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Original Article

Design and Development of Fast Disintegrating Tablet to form Sustained Release Suspension of Cefixime by Extrusion and Spheronization Technique

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Abstract

The aim of present research work was undertaken with the objective of design and development of Fast disintegrating tablet to form sustained release suspension of Cefixime by Extrusion and Spheronization technique using sodium alginate, Eudragit RS100 and Eudragit RL100 as a release retardant polymer for geriatric and pediatric patients. Pellets were prepared by Extrusion and Spheronization technique using various concentration of polymer (sodium alginate, Eudragit RS100 and RL100). Pellets were evaluated for % drug loading, % friability, flow property, particle size, CPR and statistical data was evaluated. Optimize batch of pellets was used in formulation of Fast Disintegrating Tablets by using 3^2 factorial design. The drug: polymer ratio (X1) and speed of spheronization (X2) were selected as independent variables, while t_{50}, t_{90}, Q_6, n and k were selected as dependent variable. FDT was prepared using suspending agent and superdisintegrant to form sustained release suspension. FDT was evaluated for % drug content, %friability, weight variation, disintegration time and in-vitro dissolution study. The formulated suspension was also evaluated for sedimentation volume, redispersibility, viscosity and stability study. Optimize batch was compared with marketed product (ZIFI100). Cefixime pellets of all batches showed flow property in acceptable range, and % friability in <1%. All the batches exhibited appropriate percentage yield, particle size, Q_6, t_{50}, t_{90}, Diffusion coefficient (n) and Release rate constant (k). Optimized formulation (F9) showed 98.76% drug release at the end of 12 hrs and maximum similarity factor (f_2=77.90) and minimum dissimilarity factor (f_1=3.09) with Theoretical release profile of Cefixime. 6% of Crosscarmelose sodium disintegrate tablet in <50 sec. Batch F7- F9 showed disintegration in 42-43 sec. optimum concentration of xanthan gum was found to be 0.5% as suspending agent. F9 batch showed less disintegration time and number of strokes required very less of 7.0. Optimize formulation was stable after 18 days. Cefixime reference suspension showed good property and dissolution profile compared to marketed product (ZIFI100).

1. Introduction

Oral liquids are homogenous preparations containing one or more active ingredients dissolved or suspended in a suitable vehicle. They are intended to be swallowed either undiluted or after dilution. Suspension is a heterogenous system consisting of internal phase or suspended phase, which is made up of the particulate matter, dispersed uniformly with mechanical agitation throughout the external phase with the help of suspending agents, which is generally a liquid or semisolid. The particle size in the suspension ranges above 0.1µm. The dispersed phase may consist of discrete particles or it may be a network of particles, resulting from particle-particle interaction. The drugs are dispersed as suspensions for different reasons, but the most common one is poor aqueous solubility. The suspension offer greater stability to drug as it is not in solution form and in some cases enhanced bioavailability also occurs. The suspension can be easily administered to children of different ages by adapting the volume to swallow [1].

Cefixime is third generation cephalosporin antibiotic of the amino thiazol class. Cefixime exerts its bacterial effect by inhibiting protein synthesis and so inhibiting cell wall biosynthesis of bacteria. It's having shorter half life (3-4 hr), which enables daily single dose (400 mg) or twice a day (2*200 mg). Cefixime is used to treat many of bacterial infection. It is mainly used to treat peptic- ulcer, typhoid- fever, pneumonia, urinary tract infection, etc. In children less than 6 months, cefixime has not established its safety and efficacy. Cefixime is poorly water soluble drug, when it formulated as pellets, showed enhancement in bioavailability of drug [2].

Multiparticulate dosage forms such like beads, microspheres, microcapsules, pellets now to be most popular rather than non disintegrating single unit dosage forms. They having more surface area by which disintegrate more uniformly in GIT, resulting in more absorption and more bioavailability and reduce local irritancy and also avoid the unwanted intestinal retention of polymeric material. Also, the multiparticulate dosage forms are being formulated as liquid suspensions that are the ideal dosage form for pediatrics and geriatric patients due to their flexibility in measurement of dose, ease of swallowing, pleasant taste and attractive coloring and flavoring agent [3].

The concept of pellets can be utilized to provide a long lasting release of drug for local and systemic action. Extrusion and Spheronization generates multiunit matrix based particulate system that produce multiparticulate with spherical shape, good flow properties, low friability and uniform packing characteristics. Pellets can accommodate high drug loads, and modified drug release [4]. Whereas suspension includes taste masking of drug, higher patient compliance, reduce side effects and increase in rate of absorption of drug.

2. Materials and Methods

2.1 Materials

Cefixime was obtained as a gift sample from National pharmaceuticals, India. Eudragit RS100 and Eudragit RL100 were obtained as a gift sample from Evonic Degussa, India. Sodium alginate and Xanthan gum were obtained as gift sample from Finar chemicals, Mumbai, India. Crosscarmelose sodium was obtained as a gift sample from Lesar Chemicals Ltd. Mumbai, India. Microcrystalline cellulose was obtained as a gift sample from Chemodyes Corporation. All others reagents and chemicals used were of analytical reagent grade.

2.2 Methods

2.2.1 Preparation of Cefixime Pellets

Pellets were prepared by Extrusion and Spheronization technique. Cefixime as active ingredient, polymers (Sodium alginate, Eudragit RS100 and Eudragit RL100) and others ingredients were mixed in polyethylene bag for 5 min. In above mixture isopropyl alcohol (IPA) was added to make dump mass in mini-mixer (Table **1**). Prepare dump mass were subjected to undergoes to extrusion then, resultant extrudate subjected to Spheronization to get desired pellets at specified speed (700rpm, 800rpm and 900rpm) for 15 minutes. Pellets were formed and Collected in tray. Pellets were dried in hot air oven at temperature of 50 ^{0}C.

Table 1: Formulation Composition of Cefixime Pellets

Ingredient (%)	Formulations code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Spheronization Speed (rpm)								
	500 rpm			700 rpm			900 rpm		
Cefixime	20	20	20	20	20	20	20	20	20
Eudragit RS100	10	15	20	10	15	20	10	15	20
Sodium alginate	20	15	10	20	15	10	20	15	10
MCC	40	40	40	40	40	40	40	40	40
PEG400	1	1	1	1	1	1	1	1	1
$CaCO_3$	5	5	5	5	5	5	5	5	5
DCP	4	4	4	4	4	4	4	4	4
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

2.2.2 Preparation of Fast Disintegrating Tablets

Accurately weigh all the ingredients. Mix all the excipients (Xanthangum, crosscarmelose sodium, sodium citrate, sodium benzoate, flavor, color, magnesium Stearate and talc) according to geometric ratio. Take 200 mg Eq. Wt. of cefixime pellets. Mix cefixime pellets with above materials and add sucrose up to 1500 mg of the total weight of mixture (Table **2**). Set the die cavity by 16mm punch in tablet punching machine. Take all above materials in die cavity and compress the tablet and evaluate it.

Table 2: Formulation Composition of Fast Disintegrating Tablets

Ingredients (%)	Formulations code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime Pellets	200mg eq. wt. of cefixime								
Xanthan Gum	0.1	0.3	0.5	0.1	0.3	0.5	0.1	0.3	0.5
Crosscarmelose Sodium	2	2	2	4	4	4	6	6	6
Sodium Citrate	1	1	1	1	1	1	1	1	1
Sodium Benzoate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cherry Flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Colour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Sucrose	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg	Up to 1500 mg

2.2.3 Preparation of Reconstitutable Sustained Release Suspension

The fast disintegrating tablet was put in 30 ml of pure water containing glass and it disintegrates and form suspension.

Optimization of Variable Using Full Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design, 2 factors were evaluated; each 3 levels and experimental trials were performed for all 9 possible combinations. The polymer to copolymer ratio of sodium alginate and Eudragit RS100 (X1) and spheronization speed (X2) were chosen as independent variable in 3^2 full factorial design (Table **3**), while Q_6 (% drug release at 6 hours), t_{50} (time required for 50% drug release), t_{90} (time required for 90% drug release) were taken as dependent variables.

