Original Article

DESIGN AND OPTIMIZATION OF PEDIATRIC CEFUROXIME AXETIL DISPERSIBLE TABLET CONTAINING ION-EXCHANGE RESIN

NISHANT OZA*, SWATI SAGAR

C. U. Shah College of Pharmacy and Research, Wadhwan City 363030, Gujarat, India
Email: ozanishant@gmail.com

ABSTRACT

Objective: The aim of present work was to develop of pediatric cefuroxime axetil 125 mg dispersible tablets by using ion exchange resin as a taste masking agent and quality target product profile was defined based on the properties of the cefuroxime axetil.

Methods: Initially, cefuroxime axetil and various resin complexes (DRC) were prepared with different conditions and evaluated for taste masking and drug loading. Optimized DRC was used to formulate the dispersible tablet. A 3^2 full factorial design was employed to study the effect of mannitol (X_1) and microcrystalline cellulose PH-101 (X_2) on drug release at 10 min and time taken to 80% drug release. In the present study, the following constraints were arbitrarily used for the selection of an optimized batch: $Q_{10}>65\%$ and $T_{80\%}<30$ min. Multiple linear regression analysis, ANOVA and graphical representation of the influence factor by 3D plots were performed by using Sigmaplot 11.0. Checkpoint batch was prepared to validate the evolved model.

Results: Among the various drug resins complex DRC-9 was found with less bitter taste which was containing kyron T-114 and among the all factorial batch F_7 showed highest drug release at 10 min (Q_{10}) and lowest time taken to 80% drug release (T_{80}) hence batch F_7 was selected as an optimized batch and it's found to be stable in the stability evaluation.

Conclusion: The results of full factorial design indicate mannitol and MCC PH-101 have a significant effect on drug release.

Keywords: Taste masking, Ion exchange resin, Cefuroxime axetil, Dispersible Tablet, 3^2Full Factorial Design

INTRODUCTION

Oral route of drug administration is the most appealing route for drug delivery. Among the various dosage forms tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, and stability compared with other forms etc. A number of orally administered drugs exhibit natural bitter taste that creates an unpleasant feeling in the mouth [1, 2]. Therefore, it is necessary to reduce or mask the bitterness for enhancing patient acceptability and improving oral palatability of bitter drugs. Cefuroxime axetil has a broad spectrum antibacterial agent with a bitter taste, so it is necessary to mask the bitter taste for pediatric patients [3, 4]. Different methods have been suggested for masking of the bitter taste, which includes coating, inclusion complexes, molecular complexes, solid dispersion, microencapsulation, multiple emulsions, liposome's, Prodrugs and mass extrusion method from that ion exchange resin is one of most extensively method to overcome this problem [5, 6].

The present study was aimed to prepare the drug-resin complex (DRC) of cefuroxime axetil and evaluate for taste and drug loading. It was compressed into tablets by direct compression method. A 3^2 full factorial design was employed to study the effect of mannitol (X_1) and MCC PH-101 (X_2) on drug release at 10 min (Q_{10}) and time is taken to 80 % drug release (T_{80}). In the present study, the following constraints were arbitrarily used for the selection of an optimized batch: $Q_{10}>65$ % and $T_{80\%}<30$ min [7, 8].

MATERIALS AND METHODS

Materials and reagents

Cefuroxime axetil was received as a generous gift from Lincoln pharmaceutical Ltd., Ahmedabad, Gujarat, India. Kyron T 114 and kyron T 134 was obtained from Corel pharma ltd., Ahmedabad, Gujarat, India. Microcrystalline cellulose PH 101 and mannitol were purchased from Astron chemicals, Mumbai, Maharashtra, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Drug excipients compatibility study

The physicochemical compatibilities of the drug and excipients were tested by differential scanning calorimetric (DSC) analysis. Thermograms of cefuroxime axetil, drug-resin complex and drug-excipients physical mixture were derived from DSC with a thermal analysis performed by using an automatic thermal analyzer system (DSC 60, Shimadzu, Japan). The analysis was performed at a rate of 20 °C/min from 50 °C to 300 °C under a nitrogen flow of 25 ml/min [9, 10].

Development and evaluation of drug-resin complex (DRC)

In the batch process, the activated resin was placed in a beaker containing deionised water and allows swelling for 30 min. accurately weighed cefuroxime axetil was added and stirred for different periods of time at various pH as shown in table 3. The mixtures were filtered and the residue was washed with deionised water to remove the loosely adsorbed drug from the surface. DRC was allowed to dry at room temperature and was stored in a tightly closed container. DRC was evaluated for taste and drug loading. Taste of drug-resin complexes was subjected to gustatory sensory evaluation test performed by a panel of ten volunteers. The volunteers were selected randomly and instructed to rate the samples as per the taste evaluation scale. For drug loading analysis 50 mg of DRC was added in 0.1 N HCL and kept in a sonicator for 30 min. The samples were withdrawn and taking absorbance at 277 nm [11, 12].

Preliminary trail of cefuroxime axetil 125 mg dispersible tablets

Cefuroxime axetil 125 mg dispersible tablets was prepared according to the formula given in table 1. All the ingredients were passed through 60# sieve separately and mixed in geometrical order. First MCC, mannitol, SSG were mixed together then add the DRC and mixed for 10 min. Finally, sodium saccharin or aspartame, sodium stearyl fumarate or magnesium stearate and talc were mixed for 10 min. Compression was carried out using 11 mm punch set. All the batches

were stored properly and evaluation was carried out [13, 14].

