspheres for pediatric use. The required amount of microspheres were mixed with the xanthan gum, flavors and sweeteners and resultant powder was reconstituted by sufficient quantity of water to prepare suspension. Reconstituted suspension was evaluated for pH, taste. Result obtained concludes that dosage form shows controlled release of drug.

EVALUATION OF RECONSTITUTABLE SUSPENSION

Determination of pH

Change in pH of the suspension followed by reconstitution was measured by using a digital pH meter.

Viscosity

The rheological behavior of the suspension was determined by using Brookfield viscometer.

Determination of drug content

5ml suspension equivalent to 100 mg of drug was suspended in 100ml of phosphate buffer pH 7.4 and the mixture was vortexed for 15 min. The supernatant was collected and filtered, 1ml of the filtrate was pipetted out and diluted to 100ml and analyzed for the drug content using UV spectrophotometer at 233nm

Measurment of particle size

The particle size was measured using an optical microscope (Labomed CX RIII, Ambala, India). The slide containing suspension particles was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer.

Sedimentation volume

50ml of suspension was taken in 100 ml stopped graduated measuring cylinder. The suspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the volume of sediment was noted. This is the original volume of sediment (H0). The cylinder was kept undisturbed for 14 days. The volume of sediment read at 0 day, on 7th day and on the 14th day was considered as final volume of sediment (Hu).

Sedimentation volume=H_u / H_0

Determination of redispersibility

The redispersibility of the suspension was checked by moving the stopered cylinder upside down until there was no sediment at the bottom of the cylinder.

Kinetic Data Analysis: Drug release models

There are several models to represent the drug dissolution profiles. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in the function of some other parameters related with the pharmaceutical dosage forms. The kind of drug, its polymorphic form, crystallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetics.

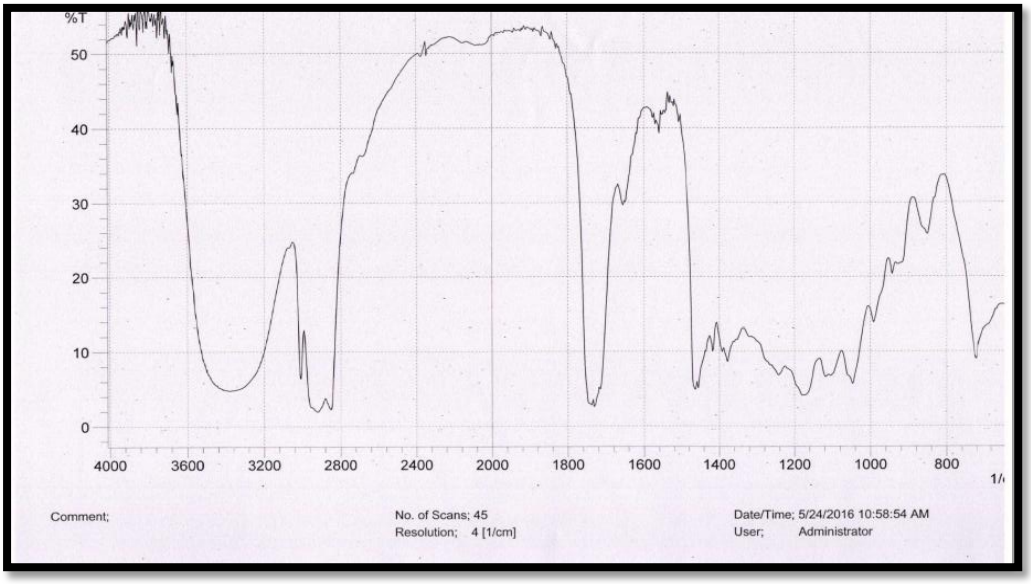
Stability studies

The prepared suspension was subjected to short term stability study for a period of three months as per ICH guidelines. In the present study, stability studies were carried out at 40 °C / 75% RH up to three months. Stability chamber was used. Physical stability was analyzed by change in appearance and chemical stability was analyzed by the change in the drug content and pH of the suspension.

RESULTS AND DISCUSSIONS

Determination of FTIR Spectroscopy

The FTIR spectroscopy of cefixime trihydrate is carried out**.** The spectrum complied with the reference drug



FTIR spectrum of cefixime trihydrate

Solubility Study

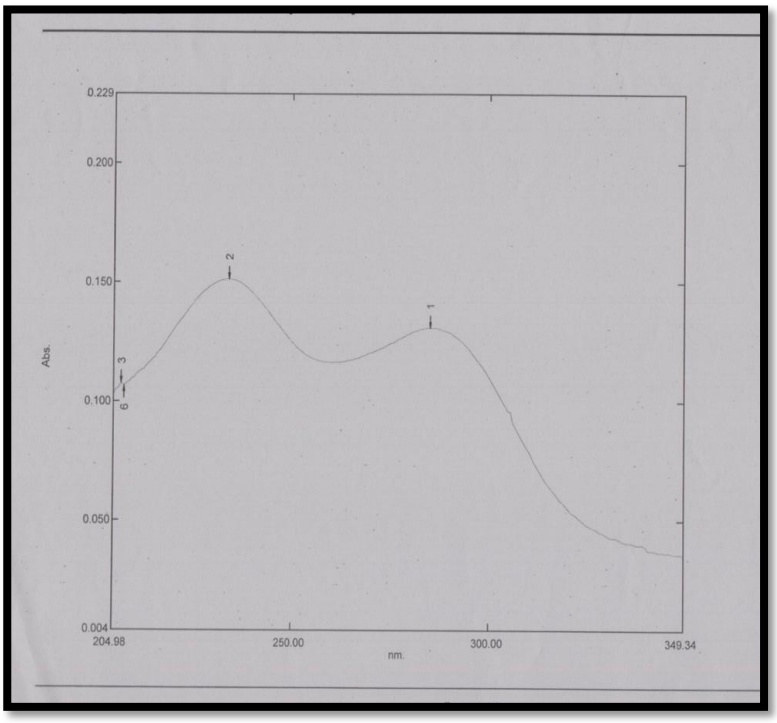
From the solubility studies it was shown that it is freely soluble in methanol, dimethyl sulfoxide, glycerin, propylene glycol and sparingly soluble in acetone and practically insoluble in water.