A 3^2 randomized full factorial design was used in development of dosage form. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response (Equation 1).

$$Y=b_0+b_1X_1+b_2X_2+b_{11}X_1X_1+b_{22}X_2X_2+b_{12}X_1X_2 \quad \text{..... (1)}$$

Where,

Y = dependent variable

b_0 = arithmetic mean response of the 9 runs

b_i =estimated coefficients for the factor X_i

The main effect (X_1andX_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are change simultaneously. The polynomial terms (X_1X_1, X_2X_2) are included to investigate nonlinearity [5,6].

Table 3: Low, Intermediate and High level values for each factor

Selection of level for independent variable		
Coded Value	X1 (Ratio of polymer to copolymer, ratio in %)	X2 (Speed of Spheronization)
-1	10:20	500
0	15:15	700
+1	20:10	900

***X1=polymer ratio, X2=spheronization speed**

Table 4: 3^2 Full Factorial Designs for Pellets

Batch Code	Coded Value		Uncoded Value	
	X1	X2	X1 (%)	X2 (%)
1	-1	-1	10:20	500
2	0	-1	15:15	500
3	+1	-1	20:10	500
4	-1	0	10:20	700
5	0	0	15:15	700
6	+1	0	20:10	700
7	-1	+1	10:20	900
8	0	+1	15:15	900
9	+1	+1	20:10	900

***X_1**= Ratio of polymer, **X_2**= Spheronization speed

The composition of factorial design batches (F1-F9) is shown in table **4**. The prepared formulations were evaluated for flow property, % practical yield, % drug loading, particle size, friability and in vitro drug release study.

2.3 Validation of Experimental Design

2.3.1 Check Point Batch

Polynomial equations were generated using Statistica 8 for selected responses like % yield, particle size, encapsulation efficiency, Q_6,Q_8, $t_{90\%}$, Exponential constant (n) and release rate constant (k).The generated polynominal equations were further reduced on the basis of significant terms obtained by applying ANOVA. The design was validated by preparing an extra check point formulation. The predicted values for response were determined on the basis of respective polynomial equations whereas the experimental values were determined by evaluating formulation for dependent variable. The predicted and experimental values of responses were compared for statistical significance using paired *t* –test [7].

2.3.2 Drug-Excipient Compatibility Studies

Fourier-transformed infrared (FT-IR) spectroscopic studies were performed to check the compatibility between drug and polymer in formulations. The FT-IR spectra of drug alone and with formulation polymers were obtained by KBr (Potassium Bromide) disk method and compared with the standard FT-IR spectrum of the pure drug.

2.3.3 Evaluation of Flow Properties of Pellets

Prepared pellets were evaluated for various parameters such as angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner's ratio [8, 9, 10].

2.4 Evaluation of Optimized Batches of Pellets

2.4.1 Friability

Accurately weighed quantity of pellets (3 gm) were taken from final batch of pellets and placed in a Friabilator and tumbled for 100 revolutions at 25 RPM. Twelve steel balls (Weighing 0.445 gm each) were used as attrition agent. Subsequently, the pellets were sieved through sieve no. 20 [11]. The weight loss (%) is calculated as (Equation 2):

$$F\ (\%) = (W_i - W_r / W_i) * 100 \quad \ldots\ldots\ldots\ldots\ldots\ (2)$$

Where, W_i is initial weight of pellets before friability testing, and W_r is the weight of pellets retained above the sieve after friability testing.

2.4.2. Drug loading (%)

The 100 mg Pellets were crushed and was dissolved in 10 ml methanol and then transferred to 100 ml of 0.1 N HC1 in volumetric flask. The solution was analyzed at 285 nm using double beam UV-Vis spectrophotometer after suitable dilution. The % drug loading was calculated from calibration curve [12,13].

2.4.3. Practical yield (%)

The percentage of production yield (wt/wt) was calculated from the weight of dried pellets (w1) recovered from each of batches and the sum of the initial dry weight of starting materials (w2). The formula for calculation of percentage yield is as follows in Equation 3 [14].

% Practical Yield = (Practical Value / Theoretical Value)*100 …….. (3)

2.4.4. *Particle size and size distribution*

The size and size distribution of the pellets produced was determined by agitation for 10 min with a sieve shaker fitted with a progression of standard sieves. From the weight retained on each sieve particle size is determined from standard sieve aperture size as per Indian pharmacopeia.

2.4.5 *In-Vitro* Dissolution Study

The in vitro dissolution study of 200 mg eq. wt. of cefixime pellets were performed as described in Indian Pharmacopoeia 2010 using USP apparatus II fitted with paddle (50 rpm) at 37°C ± 0.5°C using Simulated gastric fluid (pH 1.2; 700 ml) as a dissolution medium for first 2 hour and followed by phosphate buffer (pH 7.2; 900ml) by adding 200 ml of 0.2 mol/L tri sodium phosphate in dissolution media for remaining hours. At the 1 hrs time intervals, 5ml samples were withdrawn, and analysed at 285 nm in 0.1n HCL and 288 nm in 7.2 pH phosphate buffer using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve which is developed in the range of 4-20 µg/ml for 0.1N HCl and pH-7.2 phosphate buffer. All dissolution experiments were done in triplicate, under sodium lamp[15].

2.5 Evaluation of Fast Disintegrating Tablets

The prepared fast dissolving tablets were evaluated for hardness, thickness, weight variation, thickness, friability, content uniformity, disintegration time, wetting time and *in vitro* dissolution studies. Hardness of the tablets was tested using Rimek-K-DHT 100. Friability of the tablets was tested using Roche friabilator (Electrolab EF-2-USP). The thickness of the tablets was tested using vernier caliper (Mitutoyo CD-6, Japan). Weight variation test was performed according to Indian Pharmacopoeia 2010.

2.5.1 *In-vitro* drug release study

In-vitro drug release study for the prepared tablets were performed as described in Indian Pharmacopoeia 2010 using eight-station USP type II (Paddle) apparatus at 37°C ± 0.5°C and 50rpm speed. The dissolution studies were carried out in 900ml media of acid buffer of pH 1.2 for two hour and in phosphate buffer of pH 7.2 for remaining hours under sink condition. At predetermined time intervals, a 10 ml sample was withdrawn and replaced with fresh dissolution medium to maintain the volume constant. The samples withdrawn were filtered through a whatman filter paper and drug content in each sample was analyzed by double-beam UV-spectrophotometer (Shimadzu 1800, Kyoto, Japan) after suitable dilution at 285nm (1.2 pH of 0.1N HCl) and 288nm (7.2 pH phosphate buffer). The amount of drug present in each sample was calculated with the help of appropriate calibration curve and compared with reference standard.

2.6 Evaluation Parameter of Reconstitutable Suspension

2.6.1 Organoleptic property of suspension

It was evaluated by visual inspection, odour and colour was evaluated for each of batch of suspension.

2.6.2 pH

The pH of reconstitutable suspension was determined by using digital pH meter.

2.6.3 Viscosity

The viscosity of suspension was determined by Brookfield viscometer. In adepter 15 ml of suspension was taken and the adepter is set over the viscometer by a stand such a way that spindle is completely immersed in the suspension. Spindle number 3 was used.

2.6.4 Sedimentation volume

10 ml of each suspension was taken in 50 ml stopper 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 height of sediment was noted. This was the original height of sediment (H_0). The cylinder was kept undisturbed for 7 days. The height of sediment read at every 24 hr for 7 days was considered as final height of sediment (Hu) (Equation 4).

2.6.7 Sedimentation Volume (F) = Hu/H_0 …….. (4)

The ultimate height of the solid phase after settling depends on concentration of solid content. To obtain an acceptable suspension, F should be at least 0.9 for 1hour but a longer period was preferred for our purpose.