Evaluation of cefuroxime axetil 125 mg dispersible tablets

Thickness, hardness, weight variation, % friability and disintegration test of the formulations were measured as described by Yadav K *et al.,* Khar RK *et al.,* Madgulkar AR *et al.,* and Lakade SH *et al.,* respectively [15-18].

Wetting time: It can be measured by using five circular tissue papers of 10 cm in diameter, which are placed in a petridish of 10 cm diameter. 10 ml of eosin solution is added to the petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet is noted as the wetting time.

The fineness of dispersion: It is an assessment of the grittiness which arises due to the disintegration of the tablet into coarse particles. The test was performed by placing two tablets in 100 ml

water and stirring it gently, till the tablets get completely disintegrated. The formulation was considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μm without leaving any residue on the mesh.

In vitro dissolution study: Drug release studies were carried out using by USP II dissolution test apparatus at 37±0.5 °C and 50 rpm. In this study, 0.1 N HCl (pH 1.2) was used as a dissolution medium. Aliquots of 5 ml were withdrawn at predetermined time intervals and an equal amount of fresh dissolution medium was added. The solution was suitably diluted and assayed at 277 nm using a UV-Vis double-beam spectrophotometer.

Taste analysis: All the batches of tablets were subjected to the gustatory sensory evaluation test performed by a panel of ten volunteers. The volunteers selected randomly and instructed to rate the samples as per the taste evaluation scale [19, 21].

Table 1: Preliminary trail formulation of cefuroxime axetil 125 mg dispersible tablets

S. No.	Ingredients	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14
1	DRC*	543	543	543	543	543	543	543	543	543	543	543	543	543	543
2	Crosspovidone	20	25	-	-	-	-	-	-	-	-	-	-	-	-
3	Croscarmellose Sodium	-	-	20	25	-	-	30	-	30	-	-	-	-	-
4	Sodium Starch Glycolate	-	-	-	-	20	25	-	30	-	30	40	45	30	30
5	Aspartame	20	20	20	20	20	20	-	-	-	-	-	-	-	-
6	Sodium Saccharin	-	-	-	-	-	-	20	20	20	20	20	20	20	20
7	MCC PH-101	56	51	56	51	56	51	46	46	-	-	-	-	15	31
8	Mannitol	-	-	-	-	-	-	-	-	46	46	46	46	31	15
9	Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5
10	Magnesium Stearate	7	7	7	7	7	7	7	7	-	-	-	-	-	-
11	Sodium Stearyl Fumarate	-	-	-	-	-	-	-	-	7	7	7	7	7	7
12	Flavour	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total		656	656	656	656	656	656	656	656	656	656	666	671	660	660

*Drug resin complex (DRC) contain 125 mg cefuroxime axetil and kyron T-114

Optimization of excipients amount by using 3^2 full factorial design

A 3^2 full factorial design was used in the present study. Formulation of factorial batches was shown in table 2. On the basis of preliminary results, the amount of mannitol (X_1) and the amount of MCC PH-101 (X_2) were chosen as independent variables in 3^2 full factorial design, while % drug release at 10 min ($Q_{10\%}$) and time required for 80% drug release (t_{80}). were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factor by contour plots were performed using Sigmaplot 11.0. The experimental runs and measured responses of 3^2 full factorial design batches of cefuroxime axetil dispersible tablets were depleted in table 6. [22-24].

Stability study

Optimized batch was packed in aluminum foil and was placed for

stability study at 40°C/75% RH for 3 mo. Sample was evaluated after 3 mo for physical parameters and *In vitro* dissolution. The dissolution profile of the product was compared using the similarity factor, f_2, which was calculated by the following formula.

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

where the log is logarithm to the base 10, n is the number of time points, $\sum$ is summation over all time points, R_t is the mean dissolution value of the reference profile at time t and T_t is the mean dissolution value of the test profile at the same time point. The USFDA draft guidance document contains more information on the similarity factor (f_2). The value of the similarity factor (f_2) between 50 and 100 suggests that the two dissolution profiles are similar [25-27].

Table 2: Formulation of factorial batches of cefuroxime axetil 125 mg dispersible tablets

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	DRC	543	543	543	543	543	543	543	543	543
2	SSG	30	30	30	30	30	30	30	30	30
3	Mannitol	15	15	15	25	25	25	35	35	35
4	MCC (PH 101)	15	25	35	15	25	35	15	25	35
5	Sodium Saccharin	20	20	20	20	20	20	20	20	20
6	Talc	8	8	8	8	8	8	8	8	8
7	Sodium Stearyl Fumarate	7	7	7	7	7	7	7	7	7
8	Flavour	5	5	5	5	5	5	5	5	5
	TOTAL	643	653	663	653	663	673	663	673	683

