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RESEARCH ARTICLE

Systematic Formulation Approach for Development and Evaluation of Cefixime Granules for Pediatric Application

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ABSTRACT

The present study was aimed to apply quality by design to develop stable and flexible pediatric granules of BCS class II drug Cefiximeto improve dissolution profile using Soluplus®. Thegranules were prepared by employing the wet granulation technique. The concentration of Soluplus®(X1), Croscarmellose sodium(X2), Sodium bicarbonate(X3) were identified as critical material attributes(CMA). The critical quality attribute (CQA) are percentage drug release in 20 minutes (Y1) and dispersion time (Y2). All 17 batches were evaluated for micromeritics properties, drug content, particle size distribution, dispersion time, granules' strength/friability, *In vitro* drug release, comparison with marketed product and stability study. All 17 batches from the Box Behnken showed all the test results values within limits, indicating that the prepared granules were of standard quality. The optimized batch of granules showed 94.45±0.26% drug release in 20min, while the dispersion time was 90.85±0.04 sec and the similarity factor (f2) was 56.39 to marketed product (ZIPRAX). In addition, the optimized batch exhibited no significant change in drug content, dispersion time, *in vitro* drug release after storage at 40°C ±2°C and 75% RH ± 5% RH for one month. The formulated granules showed better drug release and dispersion time. The granules can be reconstituted with water to prepare dispersion of the drug just before use to improve compliance of paediatric patients.

Keywords: Cefixime; granules; Quality by design; Box Behnken design; Soluplus®; Design space

INTRODUCTION

Paediatrics are very heterogeneous patient groups, ranging from new-born to adolescents, with significant physical and developmental differences related to dose, absorption, pharmacokinetics, sensitivities, and compliance. In addition, metabolic capacity, skin maturation, body water-to-fat ratio and protein binding may also change with age.[1–3] Also, changes in enzyme patterns can be observed, specifically in the first months of life, compared with older children or adolescents.[4] Therefore, the age groups identified by ICH have been derived mainly from physiological and pharmacokinetic differences from birth to adult.[5]

Many conventional formulations such as tablets, capsules, suspensions, syrups for paediatric use are not suitable; they have various problems in paediatrics such as choking because of considerable size and liquid dosage form difference in dosing, and stability issues.[6] The present research aimed to prepare granules to overcome the challenges mentioned above and the disadvantages and accomplish the desired features. Granules offer a great degree of flexibility in terms of presentation also in packaging. First, these formulations can be filled into capsules, although this could limit their swallowing advantage unless presented as an easy-to-open capsule to the patient. Also, granules can be marketed in single-dose sachets, which allow for higher doses than tablets or capsules. Finally, granules can be directly administered into the patients' mouth or dispersed in a vehicle before administration. Water, milk, juice, or apple sauce are potential vehicles commonly used, thus accepting these formulations in paediatrics.[4,7,8]

Several third-generation cephalosporin antibacterial drugs are present in the market, mainly to treat adults and the paediatric population.[9] Cefixime is a BCS class II drug. Thus, there is a need to increase the rate of dissolution. Hence, the study was carried out to formulate and evaluate

granules dosage form of Cefixime as a model drug and had an aim that final batch formulation parameters show better drug release. The absolute bioavailability of Cefixime under fasting or fed conditions is approximately 40-50%. However, time to maximal absorption is increased by about 0.8 hours when administered with food. It is absorbed from the entire GI tract.[10,11] The dose of Cefixime in children older than or equal to 6 months is 8 mg/kg/day) divided every 12 to 24 hours.[12]

In the present work, Soluplus® was selected as a dissolution enhancer to increase BCS class II drug Cefixime. Due to the amphiphilic character of the polymer, it forms micelles in aqueous media and can be used to solubilize poorly water-soluble drugs.[9,10,12] An important issue is to design an optimized formulation with an appropriate dissolution rate in ashort period and minimum trials. The goals of implementing pharmaceutical QbD are to reduce product variability and defects. It is achieved by designing robust formulation and manufacturing processes and establishing clinically relevant specifications. The key elements of pharmaceutical QbD can include the QTPP, CQA, CMA, CPP. Finally, product and process capability are assessed and continually improved post-approval during product life cycle management.[12–16]

MATERIALS AND METHODS

Materials

Materials used in this study were obtained from different sources. Cefixime was a gift sample from Baroque Pharmaceuticals Pvt. Ltd, Gujarat. Soluplus® was a gift sample from BASF, Mumbai. Pearlitol DC 400 was a gift sample from Signet Chemical Corporation Pvt. Ltd, Mumbai. All other chemicals were of analytical grade.

Defining the QTPP and CQA of Cefixime granules.