Determination of Melting point

Experimental values are in good agreement with official values. Thus, indicating purity of sample.

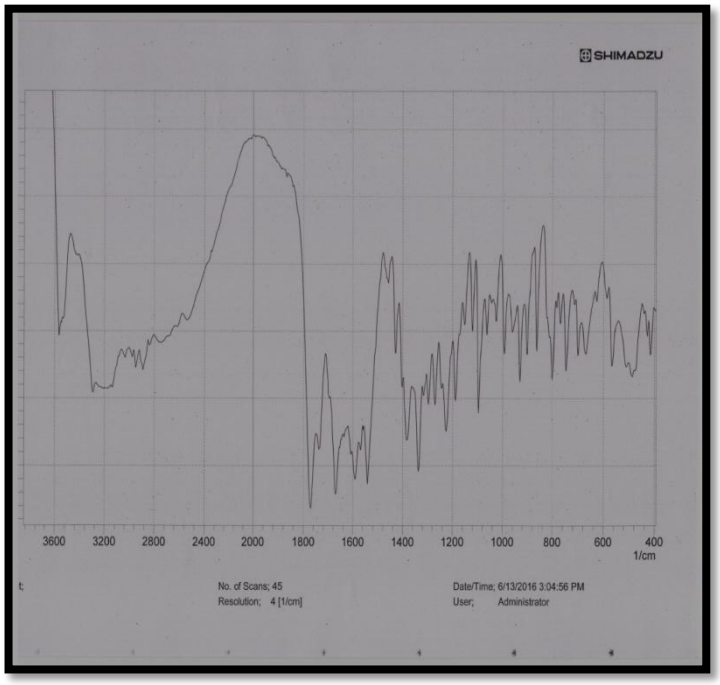
SAMPLE	MELTING POINT
Cefixime Trihydrate	**220-222^{0}C**

Determination of λ max



λmax of cefixime trihydrate

DRUG EXCIPIENT COMPATIBILITY STUDY



FTIR spectrum of drug and excipients

As described in the methodology section the Fourier Transform Infrared spectroscopy studies were carried out for pure drug (Cefixime Trihydrate) and for the Cefixime trihydrate and various Polymer physical mixture. The results are summarized in above Figures and there were no changes in the major peaks of Cefixime Trihydrate and polymers. This revealed that the drug and the polymer are compactable with each other.

Evaluation of cefixime trihydrate microspheres

Micromeritic properties:

Micromeritic properties of microspheres were evaluated such as bulk density, angle of repose It can be observed from the that all the batches of microcapsules have bulk density are less than 1.2gm/cm^3 and angle of repose less than 30º C indicates good flow properties. It was found that hausner's ratio of microspheres were less than 1.25 and is satisfactory. This helps to form free flowing powder blend for reconstitution and thereby ensuring dispensing of required dose accurately in the bottle.

Micromeritic properties:

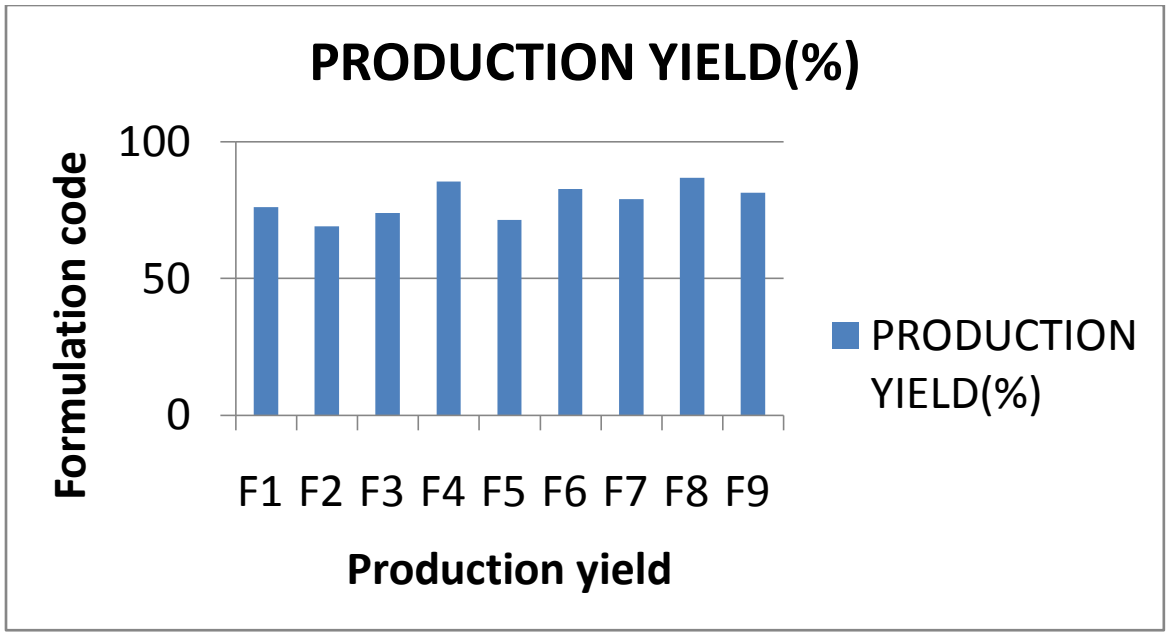
Sl.No	Properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Angle of repose	29^0 03’	28^0 91’	28^0 32’	29^0 15’	27^0 08’	29^0 3’	27^0 7’	27^0 09’	29^0 21’
2	Bulk density	0.48	0.51	0.53	0.50	0.46	0.54	0.52	0.53	0.51
3	Tapped density	0.52	0.59	0.62	0.44	0.52	0.62	0.58	0.59	0.61
4	Hausner’s ratio	1.08	1.15	1.16	1.13	1.13	1.16	1.09	1.11	1.15

