Journal of Applied Pharmacy

Mogal and Derle, J Appl Pharm 2017, 9:3
DOI: 10.21065/1920-4159.1000245

Research Article Open Access

Optimization and Formulation Development of Cefixime Complex Using Spray Drying Technique: DOE Approach

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Received date: May 29, 2017; **Accepted date:** June 07, 2017; **Published date:** June 14, 2017

Abstract

Cefixime is BCS class 2/4 drug whose oral absorption is limited by its solubility and/or permeability. The use of HPBCD is proved to be better complexing agent for enhancing solubility as well as permeability of drugs. At the same time spray drying is the one step continuous drying process making it attractive technique for industrial application. Therefore, the current study was undertaken to unite the use of HPBCD and spray drying alongside with optimizing it through Design of Experiments (DOE) approach by means of Box–Behnken design for the benefit of drugs like Cefixime that needs to be redeveloped for better therapeutic efficacy. These formulations were evaluated by solubility studies, process yield and total drug content with help of independent variables like air inlet temperature, aspirator rate and pump feed rate. The optimized formulation was also characterized by SEM, FTIR analysis and *in vitro* dissolution study. Inlet air temperature was found to be the most important parameter for the spray dried material characteristics, followed by the aspirator flow rate whereas Feed flow rate was found less significant. The results indicate that formulation parameters are at least important than process parameters when designing a proper process for spray drying inclusion complex. The optimized formulation was also then compressed into tablet and was compared with marketed formulation where it showed comparable dissolution.

Keywords: Cefixime; HPBCD; Spray drying; Optimization; Quality by Design (QbD)

Introduction

The past decennary has witnessed a momentous change in pharmaceutic quality standard from an experiential procedure to more of a scientific discipline and risk-based formulation. The 2 conceptualisation are presently employed for pharmaceutic improvement, the experiential and organized (pharmaceutic Quality by Design (QbD)) approaching. QbD is a tabular risk-based, proactive approaching to pharmaceutic improvement which starts with set objectives and give importance to product and procedure apprehension and activity controlling that is supported on dependable scientific discipline and quality risk establishment [1].

Therefore, QbD is taken up with the accomplishment of definite expected attribute with wanted and planned outline through with linking the critical physical attributes and Critical Process Parameters (CPP) to the Critical Quality Attributes (CQAs) of drug system. It employs variable experimentation to interpret product and process as well as establishing a design space through and through Design of Experiments (DOE) [2].

DOE is a designed know-how in finding the relation betwixt the inputs and outputs of a procedure. In pharmaceutic advancement, inputs covariant are the unrefined physical attribute and CPP whereas outputs are the CQAs like solubility and rug release. Each unit activity has many another input variables and CQAs, it is infeasible to through an experiment analyze every. Researchers have to employment preceding information and risk establishment to determine critical input and output covariant and operation factor to be examined by means of DOE [3].

Quality by Design (QBD) encompasses designing and developing formulations and manufacturing processes which ensure predefined product specifications. The QBD is to see how process and formulating variables influence item attributes and consequent advancement of these parameters as for the last end product [3].

Therefore, critical parameters should be identified in order to monitor these parameters online in the production process. In this way, QBD is an all-encompassing idea where end product details, fabricating process and basic variables are incorporated to facilitate the last endorsement and the progressing quality control of newer medication [4]. For lacidipine, Fluidized Bed Process (FBP) process was optimized in preparing solid dosage form using quality by design [5].

Examination of process performance is used for ensuring its expected operation and delivering product's quality attribute anticipated through the design space. The examination might comprise of developmental investigation of the manufacturing progression like supplementary understanding throughout usual manufacturing. In support of definite design spaces by means of mathematical models, intermittent safeguarding might be helpful to make sure the model's giving quality products. The model's safeguarding is manageable inside an inner quality structure where the design space is unaffected.

Increasing, decreasing or else redefining the design space might be required after attainment of supplementary process information. Accordingly, considering cause of inconsistency plus their effect on downstream processing, intermediary product as well as complete product's quality is able to offer elasticity used for changing the control of upstream along with lessening the need of end product's quality test [5].

Irbesartan (IBS) dispersed system was formed via spray drying technique with HPMC E5LV [6]. Raloxifene HCl dispersions were prepared via spray drying by hydrophiles: Various grades of PVP such as Plasdone K12, K29/32 and S630 along with cellulosic polymers like HPC, HPMC, and HPMC AS [7]. The inclusion complexes of Aripiprazole with HPBCD were formed using spray drying, solvent-drop, co-grinding, as well as physical mixing [8].

The advantages of spray drying are many and include the possibility to control particle size and particle size distribution, as well as other particle characteristics. In addition, the heat stress to which the proteins are exposed during the drying process is often negligible due to the short residence time in the drying chamber [9,10]. In contrast to former method, similar to solvent evaporation, its having many benefits, like short period, dependability plus giving reproducible results, economical, particle's size manage, higher yield plus the likelihood of less organic solvent in final product [11,12]. Furthermore, spray drying is a one-step continuous drying process, which utilises less energy than freeze drying and thus makes it an attractive manufacturing process in the industry [13].