QTPP defines the overall objectives of safety and efficacy of a drug development program. The US FDA document guides QTPP, which describes the components of QTPP for new drug applications. QTPP for granules formulation is listed in Table 1. International Conference on Harmonization (ICH) Q8R2 summarizes them as QTPP.[17] The Ishikawa diagram (Figure 1) was carried out to identify the CMAs and CPPs for Cefixime granules affecting the CQAs of the drug product. Ishikawa fishbone diagram was constructed to establish the potential cause-effect relationship among the product and process variables.[18] Based on prior scientific knowledge, physical attributes and diffusion of the drug were considered CQAs of Cefixime granules. These parameters are likely to affect granules' therapeutic efficacy are summarized in Table 2.

Table 1: QTPP for granules formulation

Quality Target Product Profile (QTPP) [18–21]		
QTPP Element	**Target**	**Justification**
Therapeutic Indication	Antibiotic	Pharmaceutical equivalence requirement: Same dosage indication
Dosage form	Water dispersible Granules	Pharmaceutical equivalence requirement: Same dosage form
Route of administration	Oral	Pharmaceutical equivalence requirement: Same dosage form
Dosage strength	100 mg	Pharmaceutical equivalence requirement: Same dosage strength
Container closer system	Container closure system qualified as suitable for this drug product	As per stability

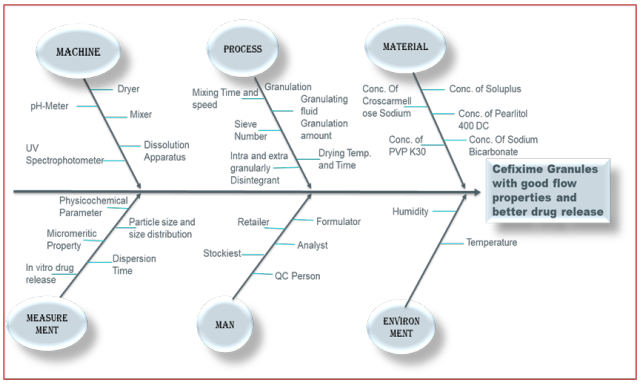

Fig. 1: Ishikawa Diagram

Formulation Development of Cefixime granules

a. The Box Behnken design is a technique that allows the identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. This design is suitable for exploring quadratic response surfaces and constructing second-order polynomial models, thus helping to optimize the process using a small number of experimental runs. For the three-level three-factor BB experimental design, a total of 17 experimental runs are required.[22] A selected Box Behnken design describes the proportion in which the independent variables Soluplus®, Croscarmellose sodium and Sodium Bicarbonate were used to formulate Cefixime granules. The % drug release and dispersion time (sec) were selected as dependent variables.

Table 2: Selected CQAs of Cefixime granules, their target, justification*

Drug product	Target	Is this a CQA?	Justification
Physical attributes	Appearance Odour Colour Granules Flow	No	Colour, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set for patient acceptability
Identification	Positive for Cefixime	Yes	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system
Excipients	Quality Profile of Excipients	Yes	Excipients are primary for a better formulation quality and stability of the granules' formulation.
Dispersion Time	< 2 minutes	Yes	It should be readily dispersible so that API will be available for administration.
Dissolution	Drug release can be displayed in phosphate buffer solution. (pH 7.2) % CDR (90% in 20 minutes and completely-dissolved in 45 minutes)	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA was investigated throughout the formulation and process development.

*(CQA – critical quality attributes, CDR – cumulative drug release)

The factor X1 (Soluplus®) at a concentration of 10%, 20%, 30%. Three levels of factor X2(Croscarmellose sodium) at a concentration of 5%, 10%, 15%. (% concerning the total weight of granules), three levels of factor X3 (Sodium Bicarbonate) at a concentration of 0.5%, 1%, 1.5% were taken as the rationale for the design of Cefixime granules. Total seventeen Cefixime granules formulations were prepared, and the composition is shown in Table 3. BB experimental design allows the designer to utilize three levels of each factor (with each factor placed at one of each equally spaced value to ensure orthogonality and near rotatability) to adequately quantify second-order response models in 17 runs, inclusive of 5-replicated centre points of a cubical design region.[22]

Preparation of Cefixime granules

The composition of granules is summarized in Table 3. Thirty gm Cefixime granules containing 100 mg of the drug were prepared by wet granulation and sieving method. PVP K30 (10 % w/v) was used as a binder. A wet coherent mass of Pearlitol DC 400, Soluplus® (Intra granularly – Half), Sodium Bicarbonate, Croscarmellose sodium (Intra granularly – Half) was prepared and passed through a 10# sieve to obtain granules. The wet granules were dried at 50o C for 15 minutes. The dried granules were collected and then screened through a 20# sieve, Soluplus® (Extra granularly - Half) and Croscarmellose sodium (Extra granularly -Half) were added. Granules were lubricated with Aerosil 200 (1%), talc (2%) and magnesium stearate (1%).[23,24]

EVALUATION PARAMETERS

Phase solubility study of the drug [25]

An excess amount of drug was added to 10 ml vials containing 2 ml of water, and then the vials were sealed. Vials were placed in an orbital shaker at room temperature for the next 24 hours. The Samples were filtered, diluted and then analyzed in a spectrophotometer at 288 nm. The test was performed in triplicate.