*Drug resin complex (DRC) contain 125 mg cefuroxime axetil and kyron T-114

RESULTS AND DISCUSSION

Drug-excipient compatibility study

Compatibility studies of pure drug with ion-exchange resin and other excipients were carried out prior to the preparation of taste masked dispersible tablet. Fig. 1 and fig. 2 shows DSC thermograms of cefuroxime axetil and kyron T-114, respectively. Fig. 3 and fig. 4 shows DSC thermograms of drug-resin complex and Drug-excipients physical mixture, respectively. The DSC analysis of the drug alone elicited a peak at 255.22 °C and complex of cefuroxime axetil with kyron T-114 shows peak of drug at 256.78 °C. Elicited peak of the physical mixture of DRC and other excipients was found to be at 254.16 °C. Thus, it was thought to indicate that there was no evidence of interactions between cefuroxime axetil, kyron T-114 and the used excipients. So, it can conclude that drug and other excipients are compatible which each other [28, 29].
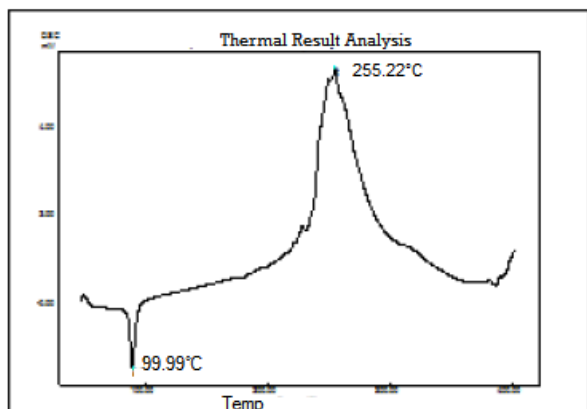

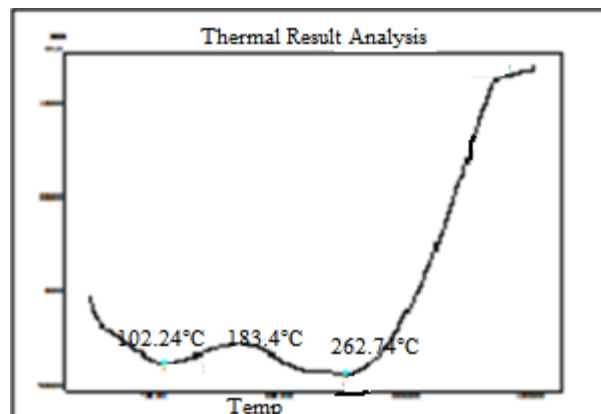**Fig. 1: DSC spectrum of cefuroxime axetil**
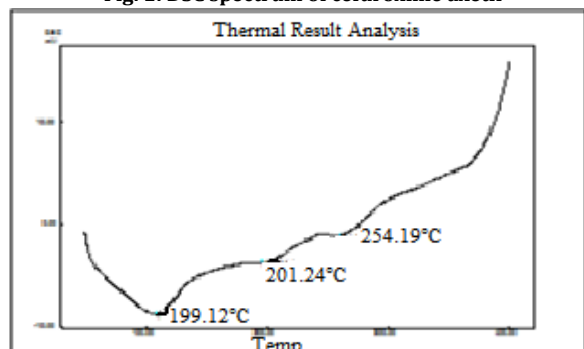

Fig. 2: DSC spectrum of kyron T-114

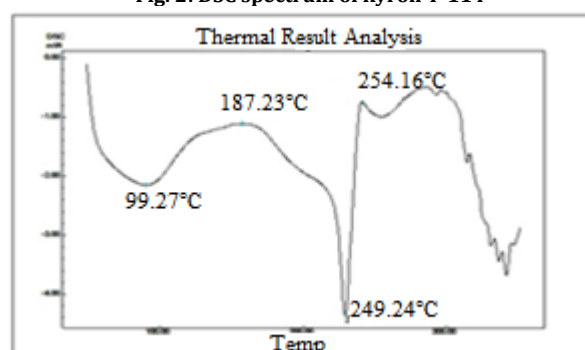**Fig. 3: DSC spectrum of drug-resin complex**

Fig. 4: DSC spectrum of physical mixture of drug-resin and excipients

Evaluation of drug-resin complex (DRC)

Trial batches of cefuroxime axetil-resin complex were prepared using different drug-resin ratio, different resins, pH and temperature. Taste and % of drug loading of all the formulation were shown in table 3. Indion-214 showed a higher percentage of drug loading but it cannot mask the bitter taste. The same condition was found with kyron T-134. Among the all batches DRC-9 showed less bitter taste and 92.70% of drug loading may be due to drug got ionised and cross-linked with kyron T-114 at pH 9. So, DRC-9 was use for further studies to prepare cefuroxime axetil dispersible tablet [30].

Table 3: Development and evaluation of drug-resin complex (DRC)

Formulation	Resin	Ratio	pH	Time(hr)	Temp	Taste	% Drug loading
DRC-1	Indion-214	1:1	7	2	30±0.5 °C	++++	59.21±1.3%
DRC-2	Indion 214	1:2	7	2	30±0.5 °C	++++	71.92±1.6%
DRC-3	Indion 214	1:3	9	3	30±0.5 °C	++++	82.24±0.8%
DRC-4	Indion 214	1:3	9	3	35±0.5 °C	+++	87.73±0.4%
DRC-5	Kyron T-114	1:1	7	2	30±0.5 °C	++++	68.23±0.7%
DRC-6	Kyron T-114	1:2	7	2	30±0.5 °C	++++	77.49±1.4%
DRC-7	Kyron T-114	1:3	7	3	30±0.5 °C	+++	84.27±1.3%
DRC-8	Kyron T-114	1:3	9	3	30±0.5 °C	++	88.39±0.7%
DRC-9	Kyron T-114	1:3	9	3	35±0.5 °C	+	92.70±0.3%
DRC-11	Dosion P551	1:2	7	3	30±0.5 °C	++++	62.80±1.5%
DRC-10	Kyron T 134	1:1	7	3	30±0.5 °C	++++	62.23±1.1%
DRC-12	Kyron T 134	1:2	7	3	30±0.5 °C	+++	76.21±1.3%
DRC-13	Kyron T 134	1:3	7	3	35±0.5 °C	+++	84.61±0.6%
DRC-14	Kyron T 134	1:3	9	3	3±0.55 °C	+++	89.62±1.2%