2.6.8 Redispersibility

Fixed volume of each suspension (10 ml) was kept in stoppered cylinder which was stored at room temperature for 7 days. The redispersibility was determined by studying number of strokes to redisperse the formed sediment at the end of 7 days of storage of the formulation [16-19].

2.6.9 Drug Release Kinetics

The rate and mechanism of *in-vitro* drug release from prepared dosage form was analyzed by fitting dissolution data into 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) Hixson-Crowell model, and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models [20].

2.7 Statistical Analysis

The statistical analysis of the factorial design batches was performed by multiple regression analysis using Microsoft Excel.

2.8 Similarity factor (f_2)

To evaluate and comparison of dissolution profiles, the dissolution profiles were analyzed using similarity factor f_2. The equation 5 for calculating f_2 is given below.

Similarity factor f_2

$$f_2 = 50X\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} x100\right\} \quad \text{..... (5)}$$

Where, n is numbers of dissolution time point, W_t is optional weight factor, R_t is reference dissolution point at time t and T_t is test dissolution point at time t. The f_2 value between 50 and 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

2.9 Dissimilarity factor (f_1)

The dissimilarity factor (f_1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves (Equation 6).

$$f_1 = \left\{\left[\sum_{t=1}^{n} n \mid \mathrm{Rt} - \mathrm{Tt} \mid\right] / \left[\sum_{t=1}^{n} n\,\mathrm{Rt}\right]\right\} \times 100 \quad \text{..... (6)}$$

Where n is the number of time points, Rt is the dissolution value of the theoretical dissolution profile at time t and Tt is the dissolution value of the formulation at time t. The values should lie between 0-15.For curves to be considered similar f_1 values should be close to 0 [20,21].

2.10 Accelerated Stability Studies

The accelerated stability study was done of optimize formulation for 18 days. To determine the change in physical properties and *in vitro* release profile on storage, optimized batch F9 were stored at 25°C±2°C/60% RH±5% RH and 40°C±2°C/75% RH±5% RH for 18 days. Samples were taken and evaluated for their redispersibility, sedimentation volume, CPR at a suitable time intervals and also, physical stability (colour, odour and pH) changes for the samples were examined [22]. Comparison of prepared suspension with marketed Cefixime Suspension (Zifi100). The prepared suspension was compared with marketed Cefixime Suspension formulation. Viscosity, redispersity, sedimentation volume, and *in-vitro* drug release study of suspension was compared.

3. Results and Discussion

3.1 Drug Excipient Compatibility Studies

As per figure 1, IR spectrum of cefixime shows N-H stretch, C-H stretch, C=O stretch, COOH stretch, CH=CH stretch at 3429.2 cm^{-1}, 3139.90 cm^{-1}, 1770.53 cm^{-1}, 1382.87 cm^{-1} respectively and indicates the purity of cefixime (Fig. **1**).

There is no significant difference in characteristic peaks of pure drug and drug excipients mixture suggesting the absence of drug. The formulation contains Cefixime, xanthan gum, Eudragit RS100, Eudragit RL100 (Fig. **2**).

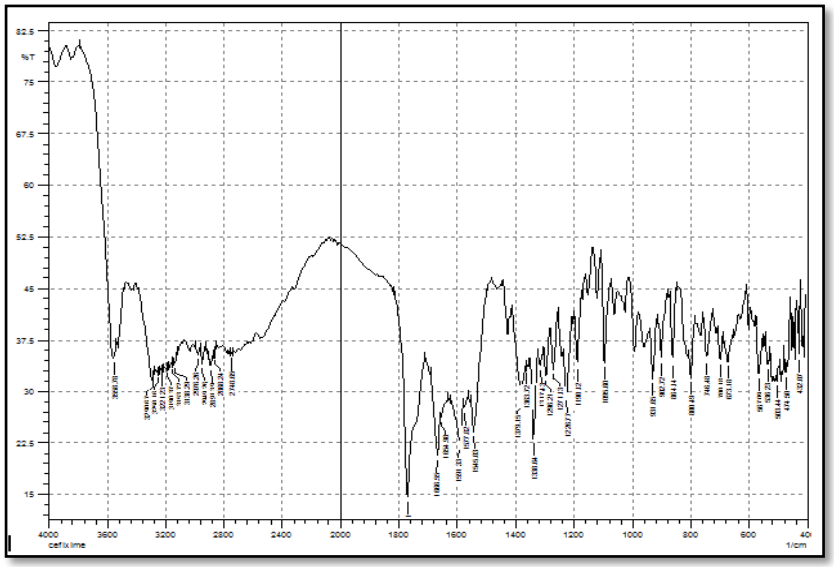

Fig. (1). FTIR study of Cefixime

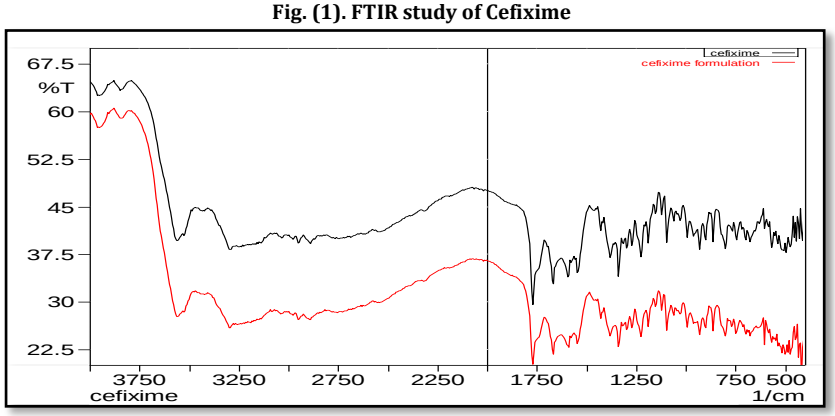

Fig. (2). Drug Excipient Interaction Study

3.2 Evaluation of Factorial Batch of Pellets

3.1. Flow property of Pellets

Pellets of proposed formulations were evaluated for Angle of repose, Loose Bulk density (LBD), Tapped bulk density (TBD), Hausner's ration (HR) and Carr's index (CI) (Table 5). Angle of repose of the all formulations was found to be in the range of 18.40 to 20.12 indicating acceptable range because of spherical shape of pellets and small size of pellets. The results of LBD and TBD for all formulations varied in the range of 0.60 g/cm^3 to 0.67 g/cm^3 and 0.67 g/cm^3 to 0.75 g/cm^3 respectively. The CI ranged from 9.80 % to 13.69 % and HR was found to be in the range of 1.10 to 1.15 indicating that all formulations showed excellent flow properties and compressibility.

Table 5: Evaluation of flow property of factorial batch of pellets

Batch Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	Carr's Index	Angle of Repose
F1	0.63	0.73	1.15	13.69	18.50
F2	0.65	0.74	1.13	12.16	19.69
F3	0.66	0.75	1.13	12.00	18.88
F4	0.61	0.69	1.13	11.59	19.13
F5	0.64	0.71	1.10	9.80	20.12
F6	0.67	0.75	1.11	10.66	18.15
F7	0.60	0.67	1.11	10.44	19.75
F8	0.62	0.69	1.15	10.14	19.29
F9	0.63	0.71	1.12	11.26	18.40

3.2 Evaluation of Pellets

Pellets were evaluated for several of evaluation parameters and they were evaluated for % friability, mean particle size, % yield and % drug loading. The result of all factorial batches (F1-F9) was shown in table **6** and that was found to be in good acceptable range.

Table 6: Evaluation of Factorial Batch of Pellets

Batch Code	% Friability (n=3)	Mean Particle Size (µm) (n=3)	% Yield of Pellets	% Drug Loading
F1	0.64 ±0.14	945 ±0.46	84	87
F2	0.63 ±0.12	939 ±0.24	82	85
F3	0.61 ±0.15	935 ±0.53	86	88
F4	0.592 ±0.11	921 ±0.54	81	86
F5	0.596 ±0.14	913 ±0.51	83	91
F6	0.601 ±0.18	894 ±0.25	79	83
F7	0.551 ±0.11	876 ±0.47	82	90.35
F8	0.562 ±0.10	866 ±0.39	78.7	87
F9	0.592 ±0.12	853 ±0.26	82.1	89.26

% friability: All batches having the % friability in acceptable range. Friability is an important parameter for pellets which shows the fractureness of pellets and which generally occurring during transportation. All formulations % friability showed in range to <1. Thus, it was in acceptable range.