Micromeritic properties of granules[23]

Flow or micromeritic properties are essential for the powder or granules for the formulation's ease of production and handling. Therefore, different micromeritic properties were measured thrice for the validation of results.

The a ngle of Repose: The angle of repose was determined by the fixed funnel method and calculated according to Equation (1). The diameter (d) of the pile and maximum pile height (h) were recorded.

$$Angle of Repose = tan - 1(2h/d) \quad (1)$$

Bulk Density and Tapped Density : 10 g of the sample was placed into a 100 ml measuring cylinder, and volume was noted. The ratio of mass (weight) to volume is known as the untapped bulk density of the material. The cylinder was subjected to a fixed number of taps (100). The mass (weight) ratio to volume is known as the tapped density of the material.

Carr's Index : Based on the bulk density and the tapped density, the percentage compressibility of the powder was determined by Equation (2).

$$\text{Carr'sindex} = \frac{\text{tapped density } (\rho t) - \text{bulk density } (\rho b)}{\text{tapped density } (\rho t)} \times 100 \quad (2)$$

Hausner's Ratio : Hausner's ratio is an indirect index of ease of measuring the powder flow using tapped density and bulk density as per Equation (3).

$$\text{Hausner's Ratio} = \frac{\text{tapped } \delta}{\text{bulk } \delta} \quad (3)$$

Table 3: Composition of Cefixime granules formulation as per experimental design*

Batch	Cefixime (mg)	Pearlitol 400 DC (mg)	Soluplus® (mg)	Sodium bicarbonate (mg)	CCS (mg)	PVP K30 (mg)	Aerosil 200 (mg)
F1	100	70	10	1	5	10	1
F2	100	50	30	1	5	10	1
F3	100	60	10	1	15	10	1
F4	100	40	30	1	15	10	1
F5	100	65.5	10	0.5	10	10	1
F6	100	45.5	30	0.5	10	10	1
F7	100	64.5	10	1.5	10	10	1
F8	100	44.5	30	1.5	10	10	1
F9	100	60.5	20	.5	5	10	1
F10	100	50.5	20	.5	15	10	1
F11	100	59.5	20	1.5	5	10	1
F12	100	49.5	20	1.5	15	10	1
F13	100	55	20	1	10	10	1
F14	100	55	20	1	10	10	1
F15	100	55	20	1	10	10	1
F16	100	55	20	1	10	10	1
F17	100	55	20	1	10	10	1

* Talc and Mg. Stearate was added 2mg and 1mg per tablet. The total weight of the tablet was 200 mg. Pearlitol 400 DC is used as a filler/diluent. (CCS – croscarmellose sodium, PVP – polyvinyl pyrrolidone)

Granules Friability [23,26,27]

10 g of granules were subjected to the Roche Friabilator and operated at 25 rpm. After 4 minutes, the granules were sieved on a 200 mesh. The number of granules passed through 200 mesh was calculated as percentage granular friability. The study was performed to check the strength of the granules. The test was performed three times with the given specifications.

Dispersion Time [28]

The dispersion time was measured in water and repeated thrice. One dose of granules (200 mg) equivalent to 100 mg of Cefixime was added to a petri dish containing water and stirred gently; the time to take granules dispersed in water and make a smooth dispersion was noted as dispersion time of granules.

Drug content [29]

Granules equivalent to 100 mg of drug was taken and dissolved separately in100 ml of phosphate buffer pH 7.2. The filtered solution was diluted to record the absorbance value (288 nm) in a UV-visible spectrophotometer. The actual drug content was calculated using Equation (4). The test was performed three times with the given specifications.

$$\% \text{ Drug content} = \frac{\text{Practical Drug content}}{\text{Theoretical Drug content}} \times 100 \quad (4)$$

Granules Size Distribution [27,30]

The particle size distribution measurement was done on the optimized batch using the nest of standard sieves 20, 40, 60, 100, and 120 mesh size. The sieves were agitated mechanically for 10 minutes on a Rotary sieve shaker. The weight of granules retained on each smaller sieve was noted, and the size distribution of optimized batch (granules dispersed in water); the formulation is checked using Malvern zeta sizer instrument.

