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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF FLUCLOXACILLIN USING NATURAL POLYMER

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ABSTRACT

Sustained release drug delivery system was meant to discharge the medication in a delayed rate to keep up plasma drug levels. The objective of the work was to design Sustained release matrix tablet of a flucloxacillin. The drug Flucloxacillin powder was examined found that Flucloxacillin was white crystalline odorless powder freely soluble in water, melting was 177 ^{0}C and Partition coefficient 0.29 ±0.06. Flucloxacillin solution was scanned in the U.V. range of 200-400 nm and λ_{max} at 238 nm. The standard curves were prepared in 0.1 N HCl using λ_{max} 238 nm.with correlation coefficient of 0.999 in the concentration range of 5-25µg/ml. Physical compatibility study revealed there is no reaction between drug and polymer. Sustained release matrix tablet bathes were prepared by the dry granulation method. Firstly, granules were prepared and Micromeritic properties bulk density between 0.62 to 0.68, tapped density ranges 0.69 to 0.83, Compressibility Index between 7.24 to 25.3, Hausner'ratio ranges 1.08 to 1.34 and angle of repose ranges 24.38 to 33.12 were calculated. Sustained release matrix tablet bathes were evaluated under following parameters e.g. hardness from 5.3 to 7.3 kg/cm^2, thickness from 2.4 to 2.7mm, diameter 9.1 for all, Weight variation from 1.75 to 6.21 %, content variation from 93.63 to 98.09 %, friability from 0.21 to1.85% and swelling index from 42 to68. On the basis these general evaluation of sustained release matrix tablet it was found, batch SR-2 shows good result. All batches were subjected for *in-vitro* Drug Release and obtained R^2 values revealed that SR-2 possessed excellent drug release profile with R^2 value 0.932. Drug Release profile of SR-2 the obtained data was expended for kinetic modeling and statistic representation and found that the batch SR-2 follows Zero Order kinetic model.

KEYWORD: Evaluation, Sustained Release, Matrix Tablet, Flucloxacillin, Natural Polymer.

INTRODUCTION

Sustained release drug delivery system was meant to discharge the medication in a delayed rate to keep up plasma drug levels.[1,2,3] The medications having shorter half life are appropriate for the sustained release drug delivery system[4,5] Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Flucloxacillin is an antimicrobial that belongs to the semi-synthetic isoxazolpenicillins group.[6.7,8] It is an antimicrobial resistant to penicillinase, an enzyme responsible for cleaving the beta-lactam ring, making the other drugs inactive against microorganisms. Flucloxacillin has very short half life period (0.75 to 01 hr.) that's why it eliminate from the body very rapidly. Sustained release matrix systems have the capabilities to maintained steady drug concentration in the blood for long time.[9,10] The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system.[11,12] These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug.[13] They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window.

MATERIALS AND METHODS

Flucloxacillin was obtained as Gift sample from Laxicare Pharma Private Limited, Ankleshwar Gujrat. The pods of okra were bought from local market, Bhopal and mucilage was extracted. HPMC K100M, Starch, Magnesium stearate and Talc were purchased from Hi-media chemicals Mumbai. UV Spectrophotometer, Systronics 2203, Dissolution apparatus, Electrolab were used.

Methods

Preformulation study

Organoleptic properties of drug: Physical properties of the drug which can be observed by sensory organs e.g. color, odor, taste, physical state, texture, etc.

Solubility behavior of drug: Solubility of Drug was tested in various solvents. A definite amount of drug was dissolved in exact amount of solvents at room temperature and observed only by the visible inspection.

Melting point of drug: Melting point of drug was determined by melting point apparatus. It is performed by filling of drug in capillary tube and capillary tube and the thermometer were put in the apparatus. Now the point was noted at which the compounds starts melting.