Production Yield of Microsphere Formation:

The percentage yield the microspheres were in the range of 69.06 % to 86.9% all the batches. These showed that production yield is quite satisfactory.

Production Yield

FORMULATION CODE	PRODUCTION YIELD(%)
F1	76.2
F2	69.06
F3	74.01
F4	85.52
F5	71.51
F6	82.79
F7	79.1
F8	86.9
F9	81.4



Plot of Production Yield of Different Batches of Microcapsules

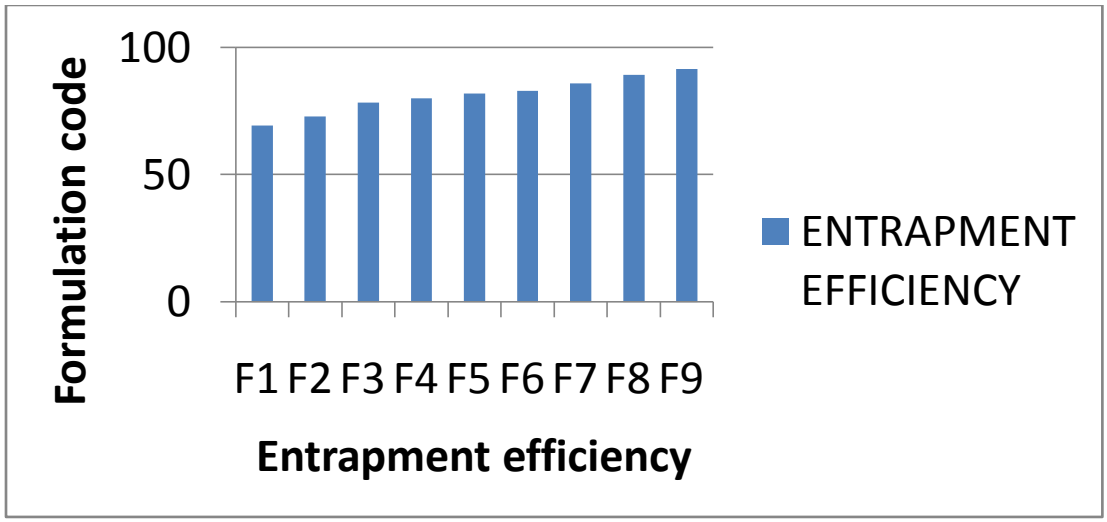
Entrapment Efficiency

% Drug entrapment in the microspheres includes drug entrapped within the polymer matrices. Entrapment efficiency depends on drug solubility in the solvent system used for processing and also on physicochemical properties of drug. As the CT has maximum solubility in selected solvent system and poorly soluble in aqueous medium, homogeneous solution of drug and polymer obtained for processing and hence drug entrapment was up to its maximum level. The drug entrapment efficiency of microspheres were in the range of 69.35% to 91.57% for all the batches.