In-vitro dissolution study [31]

The dissolution study of granules was conducted using dissolution Type II apparatus (Electrolab TDT 08L, Mumbai, India). The dissolution test was performed using 900 ml phosphate buffer (pH 7.2) at 37 ± 0.5°C. The paddles were rotated at 100 rpm. Five ml of aliquots were taken at intervals of 5 minutes to determine the immediate drug release. The absorbance of the solutions was taken at 288 nm. Cumulative percentage drug release was calculated using an equation obtained from the standard curve.[32,33] The study was performed thrice with the given specifications.

Comparison with market formulation ("ZIPRAX")

Comparison of dissolution profile of granules formulation of the optimized batch with marketed formulation (ZIPRAX – 100 mg Dry Suspension) of Cefixime was carried out. In addition, an in-vitro drug release study of the marketed formulation was carried out using USP apparatus 2, using

a paddle at a speed of 100 rpm using 900ml of phosphate buffer (pH 7.2) at 37±0.5ºC.In-vitro drug release study of Cefixime granules was performed as described in the evaluation parameter.

MODEL-INDEPENDENT APPROACH

Similarity Factor [34]

Similarity factor (f2) is approved by FDA to compare the release profiles of the drug from the test with the standard reference formulation and is represented by Equation (5).

$$f2 = 50 * \log\left\{\sqrt[2]{\left[1+\left(1+\frac{1}{n}\right)\Sigma(Rt-Tt)^2\right]}\right\} * 100 \quad (5)$$

It has a value ranging between 50 and 100. The f2 values less than 50 indicate the dissimilarity between the drug and test release profiles and reference formulation. If f2 is more excellent than 50 shows the similarity between drug release profile from test and reference formulation.

Stability study [35]

The stability studies of the optimized granules batch were carried out at 40°C±2°C and 75%±5% RH for the accelerated condition in Alu Alu blister pack according to ICH guideline. The HPMC capsule of Cefixime granules was wrapped in aluminium foil. It was kept in the humidity chamber with well-controlled temperature and humidity conditions. The samples were removed after 10, 20 and 30 days and evaluated for their drug content, in vitro release characteristics and dispersion time.

RESULTS AND DISCUSSION

Phase Solubility Study of Drug

A phase solubility study was used to check the solubility of drugs in different solvents to identify the drug's pH-dependent solubility (Figure 2). Cefixime is slightly soluble in water and highly soluble in pH 7.2 phosphate buffer. From this study, it is concluded that the Cefixime has a pH-dependent solubility.

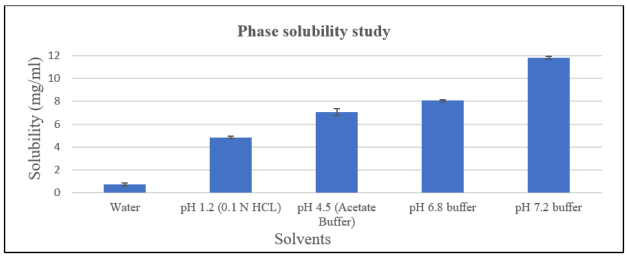

Fig. 2: Plot of Phase solubility data (n=3, data are shown as mean±SD)

Micromeritics study of granules

The free-flowing powders with good properties can be homogeneously filled in the HPMC capsules. Therefore, flow properties are essential in the formulation and industrial production of the oral solid dosage form. Results of the micromeritic properties are presented in Table 4. For all batches, the angle of repose was found in the range of 25.10±0.08 to 28.80±0.08, Carr's index was found in a range of 10.57±0.01 to 14.45±0.01, and Hausner's ratio was found to be in the range of 1.118±0.01 to 1.169±0.01. All results indicate good flow properties.

Table 4: Micromeritic properties of prepared batches according to experimental design*