Mean Particle size: Particle size was determined by sieve shaker analysis. Particle size play very important role in drug release property and mainly the spheronization speed affect the value of particle size. As Spheronization speed increase, decrease in particle size which depicted in table **6**. In above 9 factorial batches, at low speed of 500 rpm, particle size was found to be in range from 935 to 945µm for F1-F3 batches. At 700 rpm, mean particle size of F4-F6 batches were in range from 894-921 µm. At 900 rpm, F9 batch which having mean particle size 853µm due to higher speed of spheronizer. It was the smallest particle from all factorial batches**. % drug loading:** % Drug loading was carried out for F1-F9 batches and it was important to pellets. For all factorial batches, %drug loading was in range to 83-91%. % **practical yield:** % yield of pellets was calculated for all factorial batches and that was found to be in range from 78-86%. Low pellets yield occurred due to loss of material from extruder and spheronizer, during drying of t of pellets and also due to high rotational speed and dust formation occurred.

3.3 *In-vitro* drug release studies of pellets

In-vitro dissolution study for 9 batches was carried out and that was mentioned in Fig. **3**. F1, F2, F3 batches gave drug release 95.20%, 91.21%, 86.51% in 12 hours. Result showed that increase in Eudragit RS100 concentration, the drug release was retarded and it's gave drug release for long time due to these batches having large particle size. F4, F5 and F6 batches have particle size in medium range and smaller than F1-F3 batches, that having drug release in 97.85%, 93.15% and 91.35% respectively. Factorial batches F7-F9 gave drug release as 95.86%, 97.34% and 98.76% respectively. That showed that in 3 batches, concentration of Eudragit RS100 was increased and that decrease drug release and also particle size of these batches were small so drug release occurred in within 12hrs. Batch F9 showed drug release 98.76% in 12 hrs was good compared to all batches. This batch was optimizing batch and from this batch tablet was formulated.

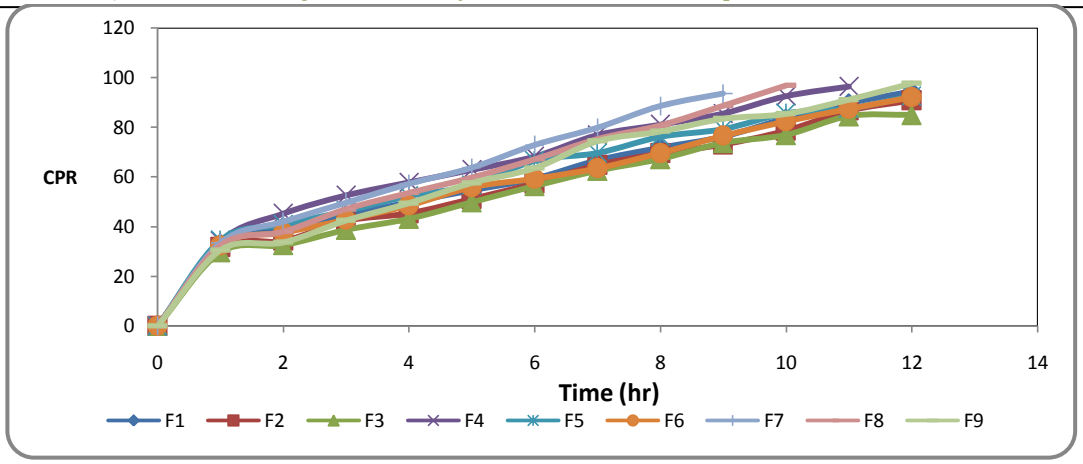

Fig. (3). Cumulative percentage release of Cefixime Pellets F1-F9.

3.4 Statistical Analysis of Factorial Batches

All batches contained pellets which contains drug and polymer -copolymer in a different ratio. In 3^2 full factorial design here takes independent variable X1 (polymer copolymer ratio) and X2 (spheronization speed). A 3^2 full factorial design was designed to study the effects of the polymer and copolymer and spheronization speed of extrusion spheronization on the Q_6, t_{50}, t_{90}, diffusion exponent (n) and release rate constant (k) of pellets. The result of analysis of variance test for all three effects indicated that the test is significant (Table **7**).

Table 7: Result of dependent variables

Batch Code	Variable Levels		t_{50}	t_{90}	Q_6	Diffusion Exponent (n)	Release rate Constant (k)
	X1	X2					
F1	-1	-1	4.02	11.16	61.09	0.435	0.2946
F2	0	-1	4.53	11.83	58.01	0.452	0.2713
F3	1	-1	5.01	12.37	55.37	0.4753	0.2483
F4	-1	0	2.82	9.58	68.78	0.4046	0.3470
F5	0	0	3.53	11.08	63.04	0.4112	0.3172
F6	1	0	4.21	11.69	59.54	0.4286	0.2903
F7	-1	1	3.06	8.35	72.19	0.4618	0.3191
F8	0	1	3.47	9.07	68.01	0.4815	0.2946
F9	1	1	3.99	10.27	62.77	0.5067	0.2657

A statistical model incorporating interactive and poly nominal terms used to evaluate the response (Equation 7).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2 \quad \text{..... (7)}$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of 9 runs, and b_1 is the estimated coefficients for the factor X_1.The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the responses changes when two factors are change simultaneously. The polynomial terms (X_1X_1, X_2X_2) are included to investigate nonlinearity.

Analysis of variance (ANOVA) was performed to identify insignificant factors. Data were analysed using Microsoft Excel software. The reduced models were developed for response variables by removing the insignificant terms with P more than 0.05. The terms with P less than 0.05 were considered statistically significance and retained in the reduced model.

1. Full and reduced model of t_{50} (hr)

$$Y = 3.51 + 0.55X_1 - 0.506X_2 + 0.0083X_1X_1 + 0.4933X_2X_2 - 0.015X_1X_2 \quad \text{..... (8)}$$

The coefficient of X1 that is, b_1 bear positive sign and coefficient of X2 that is (Equation 8), b_2 bear negative sign, and thus X1 on increasing the polymer: copolymer ratio increasing t_{50} (time in hours required for the release of 50% of the cefixime). X2 is different Spheronization speed that effect the t_{50} was highest from 500RPM containing formulation, intermediate from 700 RPM containing formulation and lowest from 900 containing formulation.

Table 8: Summary of results of regression analysis for t_{50} (hr)

Response t_{50} (hr)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	3.51	0.55	-0.506	0.0083	0.4933	-0.015	0.983	0.0006
P Value	6.5E-05	0.0026	0.0034	0.940	0.017	0.850	-	-
RM	3.84	0.551	-0.50	-	0.0083	-	0.859	0.014

Table 9: Calculation for testing the models in proportions for t_{50} (hr)

	DF	SS	MS	F	
Regression					
FM	5	3.854	0.770	36.23	Fcal = 0.024 Fcri = 9.55 Df = (2,3)
RM	3	3.366	1.122	10.174	
Residual					
FM	3	0.0638	0.02127		
RM	5	0.551	0.116		

The significance level of coefficients b_{11} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table **8**. The coefficients b_1, b_2 and b_{22} were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1, b_2 and b_{22} contribute significant information for the prediction of t_{50}. The results of testing the model in portions are shown in Table **9**. The critical value of F for α = 0.05 is equal to (DF=2, 3). Since the calculated value (F=0.024) is less than the critical value (F=9.55), it may be concluded that the omitted term do not contribute significantly to the prediction of diffusion exponent (n). The results are shown in the form of response surface plot in fig. **4**.