Entrapment Efficiency of different batch of microcapsules

FORMULATION CODE	ENTRAPMENT EFFICIENCY
F1	69.35
F2	73.01
F3	78.35

F4	**80.14**
F5	**81.95**
F6	**83.06**
F7	**85.99**
F8	**89.25**
F9	**91.57**



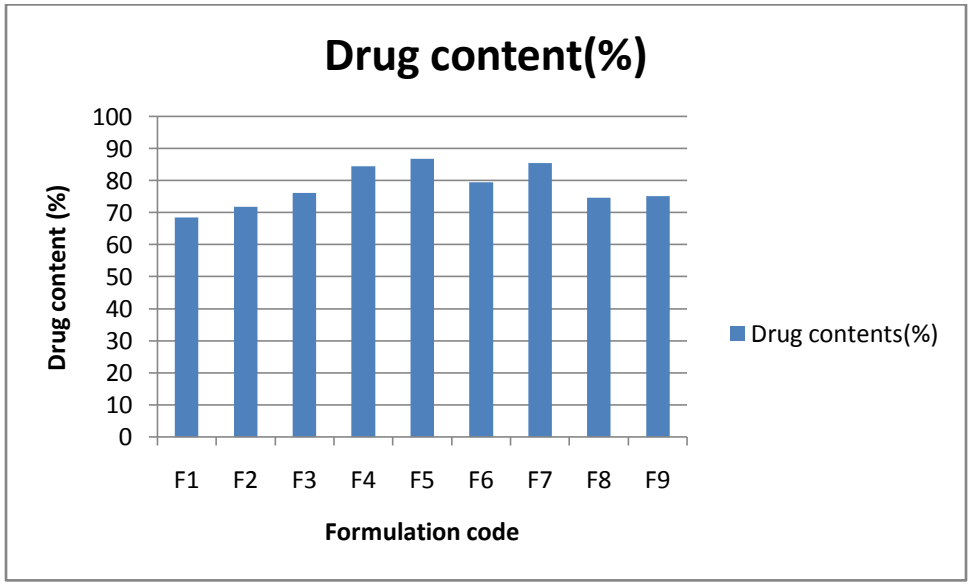
Plot of Entrapment Efficiency of different batch of microspheres

Drug content of different formulations

Drug contents of different batches of microspheres

FORMULATION CODE	PRODUCTION YIELD(%)
F1	**76.2**
F2	**69.06**
F3	**74.01**
F4	**85.52**

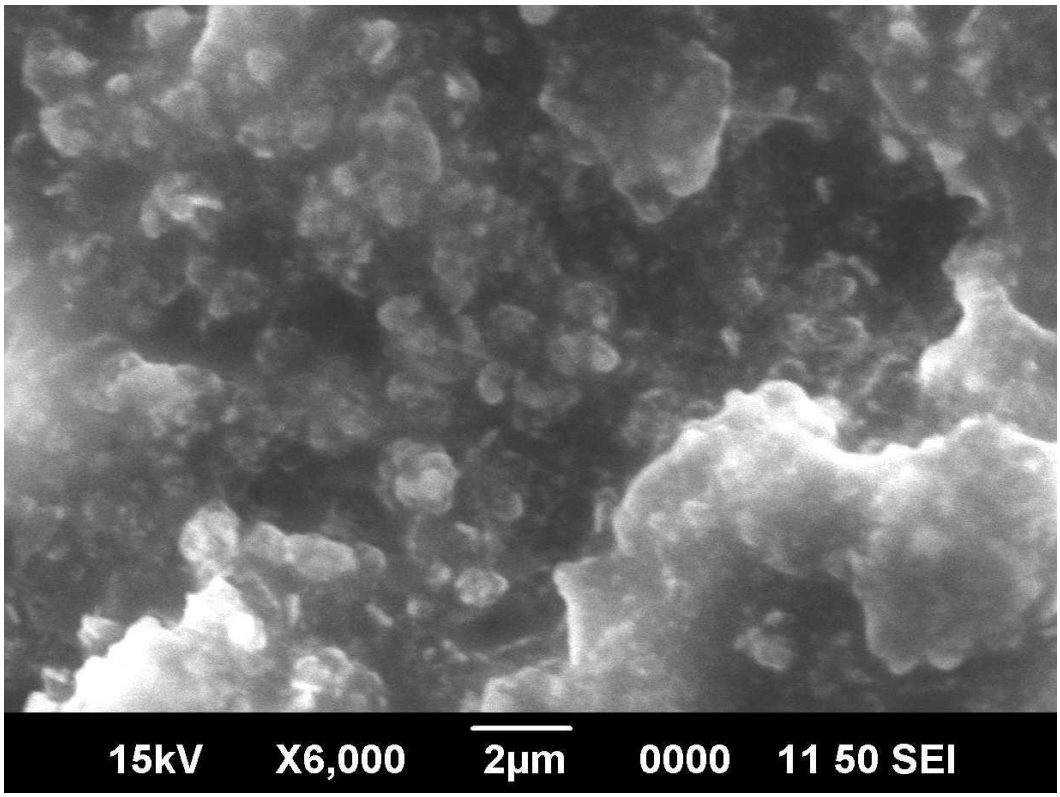
F5	**71.51**
F6	**82.79**
F7	**79.1**
F8	**86.9**
F9	**81.4**



Plot of Drug contents of different batches of microspheres

Surface morphology

The microsphere were scanned using scanning electron microscope. The scanning electron micrograph (SEM) of microsphere showed that microcapsules were spherical in shape with the presence of rough porous polymeric film.