Partition Coefficient of drug: The partition coefficient of drug was determined in solvent system n-octanol/distilled water. Accurately weighed quantity of drug (20mg) was taken in separating funnel containing 20ml n-octanol, 20ml distilled water. Then the funnel was vigorously mixed and kept to equilibrate for 6 hrs. The contents of both phases were separated. After appropriate dilution, the aqueous phase was analysed for drug against reagent blank solution using Systronics 2203 UV spectrophotometer. The drug concentration in n-octanol phase determined by subtracting the amount in aqueous phase from the total quantity of drug added to the vial. The partition coefficient value "p" was calculated by the following equation-

$$\mathbf{P_{O/W} = C_{Oil} / C_{water}}$$

Where, $P_{O/W}$: Partition coefficient is oil in to water

$C_{oil:}$ concentration of drug in oil

$C_{water:}$ concentration of drug in water

UV Spectrophotometer analysis

Determination of λ_{max} of drug: 10 mg of exactly weighed Drug was dissolved in adequate quantity of 0.1N HCl in 10 ml volumetric flask and shaken. The volume was made upto 10ml. Aliquots of the above solution were taken and dilute to get drug concentration in the range of 5-25 µg/ml. Finally, 10µg/ml solution was scanned between 200-400 nm on a UV-Visible spectrophotometer.

Preparation of standard curve in distilled water: From the above stock solution different aliquots were prepared. The absorbances of resulting dilutions (5-25 µg/ml) were taken at 238 nm on a UV-Visible against distilled 0.1N HCl as blank. Linear regressed calibration curve was prepared.

Physical compatibility study between Drug and Polymer

Compatibility study of Drug with excipient was performed under different storage condition for 07 days. Drug and excipients were physically mixed and the physical mixture was divided

in four parts, filled in glass vial and kept under different temperature and relative humidity condition. The control sample and a vial containing only drug was sealed and kept as such in low temperature condition (2-8^{0}C), room temperature and high temperature (40-45^{0}C). After 07 days the samples were withdrawn and physically observed for change in the physical characteristic of the drug-excipient mixture.

Method of formulation of granules

Granules were prepared by wet granulation method. Okra gum and drug were mixed homogeneously by pestle mortar. Lactose was used as filler and channeling agent. PVP solution in Ethanol was used as granulating agent. Granules were prepared by 30 mesh screen. Prepared granules were dry on hot air oven and stored in dry and cool place or in desiccator.

Characterization of prepared granules

a) **Tapped density:** It is the ratio of total mass of granules to the tapped volume of the powder. The volume was measured by tapping the granules for 50 times. Then the tapping was done. Then the tapping was done for 75 times and the taped volume was noted (the different between these two volume should be less than 2%). If it is more than 2% tapping is continue for 125 time and tapped volume was note.

$$\mathbf{D_t = m/V_I}$$

Where,

m – mass of the granules

V_I – tapped volume of the granules

b) **Bulk density (D_b):** It is the ratio of the total mass of the granules to the bulk volume of the granules. It was measured by poured the weight granules (passed through standard sieve) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density was calculated according to the formula mention below. It is expressed in g/cc and is given by-

$$\mathbf{D_b = m/V_0}$$

Where,

M – mass of the granules

V_0 – bulk volume of the granules

c) **Carr's compressibility index:** The flow ability of the granules can be evaluated by comprising the Bulk Density (BD) and Tapped Density (TD) of granules and the rate at which it packed down. Compressibility Index of the granules was determined by the Carr's compressibility index:

CI (%) = TD-BD/TD X 100

d) **Hausner's ratio:** It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5, it was determined by the ratio of tapped density and bulk density.

HR = Tapped Density/ Bulk Density

e) **Angle of repose (θ): T**his is the maximum angle possible between the surface of a pile of the granules or granules and the horizontal plane. The angle of repose of granules was determined by the funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The granules sample was passed through the funnel until it form a heap. Further, adding of the granules was stopped as soon the heap touches the tip of the funnel. The circle was drawn across it without disturbing pile. The radius and the height of the heap was noted down. The same procedure was repeated for three times and the average value was taken. The angle of repose was calculated by using equation.