++++= Very bitter,+++= Bitter,++= Less bitter,+= Very less bitter

(n=6)

Preliminary trail batch evaluation of cefuroxime axetil 125 mg dispersible tablets

Table 4 shows the results of pre-compression, post-compression and *In vitro* drug release at 45 min of preliminary trail batches of dispersible tablets. The hardness and friability of all the formulation was found to be in a range of 1.9 to 3.9 kg/cm³and 0.30 to 0.70 respectively. Trail batches of dispersible tablets indicate that hardness dependent on MCC and mannitol concentration. Batch X5 and X6 shows less disintegration time compared to batch X1, X2, X3 and X4. Croscarmellose Sodium was increased in batch X7 but it will

not impact on disintegration time. So, sodium starch glycolate was used as super disintegrants for further Preliminary trial batch. Sodium starch glycolate further increase in batch X11 and X12 but it decreases hardness of tablet and less impact on disintegration time. In Batch X13 and X14; MCC and mannitol was taken as filler for tablet. X13, X14 gave 94.61% and 89.65% drug release in 45 min, respectively. The results of preliminary study revealed that MCC or mannitol alone was not sufficient to achieve the desired release profile. Hence, further trials were carried out using combination MCC and mannitol in order to understand their effect and to optimize concentration of both for desired release profile [31, 32].

Table 4: Preliminary trail batch evaluation of cefuroxime axetil 125 mg dispersible tablets

S. No.	Ingredients	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14
1	Angle of repose (°)	30.96 ±1.47	29.98 ±1.22	29.05 ±1.87	27.75 ±0.56	26.56 ± 1.36	27.34 ±1.58	25.82 ±0.86	28.61 ±1.47	27.34 ±1.65	25.82 ±1.23	27.75 ±1.32	28.17 ±1.38	29.05 ±1.24	29.51 ±1.60
2	Bulk density	0.41 ±0.07	0.42 ±0.03	0.40 ±0.03	0.43 ±0.02	0.39 ±0.04	0.42 ±0.06	0.38 ±0.07	0.45 ±0.05	0.42 ±0.04	0.40 ±0.05	0.39 ±0.06	0.40 ±0.09	0.41 ±0.08	0.39 ±0.03
3	Tapped density	0.58 ±0.01	0.58 ±0.02	0.57 ±0.03	0.59 ±0.02	0.56 ±0.03	0.57 ±0.03	0.57 ±0.03	0.61 ±0.01	0.58 ±0.01	0.57 ±0.03	0.57 ±0.04	0.58 ±0.03	0.57 ±0.01	0.57 ±0.03
4	Carr's index	30.10 ±1.17	28.06 ±1.35	28.72 ±2.12	26.80 ±1.34	29.13 ±0.57	25.92 ±2.21	32.99 ±2.11	25.85 ±1.22	27.54 ±2.17	29.36 ±2.01	32.30 ±1.37	31.12 ±0.45	27.98 ±0.78	30.65 ±0.87
5	Hausner's ratio ratio	1.40 ±0.12	1.39 ±0.10	1.40 ±0.13	1.37 ±0.03	1.41 ±0.04	1.35 ±0.11	1.49 ±0.13	1.35 ±0.03	1.38 ±0.04	1.42 ±0.05	1.48 ±0.14	1.45 ±0.07	1.39 ±0.08	1.44 ±0.04
6	Avg. weight (mg)	654.44 ±6.67	653.24 ±5.25	657.32 ±5.49	653.67 ±4.46	653.24 ±6.46	651.57 ±3.56	650.92 ±4.18	656.27 ±4.57	650.11 ±4.87	654.47 ±1.48	651.35 ±5.47	670.47 ±7.45	661.6 ±8.45	651.45 ±6.45
7	% Drug content	98.17 ±0.33	98.58 ±1.32	97.41 ±0.83	99.27 ±1.02	99.25 ±0.41	98± 0.90	98.65 ±0.70	96.44 ±0.56	95.4 ±0.22	99.17 ±0.33	99.58 ±1.32	98.41 ±0.83	98.27 ±1.02	99.25 ±0.41
8	Hardness (kg/cm²)	3.61± 0.72	2.93± 0.44	3.23± 0.32	3.03± 0.41	3.32± 0.32	2.58± 0.75	3.68± 0.55	3.65± 0.22	2.85± 0.43	3.67± 0.25	2.97± 0.35	1.95± 0.48	3.25± 0.42	3.25± 0.6.
9	Thickness (mm)	7.35± 0.23	7.42± 0.23	7.33± 0.15	7.4 ±0.31	7.45± 0.15	7.39± 0.32	7.3 ±0.35	7.29± 0.49	7.44± 0.35	7.36± 0.23	7.57± 0.15	7.63± 0.22	7.59± 0.31	7.41± 0.11
10	Friability (%)	0.39 ±0.07	0.63 ±0.06	0.36 ±0.01	0.45 ±0.04	0.74 ±0.02	0.73 ±0.04	0.55 ±0.05	0.35 ±0.05	0.59 ±0.01	0.74 ±0.06	0.69 ±0.08	0.35 ±0.06	0.52 ±0.02	0.71 ±0.03
11	Wetting time	14±1	13±2	13±1	11±1	12±2	12±2	11±1	12±2	11±1	10±1	9±2	8±1	9±2	11±1
12	Disintegration time	30 ±1	27 ±2	29 ±1	26 ±2	20 ±1	18 ±2	17 ±2	14 ±1	15 ±2	15 ±2	13 ±1	12 ±1	14 ±1	19 ±2
13	Fineness of dispersion	Fail	Fail	Fail	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
14	*In vitro* drug release at 45 min	42.09 9±2.22	75.18 7±2.09	54.09 7±2.32	76.27 5±2.34	63.52 0±2.11	78.03 8±1.97	83.54 4±1.05	88.49 4±2.32	88.73 9±2.35	92.08 6±2.32	89.62 8±1.90	92.12 1±2.36	94.61 9±2.13	89.65 0±2.36