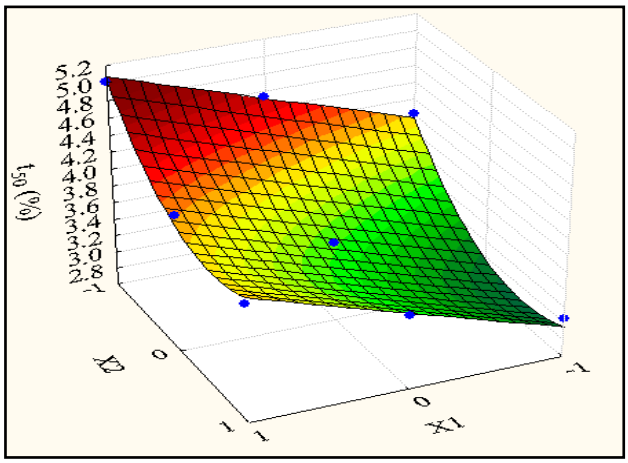

Fig. (4). Response surface plot of t_{50}

Here positive sign of the X1 variable (polymer: copolymer ratio) indicate that increase the polymer to copolymer ratio here increase the time of the percentage drug release. It may be due to increase polymer copolymer ratio so particle sizes in a shape are increase that means drug release time are increase.

Negative sign of X2 variable (spheronization speed) indicate that the here increase the spheronization speed decrease the time of the drug release due to concept here come that increase the spheronization speed there are decrease the particle size, decrease the particle size that means rapidly particle are dissolved or swallowed that means rapidly drug are released.

2. Full and reduced model of t_{90} (hr)

$$Y = 10.84 + 0.8733X_1 - 1.27X_2 - 0.09X_1X_1 - 0.275X_2X_2 + 0.177X_1X_2 \quad \text{..... (9)}$$

The coefficient of X1 that is, b_1 bear positive sign and coefficient of X2 that is, b_2 bear negative sign, and thus X1 on increasing the polymer: copolymer ratio increasing diffusion exponent (Equation 9). X2 is different spheronization speed that effect the diffusion exponent was highest from 500 RPM containing formulation, intermediate from 700 RPM containing formulation and lowest from 900 RPM containing formulation.

The significance level of coefficients b_{11}, b_{22} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table **10**. The coefficients b_1 and b_2 were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1 and b_{22} contribute significant information for the prediction of diffusion exponent (n). The results of testing the model in portions are shown in Table **11**. The critical value of F for α = 0.05 is equal to (DF=3, 3). Since the calculated value (F=1.14) is less than the critical value (F=9.27), it may be concluded that the omitted term do not contribute significantly to the prediction of t_{90}. The results are shown in the form of response surface plot in fig. **5**.

Table 10: Summary of results of regression analysis for t_{90} (hr)

Response t_{90} (Hour)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	10.84	0.8733	-1.27	-0.09	-0.275	0.177	0.982	0.0075
P Value	1.78E-05	0.0052	0.0017	0.692	0.2752	0.3112	-	-
RM	10.6	0.873	-1.278	-	-	-	0.963	4.9E-05

Table 11: Calculation for testing the models in proportions for t_{90} (hr)

	DF	SS	MS	F	
Regression					Fcal=1.146 Fcri=9.276 Df=(3,3)
FM	5	14.674	2.934	2.93	
RM	2	14.38	7.190	78.511	
Residual					
FM	3	0.2560	0.0853		
RM	6	0.549	0.0915		

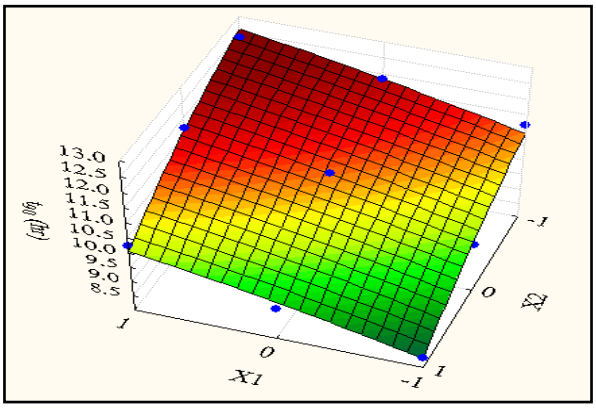

Fig. (5). Response surface plot of t_{90}

Here positive sign of the X1 variable (polymer: copolymer ratio) indicate that increase the polymer to copolymer ratio here increase the time of the percentage drug release. It may be due to increase polymer copolymer ratio so particle sizes in a shape are increase that means drug release time are increase.

Negative sign of X2 variable (spheronization speed) indicate that the here increase the spheronization speed decrease the time of the drug release due to concept here come that increase the spheronization speed there are decrease the particle size, decrease the particle size that means rapidly particle are dissolved or swallowed that means rapidly drug are released.

3. Full and reduced model of Q_6 (%)

$$Y = 63.60 - 4.06X_1 + 4.75X_2 + 0.27X_1X_1 - 0.88X_2X_2 - 0.925X_1X_2 \quad \text{..... (10)}$$

The coefficient of X1 that is, b_1 negative sign and coefficient of X2 that is, b_2 bear positive sign, and thus X1 on increasing the polymer: copolymer ratio decrease the Q6 (Equation 10). X2 is different spheronization speed that effect the diffusion exponent was highest from 500RPM containing formulation, intermediate from 700rpm containing formulation and lowest from 900 containing formulation.

Table 12: Summary of results of regression analysis for Q_6 (%)

Response Q_6 (%)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	63.60	-4.06	4.75	0.27	-0.88	-0.925	0.992	0.0022
P Value	1.7E-06	0.0010	0.0006	0.6592	0.210	0.099		
RM	63.2	-4.06	4.75	-	-	-	0.971	2.3E-05

Table 13: Calculation for testing the models in proportions for Q_6 (%)

	DF	SS	MS	F	
Regression					
FM	5	239.55	47.91	78.13	Fcal=2.78 Fcri=9.27 Df=(3,3)
RM	2	234.43	117.21	101.09	
Residual					
FM	3	1.8396	0.6132	-	
RM	6	6.95	1.159	-	

The significance level of coefficients b_{11}, b_{22} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in table **12**. The coefficients b_1 and b_2 were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1 and b_{22} contribute significant information for the prediction of diffusion exponent (n). The results of testing the model in portions are shown in Table **13**. The critical value of F for α = 0.05 is equal to (DF=3, 3). Since the calculated value (F=2.78) is less than the critical value (F=9.27), it may be concluded that the omitted term do not contribute significantly to the prediction of Q_6 (%). The results are shown in the form of response surface plot in Fig. **6**.

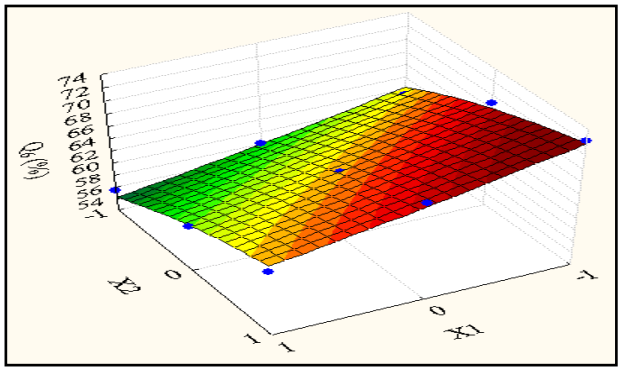

Fig. (6). Response surface plot of Q_6 (%)

4. Full and reduced model of diffusion exponent (n)

$Y = 0.4122 + 0.0182X_1 + 0.014X_2 + 0.0037X_1X_1 + 0.0539X_2X_2 + 0.0011X_1X_2$ ..... (11)

The coefficient of X1 that is, b_1 bear positive sign and coefficient of X2 that is, b_2 bear positive sign, and thus X1 on increasing the polymer: copolymer ratio increasing diffusion exponent (Equation 11). X2 is different spheronization speed that effect the diffusion exponent was highest from 500rpm containing formulation, intermediate from 700rpm containing formulation and lowest from 900rpm containing formulation.