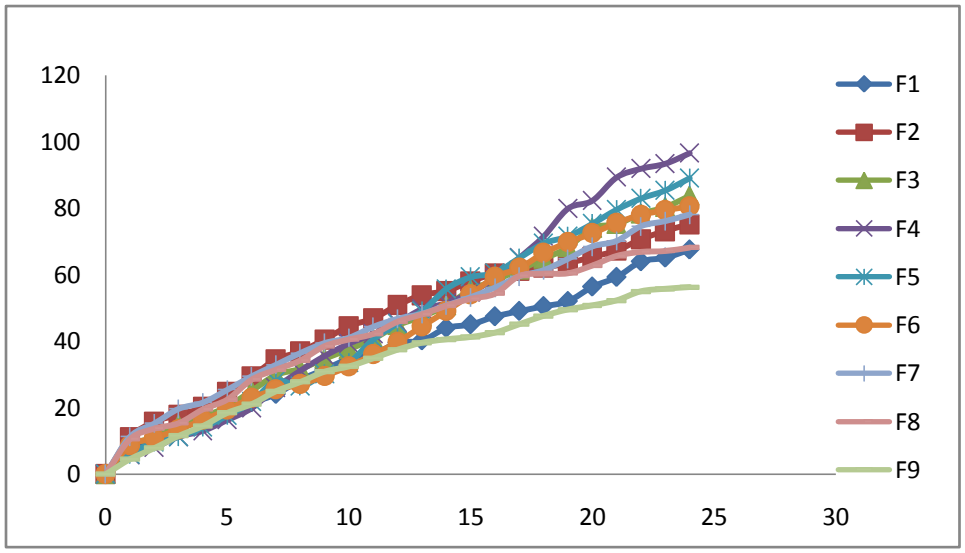
SEM image of formulation F4

***In-vitro* cumulative drug release of microspheres**

USP Paddle method was used to study the release of drug from suspension. 900 ml of phosphate buffer (pH 7.4) was placed in dissolution vessel which was allowed to equilibrate at room temperature of 37±0.5 ºC. A suspension sample equivalent to a typical dose (5 ml) was taken on weight basis using a suitable syringe-cannula system and quantitatively transferred into the dissolution vessel midway between the surface of dissolution medium and the top of the rotating blade. The specific gravity of each sample was determined to express the percentage of drug dissolved in the sampled volume. 5ml of sample solution was withdrawn at predetermined time intervals, filtered through a Whitman filter paper, diluted suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Samples were analyzed at 233nm

***In vitro* drug release data of Cefixime Trihydrate microspheres**

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	7.15	11.05	8.5	5.75	6.01	8.62	11.27	10.55	4.54
2	10.83	15.78	11.1	8.05	9.57	10.84	15.25	13.71	7.85
3	14.01	17.81	14.8	11.28	11.25	13.51	19.65	15.34	11.52
4	16.99	20.19	17.24	13.07	14.05	16.29	21.54	19.52	14.52
5	19.32	24.75	20.36	16.31	17.61	19.46	25.37	22.46	18.46
6	21.57	29.38	25.08	19.88	21.76	22.98	29.43	28.46	21.05
7	24.09	34.5	29.84	26.06	28.1	25.46	32.88	31.44	24.95
8	28.38	36.85	31.68	31.13	26.47	27.03	36.41	34.22	27.72
9	31.55	40.51	34.75	35.56	30.08	29.55	39.42	38.52	30.83
10	34.71	44.5	37.58	39.29	33.51	32.45	41.01	40.52	32.41
11	36.02	46.8	40.71	42.13	40.56	36.08	44.31	42.21	34.85
12	39.57	50.8	44.81	45.54	45.27	39.74	46.71	45.86	37.45
13	40.2	53.84	47.38	49.65	49.05	44.51	48.22	48.06	39.52
14	43.98	55.02	50.71	51.42	55.72	49.06	50.71	50.64	40.56
15	45.05	57.91	55.43	54.67	59.27	54.07	53.2	52.74	41.25
16	47.44	60.28	58.31	58.94	60.54	59.31	56.08	54.28	42.56
17	49.06	61.13	61.48	65.07	65.03	62.02	59.46	59.61	45.08
18	50.51	62.09	64.75	71.52	69.42	66.51	61.31	60.28	47.6
19	52.03	63.38	68.21	79.89	71.52	69.78	64.71	60.42	49.52
20	56.39	65.28	74.02	82.27	75.31	72.43	68.42	62.75	50.75
21	59.28	67.18	75.21	89.27	79.56	75.61	70.1	65.64	52.27
22	63.98	70.59	78.32	91.87	82.91	78.01	74.52	66.84	54.98
23	65.1	73.08	80.31	93.38	85.34	79.42	76.04	67.11	55.73
24	67.54	75.11	83.7	96.55	89.01	80.52	78.01	68.14	56.24



In vitro drug release of cefixime trihydrate microspheres

EVALUATION OF RECONSTITUTABLE SUSPENSIONS

Evaluation Parameter of after reconstitution oral Suspension

SL. No	Test	Observations		
		0 day	7 days	14 days
1	pH	7	6.8	**6.5**
2	Viscosity (cps)	553	**549**	**540**
3	Drug content (%)	**93.22**	**92.1**	**89.5**
4	Particle size (μm)	302	304	307

pH

The reconstitutable blend for suspension was subjected for stability for a period of 14 days. The samples were reconstituted in purified water to formulate a suspension. This was analyzed for pH at 0, 7 and 14 days after reconstitution. There was no appreciable change observed in pH.

Viscosity of suspension

Sedimentation rate depends on the viscosity of the medium. From sedimentation volume data, it can be seen that suspension is stable and easily redisperse after 14 days. Thus, viscosity of the suspension is sufficient for stability of the suspension.

Drug content of the suspension

No significant change was observed in the drug content.