(n=3)

3² full factorial design model evaluation

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$$

where, Y is the dependent variable, b_o is the arithmetic mean response of the 9 runs and any b_i is the estimated coefficients for the related factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The interaction term "X_1X_2" shows how the response changes when the two factors change simultaneously. Evaluation data of pre-compression and post-compression parameters of factorial batches and *In vitro % drug release* were presented in table

5 and table 6. Table 7 describes the effect of independent variables on dependent variables by 3² full factorial designs. The fitted equations (full model) relating the responses that is % drug release at 10 min ($Q_{10\%}$) and time required for 80% drug release (min) (T_{80}) to the transformed factor were shown in table 8. The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The results of ANOVA suggested that *F* values calculated for $Q_{10}\%$ and $t_{80}\%$ are 59.668 and 92.625, respectively (table 8). Tabulated *F* value was found to be 9.013 at α = 0.05. Calculated *F* values are greater than tabulated for all dependent variables therefore factors selected have shown significant effects. From the results of multiple regression analysis, it was found that both factors had statistically significant influence on all dependent variables as $p < 0.05$ [33, 34].

Table 5: Factorial batch evaluation of cefuroxime axetil 125 mg dispersible tablets

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Angle of repose (°)	25.11 ±0.68	25.82 ±1.21	27.34 ±1.21	23.8 ±0.38	25.11 ±0.58	27.75 ±0.44	27.75 ±0.57	28.61 ±0.46	29.05 ±1.11
2	Bulk density	0.40 ±0.02	0.38 ±0.01	0.39 ±0.03	0.41 ±0.05	0.42 ±0.03	0.42 ±0.06	0.40 ±0.07	0.42 ±0.03	0.41 ±0.01
3	Tapped density	0.57 ±0.03	0.56 ±0.01	0.58 ±0.02	0.57 ±0.02	0.59 ±0.01	0.60 ±0.04	0.57 ±0.02	0.61 ±0.03	0.59 ±0.04
4	Carr's index	29.60 ±1.18	31.99 ±0.29	32.14 ±1.12	27.85 ±1.19	29.01 ±1.15	29.21 ±0.57	29.71 ±0.67	30.73 ±0.87	30.82 ±1.18
5	Hausner's ratio	1.42 ±0.11	1.47 ±0.15	1.47 ±0.09	1.39 ±0.08	1.41 ±0.13	1.41 ±0.23	1.42 ±0.12	1.44 ±0.14	1.45 ±0.11
6	Avg. weight (mg)	641.45 ±3.44	654.65 ±3.65	61.56 ±4.35	652.08 ±5.23	664.42 ±4.66	671.83 ±5.57	662.65 ±4.64	671.19 ±5.17	681.34 ±2.64
7	% Drug content	98.27 ±0.31	99.2 ±0.13	97.13 ±0.22	99.27 ±0.24	96.65 ±0.55	97.49 ±1.43	98.45 ±0.53	99.35 ±0.67	98.24 ±0.56
8	Hardness (kg/cm ^{2})	3.62 ±0.32	2.93 ±0.31	3.35 ±0.67	2.84 ±0.56	3.22 ±0.53	3.14 ±0.62	2.74 ±0.51	3.35 ±0.45	3.25 ±0.25
9	Thickness (mm)	6.61 ±0.13	6.57 ±0.25	6.65 ±0.23	6.74 ±0.42	6.63 ±0.54	6.87 ±0.34	6.76 ±0.53	6.73 ±0.13	6.87 ±0.45
10	Friability (%)	0.67 ±0.04	0.78 ±0.08	0.47 ±0.02	0.88 ±0.07	0.72 ±0.03	0.49 ±0.06	0.54 ±0.04	0.64 ±0.05	0.68 ±0.08
11	Wetting time	18±1	17±2	14±1	13±1	11±2	10±2	8±1	10±1	12±2
12	Disintegration time	14±1	15±2	17±1	13±1	15±2	16±2	12±1	13±2	14±1
13	Fineness of dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

(n=6)