Tan θ = h/r

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

Where,

θ = Angle of repose

h = Height of the heap

r = Radius of the heap

f) **Formulation of sustained release matrix tablets:** In Granules, talc (5% w/w) and magnesium stearate (5% w/w) were added as a glidant and lubricant respectively. Tablets were compressed using 9 mm die/punch set in a single punch tablet compression machine.

Evaluation of matrix tablets

The evaluation of Matrix tablet dosage form with respect to various characteristics is vital to precisely control the dosage form behavior and to ensure batch-to-batch uniformity. The tablets were evaluated for thickness, weight variation, hardness, friability, matrixing property and *in-vitro* drug release.

(a) Thickness: The thickness of the tablets was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated.

(b) Weight variation test: To study weight variation, 20 tablets were weighted individually and the arithmetic mean weight calculated. Not more than two tablets differ from the average weight by more than 5%.

(c) Hardness and Friability: For each formulation, the hardness and friability tests of six tablets were performed using the Pfizer hardness tester and Roche friabilator, respectively.

(d) Swelling behavior of the tablet: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied in a Petridish containing pH 6.8 phosphate buffer. At the end of 0.5 h and 1 h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 1 h, weights of the tablet were noted, and the method was continued till the end of 8 h. Percentage weight gain by the tablet was calculated by formula;

S.I = {(Mt-Mo) / Mo} X 100

Where,

S.I = swelling index,

Mt = weight of tablet at time t (h) and

Mo = weight of tablet at zero time

(e) *In-vitro* drug release studies: *In-vitro* release studies were carried out in the dissolution test apparatus USP Type II. The tests were done out in 900 ml of 0.1N HCl for 12 hrs at 75 rpm at 37±0.5^{o}C. 3 ml of the aliquot were withdrawn at different predetermined time intervals (1, 2, 4, 6, 8, and 12) and filtered. Sample was analyzed at 238nm using UV/Visible spectrophotometer 0.1N HCl is used as blank. 10 ml of 0.1N HCl was replaced in the vessel after each withdrawal to maintain the sink condition. The percentage drug release was calculated using the calibration curve and was plotted against function of time to study the pattern of drug release from tablets.

Optimization of formulation

The duty of formulating a dosage form to accomplish a desirable controlled release with the selection of potential excipients that allow the formulation of matrices having controlled delivery characteristics, and it should dissolve slowly enough to work as a reservoir for the delivery. Initial dummy batches were prepared using okra gum.

(a) Optimization of drug: Polymer ratio

In preliminary trial batches, dummy batches were prepare by using guar gum in same ration as expected to take in final batches with okra gum. Ratio of drug and guar gum were optimized to get better matrixing property and prolonged release for the desired time.

Statistical treatment of data

Numerous theories/kinetics models describe drug dissolution from immediate and modified release dosage form. The release of drug from a polymeric matrix is complicated. It often involves drug diffusion, interface movement and various interactions.

In order to determine the mechanism of drug release from sustained release floating matrix tablets, the data were treated using following mathematical models:-

1. Zero order (cumulative percentage of drug released versus time)
2. First order (log percent of drug unreleased versus time)
3. Higuchi model (cumulative percentage of drug released versus square root of time)
4. Korsmeyer'- Peppas model (log of cumulative percentage of drug released versus log time)

RESULTS AND DISCUSSION

Preformulation study

The drug Flucloxacillin powder was examined for its organoleptic properties found it was observed that Flucloxacillin was white crystalline odorless powder. When tested for its solubility in various solvents, it was determined that drug sample was freely soluble in water 0.1 HCl, 6.8 pH buffer, 0.1 N HCl and 0.1 N NaOH, soluble in ethanol, Sparingly soluble in methanol. Also melting was 177 ^{0}C and Partition coefficient observed at 0.29 ±0.06. Flucloxacillin solution was scanned in the U.V. range of 200-400 nm using UV Visible spectrophotometer. The spectrophotometric method of analysis of Flucloxacillin at λ_{max} 238 nm was found to be reproducible and highly sensitive. The standard curves were prepared in 0.1 N HCl at λ_{max} 238 nm. The correlation coefficient greater than 0.999 was observed in all the cases, which indicated that, the drug follows Beer-Lambert's law in the concentration range of 5-25µg/ml. Physical compatibility study revealed there is no reaction between drug and polymer.