Table 14: Summary of results of regression analysis for diffusion exponent (n)

Response diffusion exponent (n)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	0.4122	0.0182	0.014	0.0037	0.0539	0.0011	0.987	0.0048
P Value	3.21E-06	0.0057	0.010	0.458	0.0011	0.7382	-	-
RM	0.414	0.0182	0.014	0.053	-	-	0.983	7E-05

Table 15: Calculation for testing the models in proportions for diffusion exponent (n)

	DF	SS	MS	F	
Regression					
FM	5	0.0091	0.0018	46.341	Fcal=0.427 Fcri=9.552 Df=(2,3)
RM	3	0.0090	0.0030	99.79	
Residual					
FM	3	0.00011	3.93E-05	-	
RM	5	0.00015	3.03E-05	-	

The significance level of coefficients b_{11} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table **14**. The coefficients b_1, b_2 and b_{22} were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1, b_2 and b_{22} contribute significant information for the prediction of diffusion exponent (n). The results of testing the model in portions are shown in Table **15**. The critical value of F for α = 0.05 is equal to (DF=2, 3). Since the calculated value (F=0.427) is less than the critical value (F=9.55), it may be concluded that the omitted term do not contribute significantly to the prediction of diffusion exponent (n). The results are shown in the form of response surface plot in Fig. **7**.

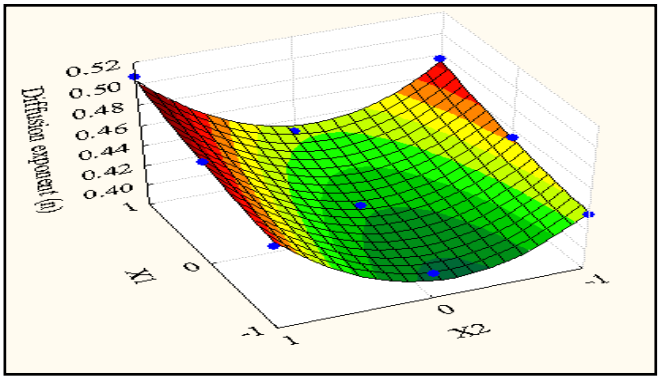

Fig. (7). Response surface plot of diffusion exponent (n)

5. Full and reduced model for release rate constant (k)

$Y = 0.3183 - 0.026X_1 + 0.010X_2 - 0.0002X_1X_1 - 0.035X_2X_2 - 0.00178X_1X_2$ ..... (12)

The coefficient of X1 that is, b_1 bear negative sign and coefficient of X2 that is, b_2 bear positive sign, and thus X1 on increasing the polymer: copolymer ratio increasing diffusion exponent (Equation 12). X2 is different spheronization speed that effect the diffusion exponent was highest from 500RPM containing formulation, intermediate from 700 RPM containing formulation and lowest from 900RPM containing formulation.

Table 16: Summary of results of regression analysis for release rate constant (k)

Response release rate constant (k)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	0.3183	-0.026	0.010	-0.0002	-0.035	-0.00178	0.99	0.0004
P Value	4.9E-07	0.00014	0.001	0.920	0.0002	0.264		
RM	0.3181	-0.026	0.010	-0.035	-	-	0.99	2.68E-06

Table 17: Calculation for testing the models in proportions for release rate constant (k)

	DF	SS	MS	F	
Regression					
FM	5	0.007376	0.0014	219.03	Fcal=0.941 Fcri=9.55 Df=(2,3)
RM	3	0.0073	0.0024	373.14	
Residual					
FM	3	2.02E-05	6.73E-06	-	
RM	5	3.29E-05	6.58E-06	-	

The significance level of coefficients b_{11} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table **16**. The coefficients b_1, b_2 and b_{22} were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1, b_2 and b_{22} contribute significant information for the prediction of diffusion exponent (n). The results of testing the model in portions are shown in Table **17**. The critical value of F for α = 0.05 is equal to (DF=2, 3). Since the calculated value (F=0.941) is less than the critical value (F=9.55), it may be concluded that the omitted term do not contribute significantly to the prediction of diffusion exponent (n). The results are shown in the form of response surface plot in fig. **8**.

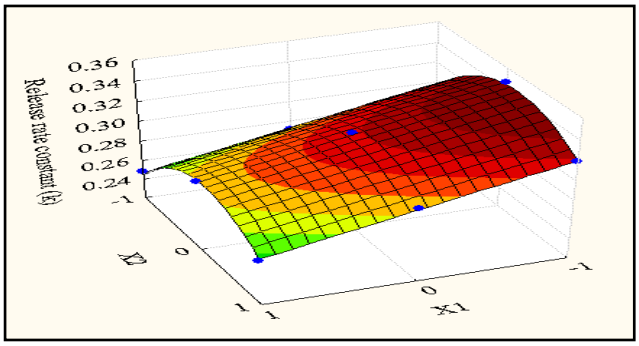

Fig. (8). Response surface plot of release rate constant (k)

Kinetic Modeling of Dissolution Data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Krosemeyer-Peppas model as evident from regression coefficients (table 20). The value of diffusion exponent (n) for F1 to F9 factorial formulations was between 0.4046 to 0.5061 so it indicates Fickian diffusion of the drug from formulation which corresponds to diffusion, erosion and swelling mechanism. Kinetic model Higuchi indicating that R^2 value of F1 to F9 was between 0.981 to 0.998 shows that drug release type was diffusion type from gel network and extended drug release for longer period of time. Kinetic Model Zero order indicating that R^2 value of F1 to F9 was in range 0.981 to 0.999 that near about 1.000 clearly mentioned that drug release from stiff gel networking was Zero order drug release that not depend on concentration of drug.

Table 18: Kinetic Modeling of Dissolution Data

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order									
S	5.59	5.481	5.42	5.912	5.297	5.346	7.564	7.139	6.374
I	27.54	25.13	22.86	33.31	31.26	27.45	26.81	25.18	24.53
R^2	0.999	0.998	0.998	0.999	0.997	0.998	0.999	0.999	0.994
First order									
S	0.040	0.041	0.043	0.039	0.037	0.039	0.0533	0.051	0.046
I	1.523	1.489	1.455	1.583	1.555	1.5164	1.522	1.504	1.491
R^2	0.991	0.989	0.987	0.986	0.982	0.989	0.993	0.996	0.976
Higuchi									
S	25.45	24.98	24.78	26.11	24.34	24.37	30.49	30.09	29.28
I	1.85	-0.12	-2.33	7.57	6.35	2.79	-0.769	-3.17	-5.400
R^2	0.984	0.985	0.987	0.991	0.992	0.986	0.985	0.985	0.988
Hixon Crowell									
S	-1.864	-1.827	-1.809	-1.970	-1.765	-1782	-2.52	-2.379	-2.124
I	24.15	24.95	25.73	22.22	22.91	24.18	24.39	24.93	25.154
R^2	-0.999	-0.998	-0.998	-0.999	-0.997	-0.998	-0.999	-0.999	-0.994
Korsemeyer and Peppas									
N	0.4350	0.4520	0.4753	0.4046	0.4112	0.4286	0.4618	0.4815	0.5061
I	-0.530	-0.566	-0.604	-0.459	-0.4986	-0.5370	-0.496	-0.530	-0.575
R^2	0.978	0.976	0.980	0.986	0.984	0.977	0.980	0.981	0.978
S= Slope, I= Intercept, R^2= Square of correlation coefficient, n = Diffusion exponent									

Kinetic Model First order indicating that R^2 value of F1 to F9 was between 0.956 to 0.986 that having less than Zero order release R^2 value (Table **18**), mentioned that drug release type was not first order release from gel network.