Particle size

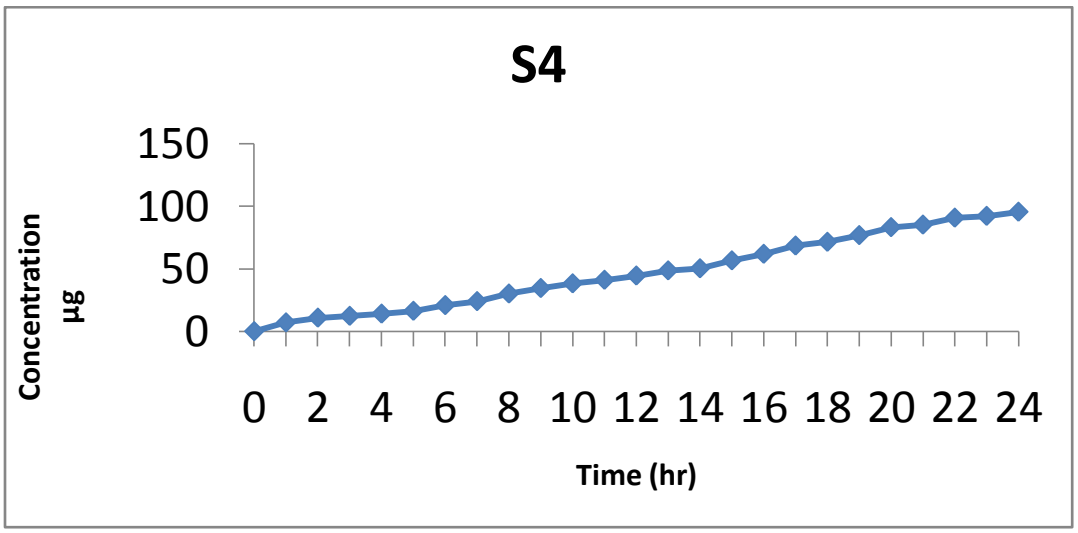
Particle size of the particles in suspension was reasonably constant even after 14 days. This indicated no crystal growth.

Sedimentation volume of suspension

The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. In prepared formulation, there was little sedimentation after 7 and 14 days and it could be easily redispersed and gave uniform dispersion after 5-6 stroke. Results are shown in Sedimentation study of suspension

Time day	**H_u**	**H_0**	**Sedimentation ratio**	**Redispersability (no. of stroke)**
0	50	50	1.0	0
7	43	50	0.86	4
14	38.2	50	0.76	6

In Vitro drug release from reconstitutable suspension



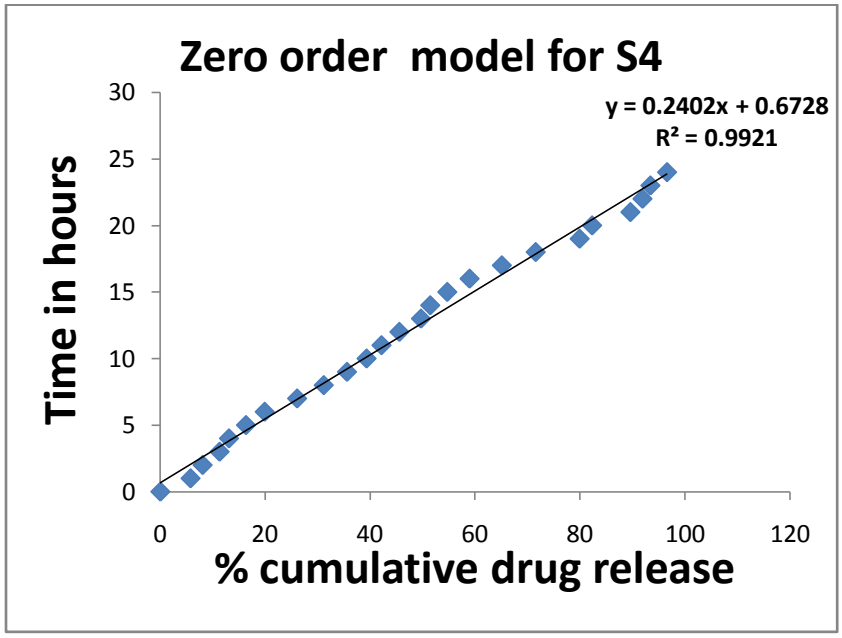
Kinetics of drug release

The results obtained from *in-vitro* release studies were plotted in different kinetic models..The release kinetics data indicates that the release of drug from both microsphere and suspension best fits to zero order and higuchi model because the correlation coefficient values are higher in case of zero order and higuchi model. The release rate is independent of the concentration of the drug. The release exponent value of Korsmeyer-Peppas is 0.7593 respectivily, which suggests that the release mechanism of drug from both microsphere and suspension followed Anomalous transport or non-Fickian diffusion.