Batch No.	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	27.23±0.05	0.31±0.01	0.35±0.02	12.423±0.04	1.142±0.04
F2	27.67±0.17	0.31±0.02	0.35±0.02	11.710±0.02	1.133±0.01
F3	28.80±0.08	0.30±0.06	0.34±0.07	13.693±0.01	1.159±0.01
F4	27.43±0.09	0.29±0.03	0.34±0.05	14.400±0.01	1.168±0.04
F5	28.33±0.17	0.29±0.03	0.34±0.02	14.196±0.01	1.166±0.01
F6	26.13±0.05	0.30±0.04	0.34±0.06	13.141±0.01	1.151±0.01
F7	28.07±0.05	0.29±0.04	0.32±0.04	10.574±0.04	1.118±0.01
F8	27.97±0.09	0.29±0.05	0.34±0.04	14.042±0.02	1.163±0.01
F9	27.97±0.05	0.29±0.04	0.34±0.02	14.221±0.02	1.166±0.01
F10	27.33±0.24	0.28±0.02	0.32±0.02	13.022±0.01	1.150±0.02
F11	27.40±0.14	0.29±0.03	0.33±0.05	14.288±0.07	1.167±0.02
F12	28.50±0.16	0.29±0.03	0.34±0.02	13.908±0.01	1.162±0.06
F13	27.70±0.22	0.29±0.02	0.34±0.05	14.454±0.07	1.169±0.09
F14	26.30±0.08	0.29±0.04	0.34±0.02	14.031±0.04	1.163±0.08
F15	25.10±0.08	0.29±0.01	0.34±0.09	13.201±0.03	1.152±0.02
F16	28.57±0.05	0.29±0.04	0.34±0.03	13.053±0.02	1.150±0.05
F17	27.57±0.09	0.28±0.01	0.32±0.01	13.083±0.01	1.151±0.04

*(n=3, data are shown as mean±SD)

Granules friability study

In general, friability or strength indicates the ability of granules to withstand the shear forces during handling and various pharmaceutical procedures. All the batches of Cefixime granules were found to have high mechanical strength, as indicated by their friability values (<1% w/w). The friability was less than 1 % (0.3-0.8%) for all the batches.

Dispersion study

All the batches of Cefixime granules dispersion time was found to be in the range between 91.0±0.8 to 197.0±0.8 seconds. Croscarmellose Sodium exhibited excellent swelling properties, leading to quick water penetration in granules. [36]

Drug content study : Testing for drug content helps ensure that a therapeutic product's strength remains within specified acceptance limits. The drug content in all 17 batches of formulations was uniform and in the range of 97.84±0.29 to 100.14±0.20 % (Table 5) within the permissible limits of USP.[37]

Table 5: Evaluation parameters of prepared batches according to experimental design*

Batch No.	Drug Content (%)	Granule Friability (%)	Dispersion time (Seconds)	In-vitro Drug Release in 20 minutes (%)
F1	99.67±0.07	0.4±0.01	154.7±0.04	52.02±0.78
F2	100.05±0.13	0.6±0.02	148.0±0.02	91.61±0.40
F3	98.64±0.07	0.6±0.01	100.7±0.04	65.37±0.12
F4	100.09±0.18	0.4±0.01	97.0±0.08	96.94±0.29
F5	99.48±0.24	0.3±0.01	171.3±0.04	56.71±0.49
F6	98.78±0.18	0.6±0.01	176.3±0.12	92.13±0.17
F7	100.09±0.18	0.3±0.01	155.0±0.08	70.67±0.28
F8	97.84±0.29	0.6±0.02	109.7±0.04	99.58±0.23
F9	99.25±0.18	0.8±0.01	197.0±0.08	75.80±0.10
F10	100.14±0.20	0.8±0.01	145.3±0.04	86.80±0.24
F11	98.78±0.24	0.3±0.01	166.0±0.08	90.10±0.21
F12	98.83±0.18	0.5±0.01	91.0±0.08	97.16±0.31
F13	98.36±0.07	0.7±0.02	121.3±0.04	90.54±0.22
F14	98.92±0.24	0.6±0.01	115.3±0.04	91.00±0.10
F15	99.34±0.24	0.6±0.02	120.3±0.04	89.96±0.17
F16	98.59±0.20	0.8±0.01	115.2±0.03	91.20±0.28
F17	98.92±0.24	0.6±0.01	120.2±0.02	89.89±0.13

*(n=3, data are shown as mean±SD)

Granules size distribution

The size distribution of the granules was determined using a mechanical sieve shaker fitted with a Standard Sieve number 20, 40, 60 and 100 having size 850μm, 425μm, 250μm and 150μm, respectively. The diameter of the mesh size mainly influenced the size of the granules. 20# remained constant for the granules preparation process, which affects the size, so granules yielded maximum in the range between 425-850 μm. All Batches having granules yielded 1-1.4 % in the range between 1000-850 μm. In all seventeen Batches, 9.1- 18.1% granules range between 250-425μm. 1- 3.8% granules range between 150-250 μm, and 77-88.4% granules range between 425-850 μm.