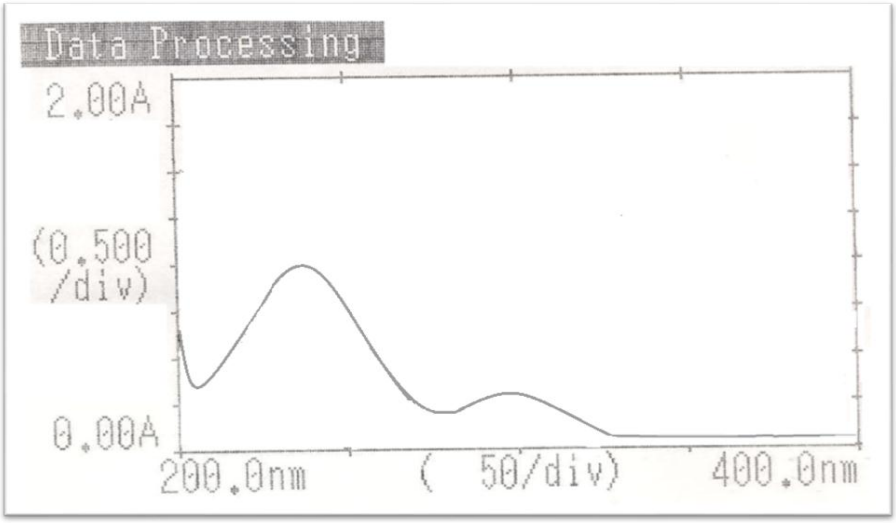

Figure no. 1: UV- spectrometry scanning (200-400 nm) of Flucloxacillin.

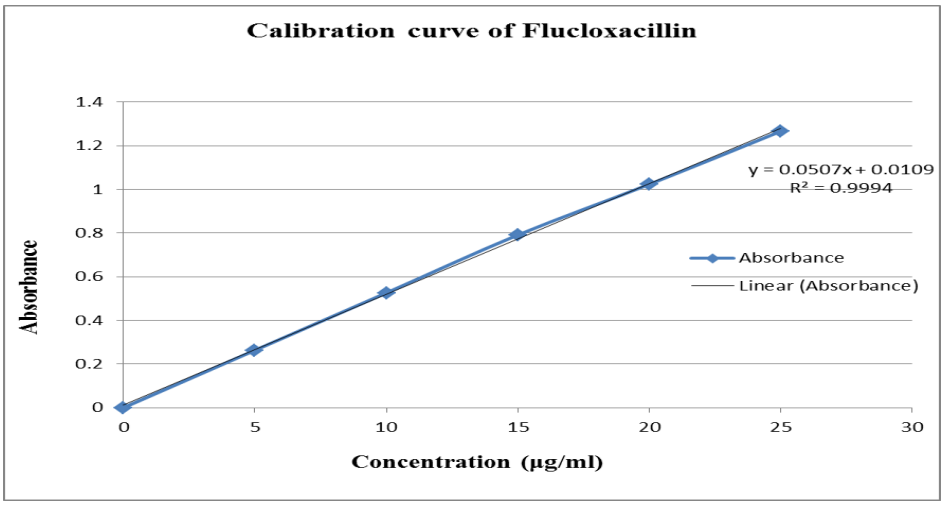

Figure no. 2: Graph showing calibration curve of flucloxacillin.

Formulation of sustained release matrix tablet

Table no. 1: Formulation of flucloxacillin sustained release matrix tablets.