Spray drying of poorly soluble drug is popular in the industry, but little has been published regarding process knowledge and design. Design of Experiments (DOE) is a well-established method for identifying important parameters in a process and optimising the parameters with respect to certain specifications [14]. Several studies have utilised DOE on the spray drying process [15-18]. The BCS class 2/4 drug, Cefixime belongs to cephalosporin class, is generally used for respiratory plus urinary tract infection. After oral administering it's slowly and inadequately absorbs as of the gastrointestinal track and in consequence, rendering it poorly bioavailable (approximately 40-50%) for the reason that of its insufficient aqueous solubility [19-23].

Many studies have been conducted for the solubility and dissolution enhancement of poorly soluble Cefixime using different techniques [24-28]. But there is still short of understanding concerning appliance of QbD used for spray drying technique in optimizing the process parameters for getting the quality product.

The QbD approach underlines the indulgent of a variety of parameters of the method designed for better management for getting required outcome. DOE plus multivariate statistical data examination are critical fundamentals of QbD, acknowledged through current International Conference of Harmonization Q8 guideline [14]. These implements make possible altering of the preparation variables at once, permit quantifying and prioritizing the responses created through them, alongside amid whichever likely interaction among them, within the definite design space.

The reported work is deficient in statistics concerning the relevance of QbD for pharmaceutical progress of Cefixime binary system with complexing agent. The formulated complexation of Cefixime showed enhanced solubility and dissolution facilitate the development of immediate release tablet for administering it orally. Consequently, this study was intended for naming CQAs and the material attribute of the binary complex plus determining the development parameter for its formulation by spray drying technique. Box–Behenken investigational design was used in finding the space design as well as determining organize space of the optimized binary complex having highest solubility, highest drug release. The effect of process parameters on various parameters has been studied. However, these studies have all focused on single prediction equations obtained from the statistical analysis.

The present study focuses on a deeper understanding of the spray drying process of Cefixime. The effect of the process parameters inlet temperature, feed and aspirator were investigated. The dependent variables include like solubility, process yield and total drug content are addressed as well. DOE is utilised to generate maximum information and lead to a better understanding of the spray drying process of Cefixime inclusion complex.

Materials and Methods

Materials

Cefixime (CFX) and HPβCD were kindly supplied by Glenmark pharmaceuticals, Sinnar, Nasik. All the reagents and solvents used or the experiments were of analytical grade.

Spray drying

Each solution for spray drying was formed with addition of Cefixime and HPβCD to 200 ml of methanol. It was exposed to ultrasonication by a bath sonicator for about 10 min. Following that spray drying was done in a lab spray dryer model LU-222 Advanced (Labultima, Mumbai, India) having the drying capacity of 1 L/h. Parameters for spray drying were 2-4 ml/min flow rate, 60-80°C of inlet temperature, with 60-70°C of outlet temperature, and aspirator value of about 40-60m^3/h.

Saturated solubility measurements of CFX

According to Higuchi and Connors (1965), Solubility estimations were done where an excess quantity of inclusion complex was incorporated in 10 ml distilled water in test tubes. The tests were sonicated for 1 h at room temperature. The topped test tubes were shaken at 25 or 45 ± 0.1°C for 24 hrs. The suspensions were sifted through membrane filter, and the separated solutions were analysed by UV-spectrophotometer at 288 nm.

Scanning electron microscopy (SEM)

The topography of pure Cefixime and spray dried IC was looked under a scanning electron microscope (SEM; JEOL model JSM-6390LV) operating at an excitation voltage of 15 kV.

Process yield (Py)

The solid dispersion yield was determined by the ratio of the weight of solid dispersion collected at dryer exit and the initial weight of raw materials taken for spray drying. It can also be defined as per cent in weight (%) is defined as the proportion among the quantity of concentrate acquired by spray drying from the supplied suspension.

The results were calculated as the percentage ratio of the final mass of solid dispersion to the initial mass of raw material (dry basis;%w/w) using the following definition:

$$Py\% = \frac{\text{Mass of binary complex} \times 100}{\text{Mass of raw material}}$$

Design of Experiments (DOE)

A three-factor, three-level Box–Behnken statistical design was utilized for assessing the consequence of input parameters on Cefixime solubility in inclusion complexation, drug content and process yield of spray drying method.

The effect of these independent variables on dependable variables (Y1: Solubility) was studied using Design Expert® 10.0.4 software. A total of 17 experiments were designed by the software with 4 centre points. Experiments were run in random order to increase the certainty of the model. Table 1 shows the independent factors along with their design levels used in this study.

The experiments were carried out following a Box Behnken design with three factors. The three factors were air inlet temperature, aspirator flow rate and feed pump flow rate. The experimental factorial design with three levels and three factors allows the determination of linear, quadratic and interactive effects. The factors and their levels are shown in Table 1.