In vitro drug release study

The drug release profiles of Cefixime granules from the prepared formulations are shown in Figure 3. The drug release study of granules containing Soluplus®, Croscarmellose sodium and Sodium bicarbonate indicated that the concentration of all three excipients influenced the release of the drug. The concentration of Soluplus® was an essential factor and affected the release behaviour of the drug from granules. Soluplus® (SP) is a graft copolymer consisting of polyethylene glycol (PEG), polyvinyl caprolactam, and polyvinyl acetate (13% PEG 6000/57% vinyl caprolactam/30% vinyl acetate); it has a PEG 6000 backbone with one or two side chains consisting of vinyl acetate randomly copolymerized with vinyl caprolactam. Due to the amphiphilic character of the polymer, it forms micelles in aqueous media. It can be used to solubilize poorly water-soluble drugs and increase the drug release of the granules.[14] 30 % Soluplus® containing batches(F2, F4, F6, F8) showed more significant release than 10 % Soluplus®. Batch F2, F4, F6 and F8 showed more excellent release 98.15±0.28, 102.33±0.17, 99.99±0.34 and 102.43±0.07 in 30 minutes.

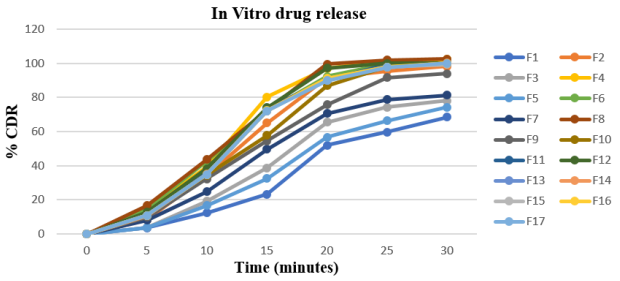

Fig. 3: The drug release profile of Cefixime granules

Data analysis and optimization of formula

The causal factor and response variables were related using a polynomial equation with statistical analysis through Design-Expert® software. A positive coefficient sign indicates a synergistic effect, while a negative term indicates an antagonistic effect upon the response. The 2D and 3D response surface plots are shown in Figure 4 and Figure 5.

Effect on Response Y1 (% CDR in 20 minutes)

The Design-Expert® software suggested a Quadratic model with a correlation coefficient (R^2) value is 0.9974, with ($p<0.001$). A high R^2value (0.99) indicates a good fit between the independent and first dependent variables (% CDR). The evolved mathematical model is

Y1 (% CDR in 20 minutes) = 90.53 + 16.94 X1+ 4.59 X2+ 5.76 X3 – 2.00 X1X2 – 1.63 X1X3 – 0.9850 X2X3 – 10.87 X_1^2 – 3.17 X_2^2 + 0.1132 X_3^2.

Significant effect on % CDR in 20 minutes of the concentration of Soluplus®. The change in % CDR of the granules can also be obtained by changing the croscarmellose sodium and sodium bicarbonate.The 2D and 3D response surface plot derives that as the concentration of Soluplus® (X1)

increase, the %CDR increase (Figure 4).

Effect on Response Y2 (Dispersion time)

The design expert software suggested a quadratic model with an R2 value equal to 0.9867, with ($p < 0.001$). The evolved mathematical model is

Y2 (Dispersion time)= 118.46 - 6.34 X1 – 28.96 X2 – 21.03 X3+ 0.7500 X1 X2 –12.58 X1 X3 – 5.83 X2 X3 + 4.94 X_1^2+ 1.69 X_2^2+ 29.67 X_3^2.

The 2D and 3D response surface plot represented that the concentration of croscarmellose sodium significantly affected the granules' dispersion time (Figure 5). The overlay plot is shown in Figure 6, which is generated by superimposing the contour plots of all the regions. The common region obtained is the overlay plot by which we can get some predicted standard batches called Checkpoint analysis. The range selected for the overlay plot was ± 10 as per USFDA criteria.

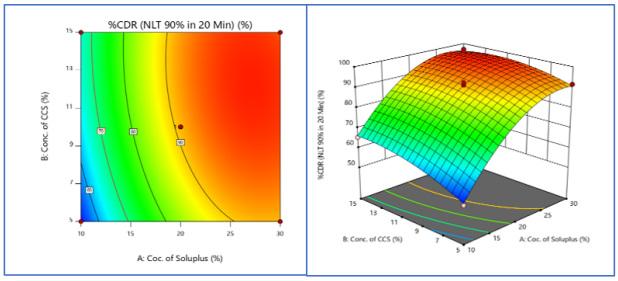

Fig. 4: 2D and 3D contour plot of Response Y1 (% drug release) (conc/coc – concentration)

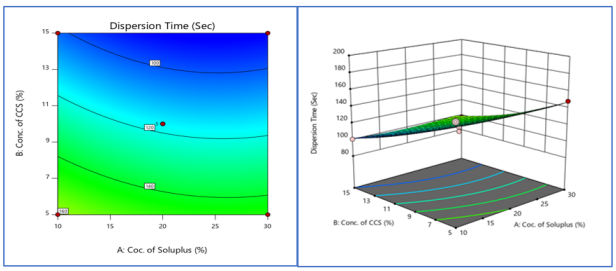

Fig. 5: 2D and 3D contour plot of Response Y2 (Dispersion time) (conc/coc – concentration)

The relative error should not be more than 5%. The optimized batch was selected based on the % CDR in 20 minutes (NLT 90%) and Dispersion Time (< 120 seconds).