Table 6: *In vitro* dissolution of factorial batches

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	49.78 ±2.31	51.02 ±1.96	50.61 ±2.42	54.62 ±1.73	57.19 ±1.85	55.65 ±2.08	59.66 ±2.19	56.26 ±2.19	54.93 ±1.73
10	58.78 ±2.09	59.36 ±2.32	60.18 ±2.09	64.61 ±1.97	66.47 ±1.05	68.83 ±2.09	69.15 ±2.32	68.63 ±2.32	66.16 ±1.97
15	62.93 ±2.22	65.15 ±2.68	65.15 ±2.33	71.44 ±2.21	72.89 ±2.09	72.79 ±2.45	74.55 ±2.10	71.25 ±2.22	70.73 ±2.21
20	69.90 ±2.36	72.08 ±2.12	72.08 ±2.24	77.67 ±2.34	79.33 ±2.34	78.81 ±2.11	81.19 ±2.12	75.42 ±2.46	75.41 ±2.34
25	77.86 ±2.13	75.84 ±2.36	77.69 ±2.13	82.47 ±2.24	85.88 ±1.89	85.37 ±1.49	89.19 ±2.47	80.42 ±1.90	80.51 ±2.24
30	81.49 ±2.25	82.49 ±1.91	84.24 ±2.16	86.15 ±2.13	89.46 ±2.13	87.71 ±2.26	93.09 ±2.25	87.59 ±2.02	87.17 ±2.13
45	83.54 ±2.45	87.50 ±2.10	88.75 ±2.09	90.86 ±2.32	92.95 ±2.46	89.66 ±2.36	96.38 ±2.12	93.03 ±2.32	91.68 ±1.97

(n=6)

Table 7: Runs and measured responses of 3^2 factorial design batches

Batch code	Spray rate (X₁)	Inlet air temperature (X₂)	% Drug release at 10 min (Q₁₀%) Y₁	Time required for 80% drug release (min) (T₈₀) Y₂
F1	-1	-1	60.18±1.09	31±2
F2	0	-1	59.53±0.49	32±1
F3	1	-1	58.36±0.85	33±1
F4	-1	0	68.83±0.77	26±2
F5	0	0	67.47±0.69	26±1
F6	1	0	64.61±1.07	27±2
F7	-1	1	69.14±1.09	25±1
F8	0	1	67.44±0.59	26±1
F9	1	1	66.15±0.55	27±2
Factors and the levels in the design				
Independent variables	Low (-1)		Medium (0)	High (1)
Mannitol (X₁)	15		25	35
MCC PH-101 (X₂)	15		25	35

(n=6)

Full and reduced model for % drug release at 10 min

$$Q_{10\%} = 67.153-(1.505\ X_1)+(4.111\ X_2)-(0.294X_1^2)-(0.270\ X_2^2)-(3.501\ X_1X_2)$$

From the 3D plot (fig. 5) and the regression coefficient values of factors, it was concluded that when MCC PH-101 concentration was increase that time drug release also increase due to its hydrophilic

nature. For drug release at 10 min, the significance levels of the coefficients b_{11} and b_{22} were found to be P = 0.454, and 0.617 repectively, so they were omitted from the full model to generate a reduced model. The coefficients b_0, b_1, b_2 and b_{12} significant at P<0.05; hence they were retained in the reduced model. [35, 36] The reduced model for drug release at 10 min:

$$Q_{10\%} = 67.153 - (1.505\ X_1) + (4.111\ X_2) - (3.501\ X_1X_2)$$

Full and reduced model for time required for 80% drug release

$$T_{80} = 26.611 + (0.833\ X_1) - (2.917\ X_2) - (-0.000\ X_1^2) - (0.167\ X_2^2) + (2.583\ X_1X_2)$$

From the 3D plot graph (fig. 6) and the regression coefficient values of factors, it was concluded that when mannitol concentration was increase that time drug release decrease may be due to its very low hydrophilic nature. For time required for 80% drug release, the significance levels of the coefficients b_{11} and b_{22} were found to be P = 1.00, and 0.584 repectively, so they were omitted from the full model to generate a reduced model. The coefficients b_0, b_1, b_2 and b_{12} significant at P<0.05; hence they were retained in the reduced model. [37, 38] The reduced model for Drug release time required for 80% drug release:

$$T_{80} = 26.611 + (0.833\ X_1) - (2.917\ X_2) + (2.583\ X_1X_2)$$

**Table 8: Results of the ANOVA for dependent variables**

Source of variation	DF	SS	MS	F value	P value
Q_{10} Dependent variable					
Regression	5	139.975	27.995		
Residual	3	1.408	0.469	59.668	0.003
Total	8	141.382	17.673		
t_{80} Dependent variable					
Regression	5	68.611	13.722	92.625	0.002
Residual	3	0.444	0.148		
Total	8	69.056	8.632		