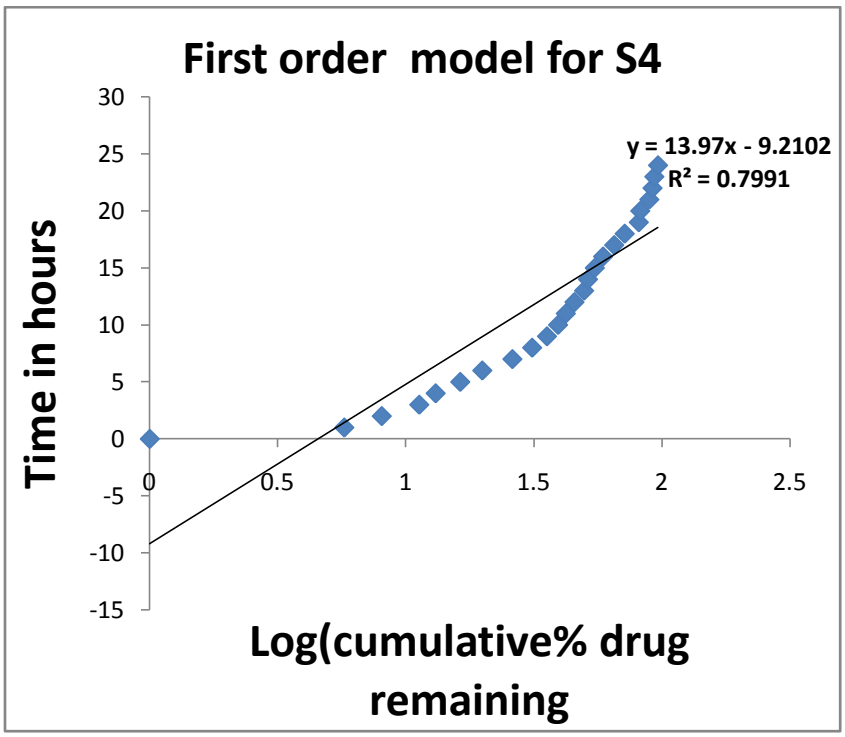
Kinetic data analysis of reconstituted suspension

Time(hrs)	%CDR	Cumulative % drug remaining	Log (Cumulative % drug remaining)	Log(%CDR)	Log(time)	Square root of time
0	0	0	0	0	0	0
1	5.75	1.0121	5.75	0.75966	0.30102	1.4142
2	8.05	1.0124	8.05	0.90579	0.47712	1.732
3	11.28	1.0127	11.28	1.0523	0.602	2
4	13.07	1.0132	13.07	1.11627	0.6989	2.236
5	16.31	1.0138	16.31	1.2124	0.77818	2.449
6	19.88	1.0149	19.88	1.2984	0.845	2.6457

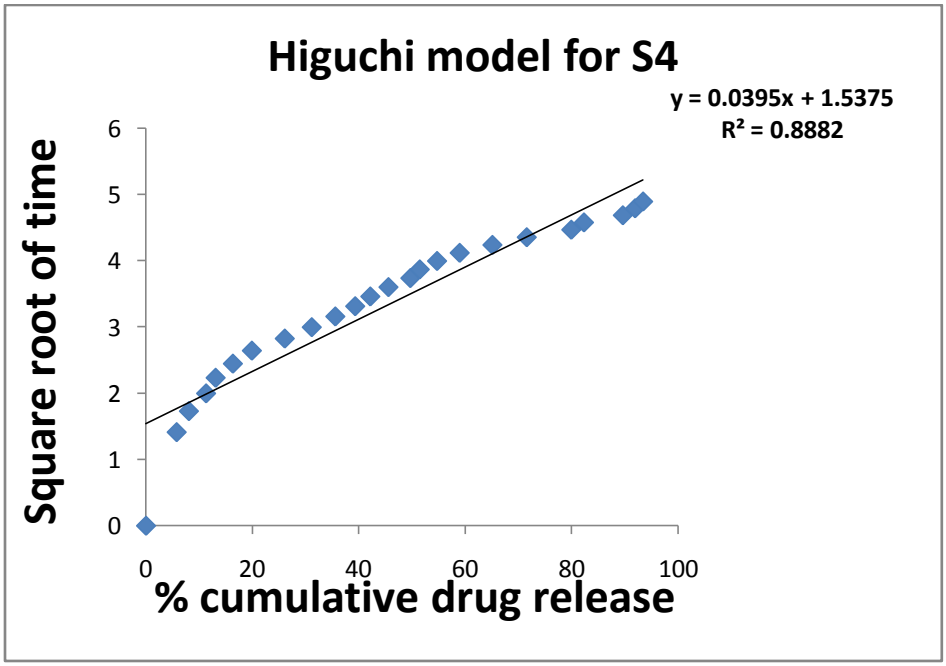
7	26.06	1.016	26.06	1.4159	0.903	2.8284
8	31.13	1.01719	31.13	1.4931	0.9542	3
9	35.56	1.0182	35.56	1.55096	1	3.1622
10	39.29	1.01916	39.29	1.5942	1.0413	3.3166
11	42.13	1.0203	42.13	1.6245	1.0791	3.4641
12	45.54	1.022	45.54	1.6583	1.1139	3.6055
13	49.65	1.0229	49.65	1.6959	1.1461	3.7416
14	51.42	1.0245	51.42	1.71113	1.176	3.8729
15	54.67	1.0271	54.67	1.73774	1.20411	4.
16	58.92	1.0319	58.94	1.7702	1.23044	4.1231
17	65.07	1.03932	65.07	1.81338	1.2552	4.2426
18	71.52	1.0561	71.52	1.85442	1.2787	4.3588
19	79.89	1.0639	79.89	1.90949	1.301	4.4721
20	82.27	1.111	82.27	1.9152	1.3222	4.5825
21	89.57	1.1446	89.27	1.9507	1.3424	4.6904
22	91.87	1.1805	91.87	1.96317	1.3617	4.7958
23	93.38	1.3749	93.38	1.97025	1.3802	4.8989
24	96.55	1.54	96.55	1.98501	1.3952	4.9241