S. no.	Ingredients (mg/tab)	SR-1	SR-2	SR-3	SR-4	SR-5
1.	Drug (Flucloxacillin)	250	250	250	250	250
2.	Okra gum	200	200	200	200	200
3.	HPMC K100M	100	150	200	250	300
3.	Starch	50	50	50	50	50
4.	Ethyl Cellulose in alcohol 1% w/v	20	20	20	20	20
5.	Talc	5	5	5	5	5
6.	Mg stearate	5	5	5	5	5
7.	Total weight of tablet	630	680	730	780	830

Pharmaceutical characterization of granules

Micromeritic properties of granules have been shown in table below

Table no. 2: Micromeritic properties of granules.

Formulation	Micromeritic properties				
	BD (g/ml)	TD (g/ml)	CI (%)	HR	Angle of Repose (θ)
SR-1	0.64 ± 0.12	0.69 ± 0.05	07.24 ± 0.21	1.08 ± 0.08	33.12 ± 0.42
SR-2	0.68 ± 0.09	0.76 ± 0.08	10.53 ± 0.09	1.12 ± 0.04	24.38 ± 0.09
SR-3	0.65 ± 0.22	0.79 ± 0.23	17.72 ± 0.20	1.22 ± 0.04	29.07 ± 0.42
SR-4	0.62 ± 0.16	0.83 ± 0.29	25.30 ± 0.17	1.34 ± 0.12	28.42 ± 0.42
SR-5	0.64 ± 0.31	0.74 ± 0.30	13.51 ± 0.14	1.16 ± 0.32	29.18 ± 0.32

Evaluation of all formulated Batches of sustained released matrix tablets

(a) Evaluation of general characters of sustained released matrix tablets

Table no. 3: Evaluation of general characters of sustained released matrix tablets.

S. no.	Parameters	SR-1	SR-2	SR-3	SR-4	SR-5
1	Hardness (Kg/cm^2)	5.3±0.32	5.7±0.23	6.2±0.11	6.5±0.43	7.3±0.62
2	Thickness (mm)	2.4	2.5	2.6	2.6	2.7
3	Diameter (mm)	9.1	9.1	9.1	9.1	9.1
4	Weight variation test (%)	3.22±0.5	1.75±0.1	4.89±0.2	5.22±0.4	6.21±0.3
5	% Content variation	96.53%	98.09%	94.33%	94.74%	93.63%
6	% Friability	0.21	0.92	1.54	1.68	1.85
7	Swelling Index	42	61	51	56	68
8	Swelling behavior	Swell & burst	Slow swelling	Slow swelling	Slow swelling	Slow swelling

(b) *In-vitro* drug release study of all formulated batches of sustained release matrix tablet

Table no. 4: *In-vitro* drug release of all formulated batches (SR-1 to SR-5).

Time (Hrs.)	Cumulative Percentage of Drug Release				
	SR-1	SR-2	SR-3	SR-4	SR-5
0	0	0	0	0	0
1	40.15	22.12	35.32	45.32	37.32
2	54.76	33.82	41.82	55.32	47.83
4	62.23	38.12	47.36	66.38	54.42
6	69.9	44.14	54.12	73.78	60.48
8	72.65	47.72	57.82	76.68	64.12
10	73.73	52.82	62.32	77.38	68.83
12	74.8	58.64	68.21	79.49	71.12
14	75.38	65.78	74.14	80.62	74.34
16	75.7	72.72	79.26	82.3	76.13
18	76.01	78.76	82.12	83.14	77.38
20	76.26	83.13	84.46	83.57	78.61
24	86.32	91.25	88.56	84.94	79.28