Table 9: Summary of regression output of factors for measured responses

Responses	Model	Coefficient of regression parameters						
		b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
$Q_{10\%}$	Full	67.153	-1.505	4.111	0.294	-0.270	-3.501	0.990
	Reduced	67.153	-1.505	4.111	-	-	-3.501	-
T_{80}	Full	26.611	0.833	-2.917	-0.000	-0.167	2.583	0.994
	Reduced	26.611	0.833	-2.917	-	-	2.583	-
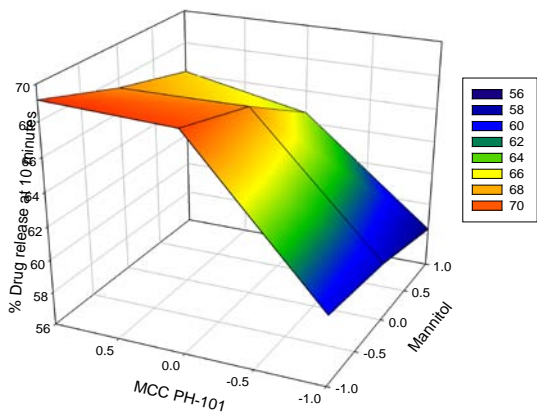
Fig. 5: 3D ssplot showing the effect of conc. of mannitol (X_1) and MCC PH-101 (X_2) on % drug release at 10 min
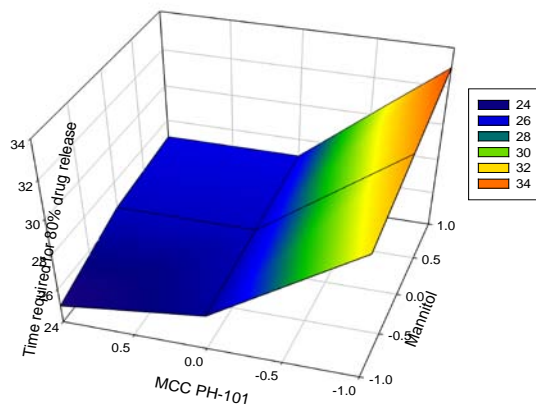
Fig. 6: 3D plot showing the effect of conc. of mannitol (X_1) and MCC PH-101 (X_2) on time required for 80% drug release

Formulation of check point batch

To validate the evolved mathematical models, a check point batches CP1 was prepared and evaluated. The observed and predicted values for batch CP1 were shown in table 10. Good correlation was found between observed and predicted values shown in table 11. Hence, it was concluded that the evolved models may be used for theoretical prediction of responses within the factor space [22].

Selection of optimized batch in factorial design study

In the present study, the following constraints were arbitrarily used for the selection of an optimized batch: Q_{10}>65 % and $T_{80\%}$<30 min. Batches F_4, F_5, F_7, F_8 and F_9 met the selection criteria. Batch F_7 showed higest % drug release at 10 min (69.149) and lowest time required for 80% drug release (25 min), Hence, Batch F_7 was selected as an optimized batch. The optimized formulation was subjected to accelerated stability study.

Table 10: Formulation and evaluation of check point batches

Batch code	Variable level			
	Coded value		Actual value	
	X_1	X_2	X_1(mg)	X_2(ml)
CP1	-0.5	-0.5	20	20

Table 11: Of check point batches and comparison with predicted value

Parameter	Actual value	Predicted value
% drug release at 10 min ($Q_{10\%}$)	63.54±1.35	64.99
Time required for 80% drug release (T_{80})	27±1	28.63

(n=6)

Table 12: Comparison of Evaluation parameters of optimized batch F_7 under stability study

S. No.	Parameters	Initial	After 3 mo
1	Hardness (kg/cm^2)	2.74±0.51	2.55±0.33
2	Average weight (mg)	662.65±4.64	660.15±2.11
3	Disintegration time (min)	12±1	13±2

(n=6)

Short term stability study

Batch F_7 was kept for stability study. The *in vitro* release profile at initial and after 3 mo was compared using similarity factor, f_2, value which was found to be 86.50. There is no significant difference in similarity factor. Evaluation parameter of stability parameter was shown in table 12.