Validation of model

After generating the polynomial equations relating the dependent and independent variables, the Cefixime granules were optimized for the Y1 and Y2. The optimum formulation was prepared according to the above values of the factors and

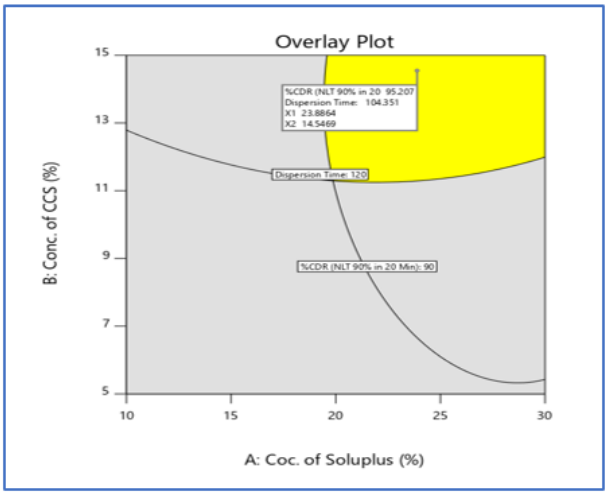

Fig. 6: Overlay plot (conc/coc – concentration)

subjected to the % drug release and dispersion time to verify the evolved models. As shown in Table 6, it demonstrated that the observed value of a checkpoint batch was relatively closer to the predicted value. The prediction error was less than 5% which validated the model applied.

All batches were evaluated through micromeritics and other evaluation parameters such as drug content, granules' strength, dispersion time and % CDR (in 20 minutes); the results are within the permissible range as shown in Table 7.

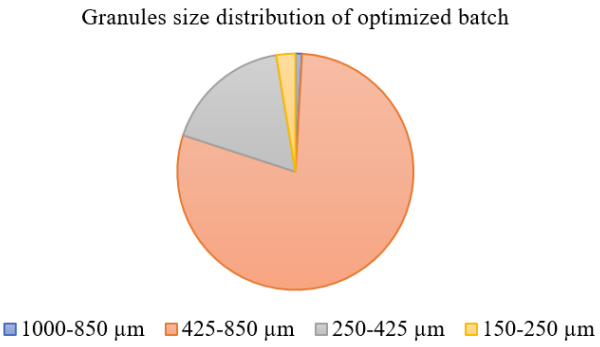

Fig. 7: Graphical representation of granules size distribution (Optimized batch)

Granules' size of distribution

Figure 7 show the size distribution study of optimized batch (before dispersion). Maximum yield of granules 79.1 % fall in the range of 425-850 μm, whereas 0.9 % granules were in the range of 1000-850 μm.

Table 6: Determination of % Error

Batch code	Response	Predicted value	Experimental value	Prediction Error (%)
Optimized Batch	X1= concentration of Soluplus®	Y1= 97.25 % CDR in 20 minutes	94.45%	2.89
	X2= concentration of Croscarmellose sodium	Y2= 93.15 seconds	90.85 seconds	2.46
	X3= concentration of Sodium Bicarbonate			
Check point Batch 1	X1= concentration of Soluplus®	Y1= 91.32 % CDR in 20 minutes	87.11%	4.61
	X2= concentration of Croscarmellose sodium	Y2= 104.94 seconds	101 seconds	3.75
	X3= concentration of Sodium Bicarbonate			
Check point Batch 2	X1= concentration of Soluplus®	Y1= 90.23 % CDR in 20 minutes	94.23%	4.43
	X2= concentration of Croscarmellose sodium	Y2= 112.73 Seconds	117 seconds	3.78
	X3= concentration of Sodium Bicarbonate			

Table 7: Evaluation Parameters of Check Point Batches of Cefixime granules formulation

Evaluation parameters	Optimized Batch	Checkpoint Batch 1	Checkpoint Batch 2
Angle of repose	21.98±0.5	23.91±0.2	22.56±0.4
Bulk density	0.72±0.2	0.81±0.2	0.74±0.2
Tapped density	0.81±0.2	0.93±0.3	0.84±0.3
Carr's Index	11.44±0.2	12.40±0.6	11.37±0.5
Hausner's ratio	1.129±0.02	1.141±0.09	1.123±0.06
Drug Content	99.11±0.07	99.72±0.20	98.64±0.07
Granules' strength	0.8±0.07	0.9±0.19	0.6±0.07
Dispersion time	90.85±0.04	101±0.8	117±0.8
% CDR (In 20 minutes)	94.45±0.26	87.11±0.19	94.23±0.07