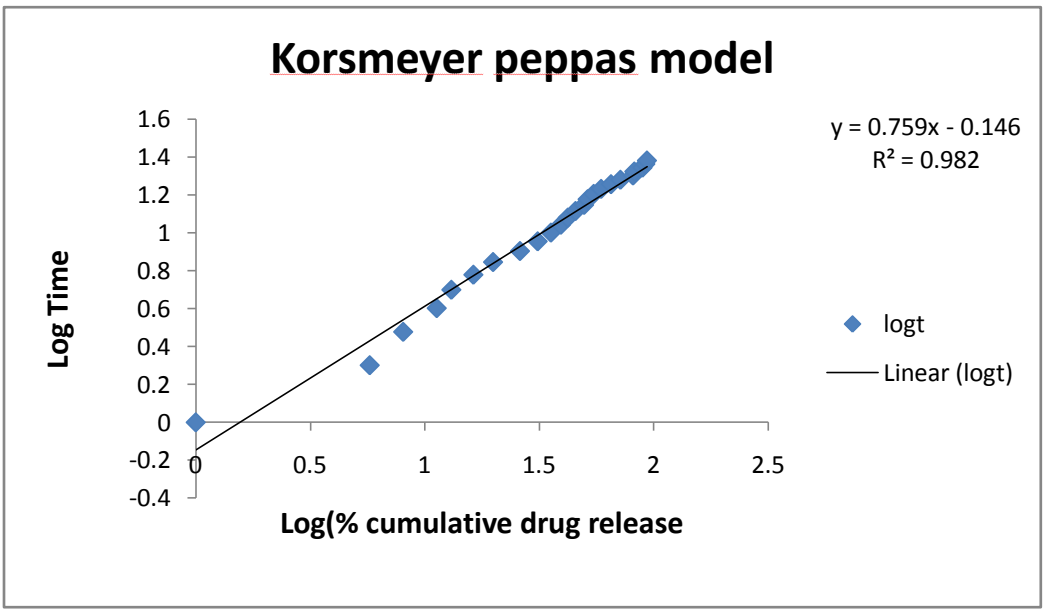
Zero order release model of S4



First order model for S4



Higuchi model for S4



Korsmeyer peppas plot for S4

The value of diffusion exponent, (n) for S4 was found to be 0.7593 respectively and indicates *Anomalous or non-Fickian diffusion* of drug from suspension. The mechanism indicates that the drug release is independent of concentration. In Fickian diffusion, the drug flux or the rate of permeation through a unit material is proportional to the concentration gradient. Diffusion process in which the *mean square displacement* (MSD) of drug grows non linearly with time are referred to as Anomalous or non-Fickian i.e. the release pattern is irregular and is independent of drug concentration. This process is evident from the invitro drug release data of cefixime trihydrate microsphere and suspension i.e. the release of cefixime trihydrate foundly decreased with increase in polymer concentration.

Stability Study

Stability studies

Conditions	Time in days	Drug Contents	pH
40º C/75%RH	0	93.2	7.4
	30	93.1	7.1
	60	92.7	6.9
	90	91.5	6.7

Stability studies were conducted for the finished reconstituted suspension at accelerated condition of 40°C /75% RH for 3 months. There is no significant change in pH and Drug content of suspension. The prepared formulation show good stability for 90 days.

CONCLUSION

Cefixime Trihydrate is a 3rd generation broad spectrum β- Lactam cephalosporin class of antibiotic administered orally in pediatric and adult patients and is extremely bitter in taste. Controlled release and masking bitter taste are the major challenges for better patient compliance particularly in an antibiotic treatment where dose and duration is important. Among the various techniques available for controlled release and bitter taste masking microencapsulation is a useful technique as it has significant advantages over the other techniques. Also a polymer used provides protection to active moiety thereby increasing its stability.

Microspheres of Cefixime trihydrate with Eudragit RL 100 prepared by the solvent evaporation method for controlled release of drug. Nine different batches of microspheres were prepared by varying the concentration of eudrajit RL100 from 0.5 to 4.5g. The drug Cefixime trihydrate was subjected to different preformulation studies. The calibration curve of Cefixime trihydrate in methanol obeys Beer-Lambert's law in 5-30µg/ml concentration range.

The prepared microsphere formulations were then subjected to evaluation parameters such as drug content, i*n vitro* drug release, entrapment efficiency, SEM Analysis. The drug content of F_1-F_9 formulations vary from 68.5-86.75. Microspheres prepared using, higher polymer to drug ratio improved the entrapment efficiency, production yield. At the lower polymer to drug ratio, there was significant increase in drug release,but entrapment efficiency and production yield is quite low. SEM images of microsphere formulation shows micron sized microspheres, The effect of polymer concentration on the *in vitro* release of cefixime trihydrate from the microspheres was also studied. It can be seen that by increasing the polymer concentration, decreases the rate of drug release from the microspheres dramatically. The best microsphere formulation was selected based on the *in vitro* release profile, it was found that formulation F4 show better drug release with minimum concentration of Eudragit RL100. Hence the reconstitutable suspension containing F4 microsphere was selected as final formulation.

Further dry powder for reconstitution was prepared from microspheres with respect to its use in pediatric population. Xanthan gum was chosen as the suspending agent for the suspension formulations. No significant change in drug content and *pH* was observed during stability studies.

A reconstitutable suspension can offer several advantages such as maintenance of the chemical stability of the active compounds until reconstitution at the start of treatment. The same suspension can be easily administered to children of different ages by adapting the volume to swallow. The results of the present study will be helpful for the preparation of oral Dosage forms of Cefixime trihydrate for pediatric population with an acceptable taste.

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