*Each value was an average of three determinations

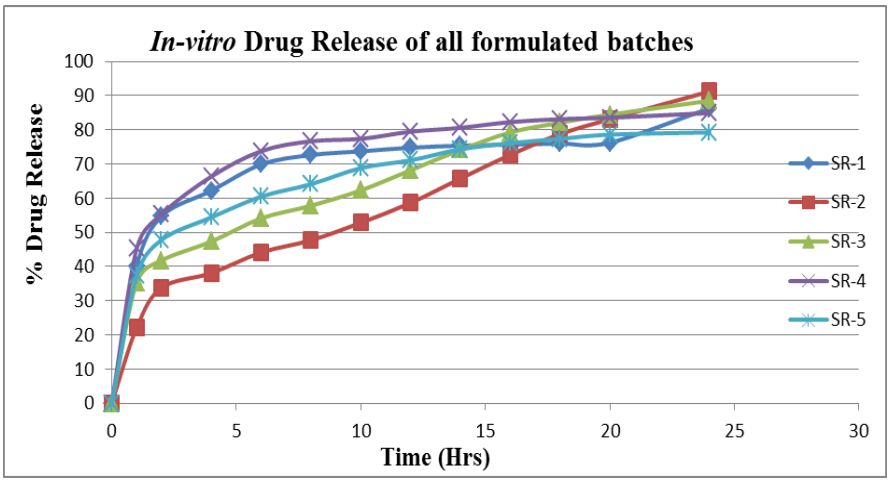

Figure no. 3: *In-vitro* drug release of all formulated batches (SR-1 to SR-5).

Table no. 5: Linearity equation and regression values of drug release.

Formulation	Equation	R^2 value
SR-1	y = 2.187x + 41.73	R² = 0.558
SR-2	y = 3.244x + 19.30	**R² = 0.932**
SR-3	y = 2.912x + 29.40	R² = 0.833
SR-4	y = 2.274x + 44.76	R² = 0.547
SR-5	y = 2.366x + 36.18	R² = 0.668

Statistical treatment of data SR-2

Table no. 6: Statistical treatment of data SR-2.

Time (hr.)	S.R.T.	Log T.	% C.R	Log % C.R	% Drug remaining	Log% drug remaining
0	0	0	0	0	100	2
1	1.000	0	22.12	1.345	77.88	1.891
2	1.141	0.301	33.82	1.529	66.18	1.821
4	2.000	0.602	38.12	1.581	61.88	1.792
6	2.449	0.778	44.14	1.645	55.86	1.747
8	2.828	0.903	47.72	1.679	52.28	1.718
10	3.162	1.000	52.82	1.723	47.18	1.674
12	3.464	1.079	58.64	1.768	41.36	1.617
14	3.742	1.146	65.78	1.818	34.22	1.534
16	4.000	1.204	72.72	1.862	27.28	1.436
18	4.243	1.255	78.76	1.896	21.24	1.327
20	4.472	1.301	83.13	1.919	16.87	1.227
24	4.898	1.380	91.25	1.960	08.75	0.942

Statistical Treatment of Data SR-2 as kinetic modeling

(a) Zero order kinetics for SR-2

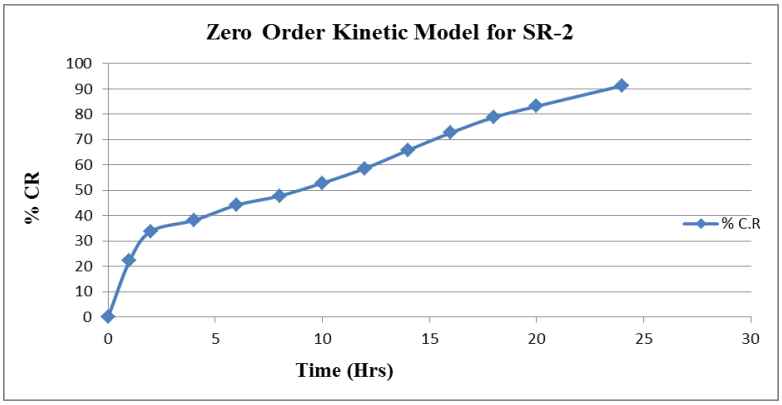

Figure no. 4: Zero order plot for SR-2.