CONCLUSION

The objective of the present investigation was to formulate, evaluate and optimize the cefuroxime axetil 125 mg dispersible tablets to achieve quick disintegration and fast release of the drug for paediatric patients. Kyron T-114 was used as teste masking agent that showed highest % of drug loading and test masking. These formulations were evaluated for the parameters like drug excipient compatibility study, thickness, hardness, weight variation, % friability, disintegration test, *in vitro* drug release and accelerated stability studies. On the basis of preliminary results, the amount of mannitol (X_1) and the amount of MCC PH-101 (X_2) were chosen as independent variables in 3^2 full factorial design, while % drug release at 10 min ($Q_{10\%}$) and time required for 80% drug release (t_{80}), were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factor by contour plots were performed using Sigmaplot 11.0. From the results of multiple regression analysis, it was found that both factors had significant influence on all dependent variables. Check point batch was prepared to validate the evolved model. Batch F_7 was selected as an optimized batch and it was found to be stable in the stability evaluation.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Deshkar SS, Pawara AS, Shirolkar SV. Formulation and optimization of floating tablets of clopidogrel bisulphate using design of experiments. Int J Appl Pharm 2018;10:126-34.
2. Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle P. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. Int J Pharm 2004;278:423-33.
3. Patel BP, Patel JK, Rajput GC, Thakor RS. Formulation and evaluation of mouth dissolving tablets of cinnarizine. Indian J Pharm Sci 2010;72:522-5.
4. Al-dhahir RK, Al-kotaji M. Formulation of orally disintegrating tablets of cinnarizine by using direct compression method. Int J Appl Pharm 2018;11:117-23.
5. Bhowmik D, Chiranjib B, Chandira RM. Fast dissolving tablet: an overview. J Chem Pharm Res 2009;1:163-77.
6. Sharma S, Lewis S. Taste masking technologies: a review. Int J Pharm Pharm Sci 2010;2:6-13.
7. Nanda A, Kandarapu R, Garg S. An update on taste masking technologies for oral pharmaceuticals. Indian J Pharm Sci 2002;64:10-7.
8. Sohi H, Sultana Y, Khar R. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm 2004;30:429-48.
9. Patel NA, Makwana ST, Patel ZP, Solanki SM, Patel MB. Formulation and evaluation of once daily sustained release matrix tablet of pramipexole dihydrochloride. Int J Pharm Res Scholars 2012;1:370-6.
10. Ain S, Kumar B, Pathak K. Development and characterization of controlled release famotidine matrix tablets containing complexes. Int J Appl Pharm 2017;9:38-46.
11. Rajendra Prasad A, Ratna JV. Development and validation of a simple UV-spectrophotometric method for the determination of ciprofloxacin HCL present in taste masked drug resin complex. Int J Appl Pharm 2018;10:37-41.
12. Sanghavi NM. Ion-exchange resins as matrix for controlled drug release. Indian Drugs 1988;26:27-32.
13. Prajapati BG, Patel SN. Formulation, evaluation, and optimization of the orally disintegrating tablet of cinnarizine. E-J Sci Technol 2010;1:9-21.
14. Patel BP, Patel JK, Rajput GC, Thakor RS. Formulation and evaluation of mouth dissolving tablets of cinnarizine. Indian J Pharm Sci 2010;72:522-5.
15. Yadav K, Yadav D, Srivastava A. Evaluation of hydrophilic, hydrophobic and waxy matrix excipients for sustained release tablets of venlafaxine hydrochloride. Drug Dev Ind Pharm 2013;39:1197-206.
16. Khar RK, Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of Zidovudine. Asian J Pharm Clin Res 2009;2:54-61.
17. Madgulkar AR. Formulation and optimization of sustained release tablets of venlafaxine resinates using response surface methodology. Indian J Pharm Sci 2009;71:387-94.
18. Lakade SH, Bhalekar MR. Formulation and evaluation of sustained release matrix tablet of anti-anginal drug influence of combination of hydrophobic and hydrophilic matrix former. Res J Pharm Technol 2008;1:410-4.
19. Puttewar TY. Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. J King Saud Univ 2010;22:229-40.
20. Anand V, Kandrapu R, Garg S. Preparation and evaluation of taste-masked orally disintegrating tablets of prednisolone. Asian J Pharm Sci 2007;6:227-38.
21. Das S, Shrikant L. Taste masking of ciprofloxacin by ion exchange resin. IJPPR 2010;1:7-13.
22. Bolton S. Optimization techniques in pharmaceutical statistics. Practical and Clinical Applications. 3rd ed. New York: Marcel Dekker; 1997.
23. Anthony NA. Pharmaceutical experimental design and interpretation. 2nd ed. Taylor and Francis Group; 2006.
24. Lionberger RA, Lee SL, Lee L. Quality by design: concepts for ANDAs. Adv Appl Pharm Sci J 2008;10:268-76.
25. Guideline IH. Stability testing guidelines: stability testing of new drug substances and products. ICH Q1A (R2) (CPMP/ICH/2736/99); 1999.
26. Singh S. Stability testing during product development. In: Jain NK. Pharmaceutical product development. CBS publisher and distributors India; 2000. p. 272-93.

27. Bajaj S, Singhla D, Sakhuja N. Stability testing of pharmaceutical products. J Appl Pharm Sci 2012;2 Suppl 3:129-38.
28. Parfati N, Rani KC, Charles N, Geovanny V. Preparation and evaluation of atenolol-β²-cyclodextrin orally disintegrating tablets using co-process crospovidone-sodium starch glycolate. Int J Appl Pharm 2018;10:190-4.
29. Nagar P, Singh K, Chauhan I, Madhu V, Yasir M, Khan A, *et al.* Orally disintegrating tablets: formulation, preparation, techniques, and evaluation. J Appl Pharm Sci 2011;4:35-45.
30. Gattu J, Lakshmi P. Comparative evaluation of natural and synthetic superdisintegrants with newer superdisintegrant kyron T-314. Acta Pharm Sci 2011;53:35-44.
31. Prajapati BG, Patel SN. Formulation, evaluation, and optimization of the orally disintegrating tablet of cinnarizine. E-J Sci Technol 2010;1:9-21.
32. Bhowmik D, Chiranjib B, Chandira RM. Fast dissolving tablet: an overview. J Chem Pharm Res 2009;1:163-77.
33. Khanam N, Alam MI, MD Yusuf Ali, QMAI Siddiqui, A Ur Rahman. A review on optimization of drug delivery system with experimental designs. Int J Appl Pharm 2018;10:7-12.
34. Anthony NA. Pharmaceutical experimental design and interpretation. 2nd ed. Taylor and Francis Group; 2006.
35. Lewis GA, Mathieu D, Phan-Tan-Luu R. Pharmaceutical experimental design. New York: Marcel Dekker; 1999.
36. Montgomery DC. Design and analysis of experiments. 5th ed. New York: Wiley; 2001.
37. Patel KN, Mehta TA. Design and optimization of nicardipine hydrochloride push-pull osmotic pump tablet using 32 full factorial design. Int J Pharm Biomed Res 2013;4:155-63.
38. Othiya OM, Patel BA, Patel KN, Patel MM. Formulation and characterization of sustained release matrix tablets of ivabradine using 3^2 full factorial design. Int J Appl Pharm 2018;10:59-66.