Comparison of Dissolution Profiles for Selection of Optimum Batch

The values of Dissimilarity factor (f_1) for batches F1, F2, F3, F4, F5, F6, F8, and F9 were less than 15 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch F9 showed minimum value of f_1 (3.09). The values of similarity factor (f_2) for batches F1, F2, F3, F4, F5, F6, F8, and F9 were greater than 50 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch F9 showed maximum value of f_2 (77.90) and result are depicted in Table **19**.

Table 19: Similarity Factor *(f_2)* and Dissimilarity factor *(f_1)* for F1-F9

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Similarity factor *(f_2)*	75.68	64.61	56.82	57.25	69.46	67.41	51.16	60.23	77.90
Dissimilarity factor *(f_1)*	4.14	6.73	10.33	11.68	5.85	5.80	17.11	10.36	3.09

Check Point Batch

The 3^2 factorial designs were run with one check point composition of which is shown in Table **20**. Batch CP1 was prepared to validate the derived equation for *in-vitro* dissolution time of pellets with one check point composition. The data for *in vitro* dissolution time for the predicted and observed values are shown in table **20**.

Table 20: Composition and Evaluation parameter and *in-vitro* dissolution of check point batch

Check point batch (CP1)	*In-vitro* dissolution study					
	t_{50}		t_{90}		Q_6	
	P	O	P	O	P	O
X1= -0.5; X2= +0.5; X3= 7.5	2.86	3.84	9.63	9.98	68.0	64.0

Check point batch (CP1)	*In-vitro* dissolution study			
	Exponential constant (n)		Release rate constant (k).	
	P	O	P	O
X1= -0.5; X2 = +0.5; X3= 7.5	0.4234	0.4718	0.3279	0.2858

***P= Predicted value; O = Observed value**

It can be observed that the predicted value and observed value for CP1 for *in-vitro* dissolution time of pellets were nearly similar with 3^2 factorial designs batches. It can be concluded that the evolved model can be used for prediction of response i.e. *in-vitro* dissolution time of pellets within the simplex space. Comparative analysis of the predicted value and experimental value using paired *t* – test indicated that there was no significant difference between the two values thereby establishing validity of generated mode. In this research work between the t_{stat} (0.60) and t_{cri} (2.77) not significant difference and t_{cri} value very high as compare to $t_{stat.}$

In the present research work, no very much difference between factorial batches and one check point composition small between predicted and experimental value.

5.8 Evaluation of Fast Disintegrating Tablets

The physical parameters such as hardness, weight variation test, % friability, % drug content, wetting time and disintegration time of all the formulated tablets were given in Table **21**. Hardness of all the tablets (F1-F9) was in the range of 3.4±0.12 kg/cm^2 to 3.7±0.12 kg/cm^2. The percentage friability ranged from 0.81±0.17 % to 0.91±0.13 % i.e. less than 1% and all batches comply this test. According to IP, ±5% weight variation is acceptable range for this test and average percent deviation of all the tablets (F1-F9) were found within the limit hence all formulation passed the weight variation test. The % drug content was found to be uniform and ranged from 95.82±0.11 % to 99.78±0.10 %. The wetting time ranged from 30±3 to 53±3. Batch F9 having wetting time 30 sec. so, from result it showed that increase in concentration of super-disintegrants resulted in decrease in wetting time. The disintegration time ranged from 42±2 to 71±2. From the result it was found that increasing of concentration of super disintegrants that resulted in decreasing the disintegration time. Batch F7 and F9 having disintegration in 42 sec.

Table 21: Evaluation of Fast Disintegrating Tablets

Batch Code	Hardness (Kg/cm^2)*	Weight Variation (mg) (n=20)	Friability (%)*	Drug Content (%)*	Wetting Time (Sec)*	Disintegration Time (sec)*
F1	3.5±0.10	1469.5 ±1.25	0.85 ±0.13	98.27 ±0.11	52 ±2	70 ±3
F2	3.4 ±0.12	1445.5 ±1.37	0.83 ±0.15	96.22 ±0.16	49 ±3	69 ±2
F3	3.6 ±0.14	1511.6 ±1.25	0.81 ±0.17	99.48 ±0.12	53 ±3	71 ±2
F4	3.5 ±0.19	1485.4 ±1.52	0.89 ±0.14	101.1 ±0.10	41 ±2	63 ±3
F5	3.4 ±0.17	1536.7 ±1.65	0.90 ±0.16	97.42 ±0.13	40 ±4	62 ±2
F6	3.5 ±0.20	1454.9 ±1.45	0.82 ±0.11	95.82 ±0.11	40 ±2	63 ±2
F7	3.7 ±0.12	1528.3 ±1.26	0.83 ±0.14	103.2 ±0.16	31 ±3	42 ±3
F8	3.5 ±0.22	1533.9 ±1.53	0.91 ±0.13	99.78 ±0.10	32 ±2	43 ±1
F9	**3.6** ±0.20	**1494.6** ±1.56	**0.81** ±0.17	**98.64** ±0.14	**30** ±3	**42** ±2

***= mean SD (n=3)**

***In-vitro* dissolution study of Fast Disintegrating Tablet**

In- vitro dissolution study for 9 formulation batches was carried out and that was mentioned in fig. **9**. F1, F2, F3 batches gave drug release 94.43%, 90.82%, 84.97% in 12 hours. Result showed that increase in polymer concentration, the drug release was retarded and it's gave drug release for long time. Also these batches having large particle size. F4, F5 and F6 batches have particle size in medium range and smaller than F1-F3 batches, that having drug release in 96.43%, 92.54% and 92.15% respectively. Factorial batches F7-F9 gave drug release as 93.56%, 96.86% and 97.79% respectively. That showed that in 3 batches, concentration of Eudragit RS100 was increased and that decrease drug release and also particle size of these batches were small so drug release occurred in within 12hrs. Batch F9 showed drug release 97.79% in 12 hrs was good compared to all batches. This batch was optimizing batch and from this batch tablet was formulated.

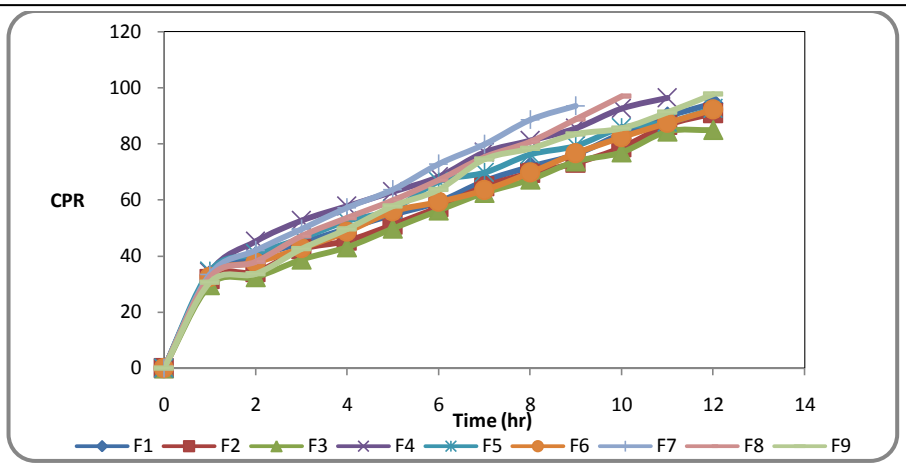

Fig. (9). *In-vitro* Drug release studies of fast disintegrating tablets of F1 to F9

Evaluation of Reconstitutable SR Suspension

Organoleptic Property of Reconstitutable Suspension

Organoleptic property of SR Suspension was evaluated and it was found that all F1-F9 batches having red color and odour was cherry. That showed in table 27.

Viscosity

Viscosity of suspension was measured by Brook-Field viscometer. Viscosity of all formulation was shown in Table **22**. Xanthan gum having used in several of concentration and that the result showed batches F3, F6 and F9 had high viscosity than other batches. High viscosity of suspension results in high sedimentation volume and better Redispersibility. As the viscosity of suspension was high, the solid materials sediment slowly and also prevents sedimentation of solid material. So the number of strokes was less required and by this redispersibility was good.