(b) First order kinetics for SR-2.

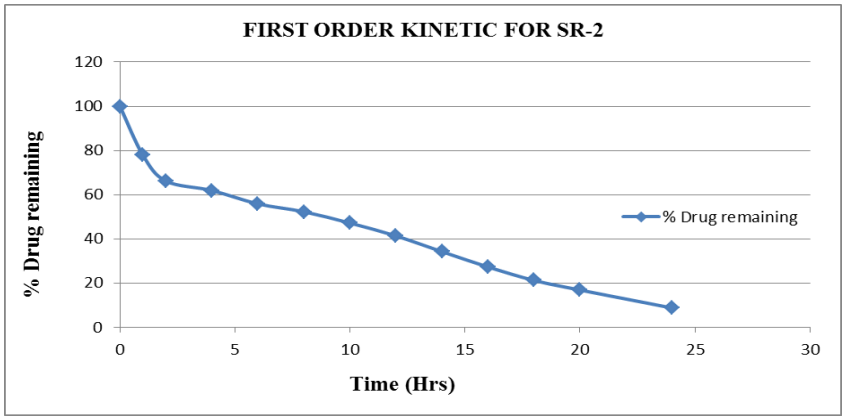

Figure no. 5: First order plot for SR-2.

(c) Higuchi Model for SR-2

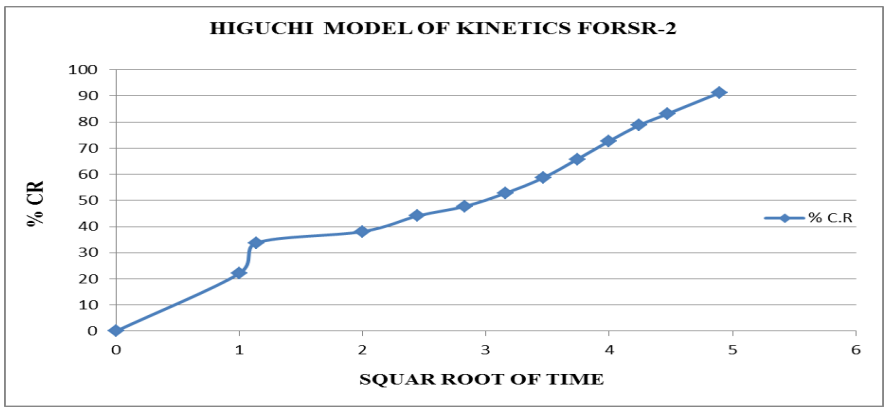

Figure no. 6: Higuchi model for SR-2.