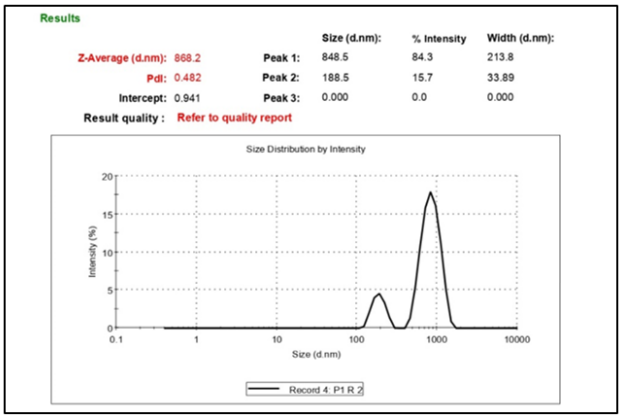

Fig. 8: Graph- Size distribution of granules after dispersed in water

Granules size distribution (After granules dispersed in water)

The granules were dispersed in water. The results revealed that the average diameter of the granules was found to be 868.2 (d. nm), which shows that the granules were converted from micrometre size to nanometer size after being dispersed in water. The results of prepared nanodispersion in water are shown in Figure 8.

Comparison of dissolution profile of optimized batch of Cefixime granules with the marketed formulation

The dissolution profile of the optimized batch and the marketed product showed 99.56±0.20% and100.12±0.20% drug release in 30 minutes, respectively. The results revealed that the Cefixime granules have a similar dissolution profile like the marketed product.

Model-independent approach

Similarity Factor

The use of similarity factor (f2) has been endorsed by the US FDA. The optimized batch's release profile was compared with the marketed product release profile. The computed values of the similarity factors were found to be 56.39 (Figure 9). Therefore, the similarity factor covers the entire drug release profile; it can be considered a robust parameter.

Stability studies of an optimized batch of Cefixime granules

The samples were removed after 10, 20 and 30 days and then evaluated for their drug content study, in vitro release characteristics, and Dispersion time. The stability study is depicted in table 8. It indicated no significant changes in drug content study, in vitro release characteristics and Dispersion time of granules, which confirmed the stability of the prepared formulation.

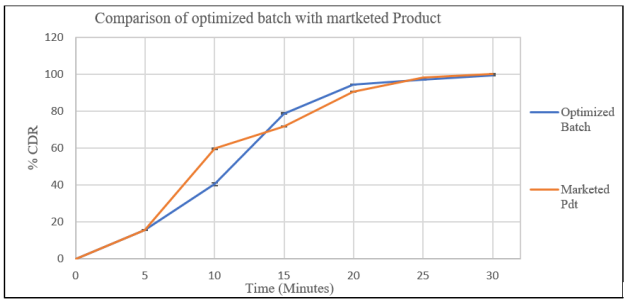

Fig. 9: Comparison of Dissolution profile of Cefixime granules formulation with Marketed formulation

Table 8: Results of stability study

Parameters	Initial	Day 10	Day 20	Day 30
drug content	99.11±0.07	99.08± 1.23	99.02±1.62	98.98±1.06
% CDR in 20 minutes	94.45%	94.49 %	94.54%	94.30%
Dispersion time	90.85 seconds	90.80 seconds	90.82 seconds	90.84 seconds

CONCLUSION

Developing pediatric formulations can be quite scientifically challenging due to unique requirements and limitations. Cefixime granules in capsule formulation will prove alternative to traditional dosage formulations. These formulations in which the capsules can be opened to release small granules of drug that can be dispersed in water or swallowed whole for adults. Granules dispersed in water help improve the compliance of children and their caretakers. In addition, these granules capsule serve as alternative formulations for infants, children, and patients with dysphagia.

The Cefixime granules formulation was systematically developed using the standard wet granulation method. The concentration of Soluplus, Croscarmellose sodium and Sodium bicarbonate had a significant effect on the formulation of Cefixime granules. The findings of the current study can be helpful to draft the control strategy for the product's life cycle management. In addition, the Cefixime will give better absorption and lead to better bioavailability.

Briefly, a patient-friendly dosage form of Cefixime was developed with sound knowledge of the impacting variables to supply quality products. In addition, a control strategy was being proposed for the industry.

ABBREVIATIONS

QTPP (Quality target product profile), CQA (Critical Quality Attribute), CMA (Critical Material Attribute), CPP (Critical Process Parameter), QbD (Quality by Design), RH (Relative humidity), CDR (Cumulative drug release).

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