Redispersibility

Redispersibility was important factor if there is no redispersion then it will lead to caking of solid content and if caking occurs then that results in non-uniform dose of drug. Because drug will remain in cake, it was measured by means of number of strokes required. Minimum number of strokes required for batches F3 and F9 was 7.

Table 22: Evaluation of Reconstitutable SR Suspension

Batch Code	pH	Viscosity (cps)	Redispersibility (No. of strokes)	Color	Odour
F1	6.9	688	11	Red	Cherry
F2	6.8	710	9	Red	Cherry
F3	6.9	735	7	Red	Cherry
F4	6.6	686	10	Red	Cherry
F5	6.7	713	9	Red	Cherry
F6	6.8	734	8	Red	Cherry
F7	6.6	690	11	Red	Cherry
F8	6.8	708	8	Red	Cherry
F9	6.5	737	7	Red	Cherry

Sedimentation Volume

The sedimentation volume was measured to check the physical stability of the suspension. The sedimentation volume has values ranging from less than 1 that was shown in Table **23**. The sedimentation volume (F) should be at least 0.9 for 1 hr but a longer period is preferred for our purpose. The sedimentation volume in above formulations is shown in Table **23**. The results showed that for formulation batch F3, F6 and F9 the sedimentation volume was 0.914, 0.9 and 0.914 respectively even after 7 days which is nearer to the standard value of sedimentation volume 1. Means no sediment of the solid content occurred at the end of 7 days. So the formulation of batch F3, F6 and F9 was better than all other formulation as they all had sedimentation volume less than batch F3, F6 and F9.

Table 23: Evaluation of Sedimentation volume of Reconstitutable SR Suspension

Formulations	Height of Sediment (cm) After								Sedimentation Volume F=Hu/Ho
	3 Min Ho	1 Day	2 Day	3 Day	4 Day	5 Day	6 Day	7 Day Hu	
F1	7.0	6.2	5.3	4.4	4.3	3.4	3.2	3.2	0.457
F2	7.0	6.4	5.2	5.0	4.8	4.7	4.4	4.3	0.614
F3	7.0	6.7	6.6	6.5	6.5	6.4	6.4	6.4	0.914
F4	7.0	6.2	5.2	4.3	4.2	3.3	3.1	3.1	0.442
F5	7.0	6.5	5.5	4.9	4.7	4.7	4.3	4.2	0.600
F6	7.0	6.6	6.5	6.5	6.4	6.4	6.3	6.3	0.900
F7	7.0	6.4	5.3	4.2	4.1	3.3	3.1	3.0	0.428
F8	7.0	6.6	5.6	5.2	4.9	4.8	4.6	4.5	0.640
F9	7.0	6.8	6.6	6.5	6.5	6.4	6.4	6.4	0.914

Accelerated Stability Study of Reconstitutable SR Suspension

The optimize formulation was evaluated to carry out accelerated stability study for 18 days and the physical property of suspension with sedimentation volume, Redispersibility, pH and % drug release was evaluated. The data depicted in table **24**. After 18 days, no change in odour and colour of suspension. The pH was found to be 6.3 and sedimentation volume was 6.1, redispersibility was found to be no. of strokes was required 8. The dissolution data was found that after 18 days 96.58% drug release occurred in 12 hours.

Table 24: Evaluation of Accelerated Stability study of Reconstitutable SR Suspension

Evaluation Parameters	Initial	After 18 days
Colour	Red	Red
Odour	Cherry	Cherry
pH	6.5	6.3
Sedimentation volume	6.4	6.1
Redispersibility	7	8
% Drug Release	97.79	96.58

Comparison of suspension with Marketed suspension (ZIFI 100)

Cefixime reconstitutable suspension was compared with marketed product of cefixime suspension and was evaluated for physical property, pH, sedimentation volume, redispersibility, % drug release. The result was showed in Table **26**.

Table 25: *In-Vitro* Dissolution Study of Marketed Suspension (ZIFI 100)

Time (min)	0	5	10	20	30	40	50
CPR	0	17.29	36.18	53.47	69.13	82.56	97.12
Standard deviation value of final batch is within limits (±1.5)							
Average of three dissolution data (n=3)							

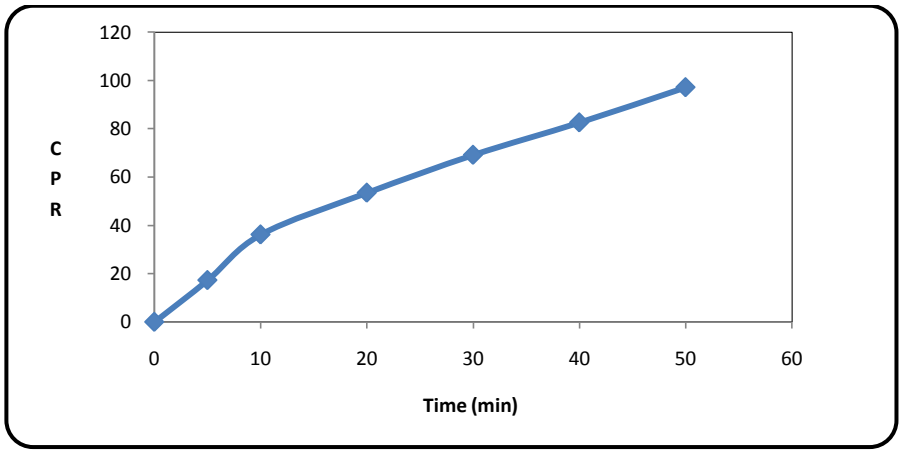

Fig. (10). *In-vitro* drug release studies of Marketed Cefixime Suspension

Marketed suspension required no. of strokes was 9 compared to reference suspension and sedimentation volume of marketed suspension was 6.1 in compared to reference. Viscosity of reference suspension was less compared to marketed suspension. The dissolution data was showed that marketed cefixime suspension had % drug release 97.12% in 50min (Fig. 10) and reference suspension had drug release 97.79% in 12hrs. The result was showed in Table **25**. So reference suspension had good property and sustained release property compared to marketed suspension so it was better and will be widely applicable in industry.

Table 26: Comparison of suspension with marketed suspension

Evaluation Parameters	Cefixime Suspension (Reference)	Cefixime Suspension (Marketed Product 'ZIFI100')
Colour	Red	Orange
Viscosity (cps)	737	791
pH	6.5	6.7
Sedimentation Volume	6.4	6.1
Redispersibility	7.0	9.0
% Drug Release	97.79 (in 12 hrs)	97.12 (in 50 min)

4. Conclusion

It was concluded that drug to polymer ratio and Spheronization speed had a significant effect on percentage yield, particle size, and drug release rate. It was found that pellets containing sodium alginate had low friability (due to higher matrix forming property) compared to pellets prepared from Eudragit RS100 and RL100 (poor matrix forming property). Drug release rate decreases with increase in the concentration of drug to polymer ratio in which single of polymer was unable to retard the drug release for 12 hrs. It was also concluded that particle size decreases with increase in spheronization speed. Optimized formulation (F9) showed 98.76% drug release at the end of 12 hrs and maximum similarity factor (f_2=77.90) and minimum dissimilarity factor (f_1=3.09) with Theoretical release profile of Cefixime. Disintegration time decreases with increase in concentration of superdisintegrant and viscosity of suspension increases with increase in concentration of suspending agent that result in better redispersibility.

Comparative analysis of the predicted value and experimental value using paired *t* – test indicated that there was no significant difference between the two values thereby establishing validity of generated mode of Evaluation parameter and *in-vitro* dissolution time of pellets with one check point composition.

Various kinetic models confirmed that in-*vitro* release kinetic of optimized batch (F9) was best fitted to zero order model & Higuchi with anomalous non-fickian release mechanism. The optimized batch was found to be stable after 18 days at accelerated condition.

Conflict of Interest

The author declares no conflict of interest.

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