(d) Korsmeyer-Peppas model of kinetic for SR-2

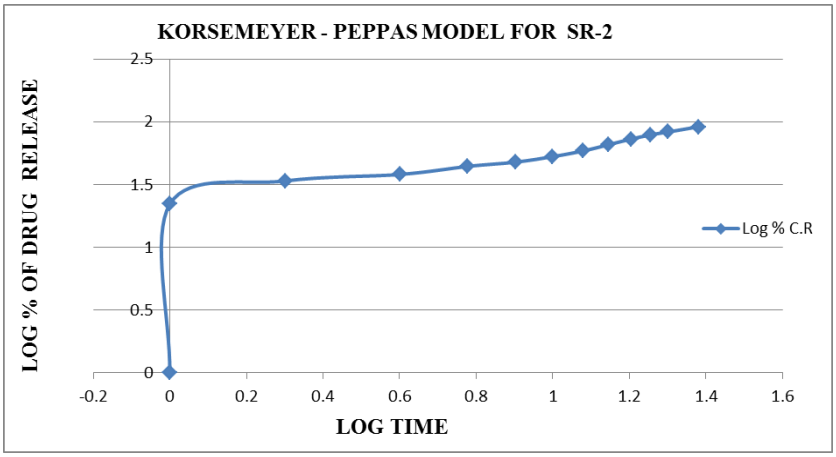

Figure no. 7: Korsmeyer –Peppas model for SR-2

DISCUSSION

The objective of the work was to design Sustained release matrix tablet of a flucloxacillin meant for antibacterial activity caused by Gram-positive and Gram-negative bacteria. To deliver the recommended total dose by oral administration, these gaining interest rapidly in the pharmaceutical industry due to their many advantages the most important being improved patient compliance especially in long delivery. Preformulation testing was the first step in the rational step in the development of dosage forms of a substance. The drug Flucloxacillin powder was examined for its organoleptic properties found it was observed that Flucloxacillin was white crystalline odorless powder. When tested for its solubility in various solvents, it was determined that drug sample was freely soluble in water 0.1 HCl, 6.8 pH buffer, 0.1 N HCl and 0.1 N NaOH, soluble in ethanol, Sparingly soluble in methanol. Also melting was 177 ^{0}C and Partition coefficient observed at 0.29 ±0.06. Flucloxacillin solution was scanned in the U.V. range of 200-400 nm using UV Visible spectrophotometer. The spectrophotometric method of analysis of Flucloxacillin at λ_{max} 238 nm was found to be reproducible and highly sensitive. The standard curves were prepared in 0.1 N HCl at λ_{max} 238 nm. The correlation coefficient greater than 0.999 was observed in all the cases, which indicated that, the drug follows Beer-Lambert's law in the concentration range of 5-25µg/ml. Physical compatibility study revealed there is no reaction between drug and polymer. The FT-IR spectrum of drug substance was authenticated using IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted. Drug and polymer compatibility study reveals that there is no interference between drug and polymer thus can be used for further formulation and evaluation purposes.

Sustained release matrix tablet bathes were prepared by the dry granulation method. Firstly, granules were prepared and Micromeritic properties bulk density between 0.62 to 0.68, tapped density ranges 0.69 to 0.83, Compressibility Index between 7.24 to 25.3, Hausner'ratio ranges 1.08 to 1.34 and angle of repose ranges 24.38 to 33.12 were calculated. Sustained release matrix tablet bathes were evaluated under following parameters e.g. hardness from 5.3 to 7.3 kg/cm^2, thickness from 2.4 to 2.7mm, diameter 9.1 for all, Weight variation from 1.75 to 6.21 %, content variation from 93.63 to 98.09 %, friability from 0.21 to1.85% and swelling index from 42 to68. Also all batches were tested for behavior, SR-1 showed swell and burst, but rest of formulations were slow swelling. On the basis these general evaluation of sustained release matrix tablet it was found, batch SR-2 shows good result. All batches were subjected for *in-vitro* Drug Release and obtained R^2 values revealed that SR-2 possessed excellent drug release profile with R^2 value 0.932. Because of excellent Drug Release profile of SR-2 the obtained data was expended for kinetic modeling and statistic representation and found that the batch SR-2 follows Zero Order kinetic model.

CONCLUSION

From the trial-and-error optimization design, flucloxacillin drug loaded Sustained Release Matrix Tablet were successfully prepared and evaluated. Preformulation study confirms purity of drug and compatibility of drug with excipients using visually and FT-IR spectroscopy. HPMC was found significant with the experimental results. It was confirmed that the increasing the concentration of HPMC increases the compressibility, hardness, and Swelling Index of tablets but decreases the drug release from matrix. Okra gum was also used in affixed amount which helpful to continuous discharge of drug. From characterization parameters and Drug release study, it was concluded that the formulation has all the parameters are acceptable as sustained release tablet, no any chemical interaction and was stable at refrigerated condition respectively. An extensive investigation is needed with reference to bioavailability and *in-vivo* drug release of batch SR-2. There is a need to develop suitable formulation for commercial exploitation. Thus, the specific objective listed in the plan of work of this thesis were achieved namely design, characterization and release studies of flucloxacillin Sustained Release Matrix Tablet.

CONFLICTS OF INTEREST

There are no conflicts of interests.

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