Factors			
Runs	**A: Air inlet temperature**	**B: Aspirator flow rate**	**C: Feed pump flow rate**
1	80	50	2
2	60	60	3
3	60	40	3
4	60	50	4
5	80	40	3
6	70	40	2
7	70	40	4
8	80	60	3
9	60	50	2
10	70	50	3
11	70	60	2
12	70	50	3
13	80	50	4
14	70	50	3
15	70	50	3
16	70	50	3
17	70	60	4

Table 1: Process independent variables used for Box–Behnken statistical design.

Each suspension for spray drying was prepared by adding fixed ratio of Cefixime and HPβCD to 100 ml of distilled water. Solution of HPβCD was prepared by making it solvable in methanol which was sonicated for 10 min. Then to resulting solution 1 g of Cefixime was added to form suspension. During spray drying the suspension was kept under magnetic stirring.

The suspensions were dried using a lab spray dryer model LU-222 Advanced (Labultima, Mumbai, India) with the drying capacity of 1 L/h. The cylindrical drying chamber is made of borosilicate glass and has an internal diameter of 13 cm and is 51 cm in height.

The liquid atomization was performed with a pneumatic spray nozzle with orifice diameter of 0.7 mm, and the dryer was operated in co-current flow. The dried products were collected and thoroughly characterized for process yield (Py), The solid dispersion yield was determined by the ratio of the weight of solid dispersion collected at dryer exit and the initial weight of raw materials taken for spray drying. solubility (S), The use of HPBCD is proved to be better complexing agent for enhancing solubility as well as permeability of drugs.and total Cefixime content (TCC).

The effects of the factors were considered significant when p-values were lower than 0.05.

Formulation of tablet (For CFX)

The optimized Cefixime-HPßCD spray dried solid dispersion was utilized for the formulation of tablet as shown in following Table 2.

Ingredient	**Functional category**	**Quantity per tablet (mg)**
Cefixime-HPβCD spray dried solid dispersion	API	200
Microcrystalline cellulose	Diluent	86.5
Magnesium stearate	Lubricant	1.5
Sodium starch glycolate	Disintegrant	9
Talc	Filler	3
Total weight		300
Each tablet contains Cefixime-HPβCD spray dried solid dispersion ≈100 mg of Cefixime, which is the conventional dose of Cefixime. All the above ingredients were mixed by simply blending and which were later on directly compressed on single punch rotatory tablet press machine.		

Table 2: Utilization of formulated tablet.

Dissolution studies

These studies were carried out by utilizing USP 8-station dissolution test assembly (Lab India) utilizing USP type II device. Dissolution study was done in a 900 ml of pH 7.2 buffer at 37 ± 0.5°C at 100 rpm. 5 ml tests were withdrawn at time interims of 5, 10, 15, 20, 30, 45 min.

The volume of dissolution medium was conformed to 900 ml to keep up sink conditions by supplanting every 5 ml aliquot pulled back with 5 ml of new pH 7.2 phosphate buffers.

The drug's concentration in tests was dictated by measuring absorbance at 288 nm. Aggregate percent drug release was ascertained at each time interim. Pure Cefixime was utilized as control for examination.

Stability studies

CFX-HPβCD spray dried samples were subjected to stability studies at 40°C and 75% RH and Ambient conditions (all for 6 months).

Samples will be checked for saturated solubility and % dissolution study.

Results and Discussion

Influence of excipients on responses

Solubility (S) Y1

The saturated solubility of Cefixime was studied in different solvents along with its prepared inclusion complex and is illustrated in Figure 1. It was found that cefixime is more soluble in methanol which justifies its use for spray drying process.

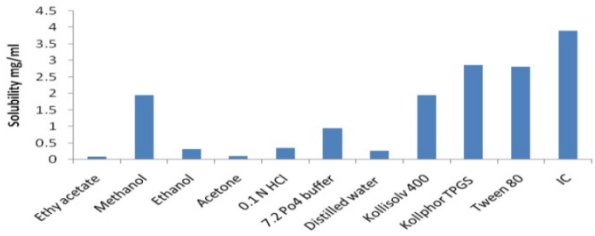

Figure 1: Saturated solubility of Cefixime in various solvents.

The prepared inclusion complex showed enhancement of apparent solubility of cefixime in distilled water as compared to pure Cefixime.

Effect of spray drying setting taking place on solubility of Cefixime solid dispersal is revealed in Figures 2 and 3. Solubility of Cefixime in water for the 17 experiment was in between 3.48 to 3.89 mg/ml.

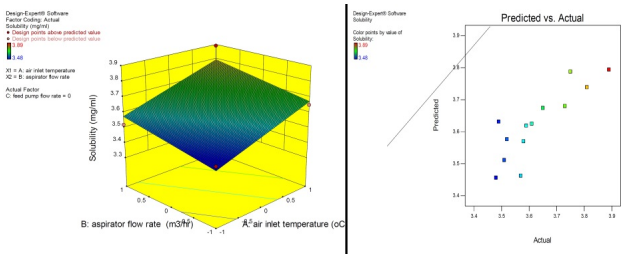

Figure 2: Response surface graph and predicted vs. actual graph for dependent response variable solubility.

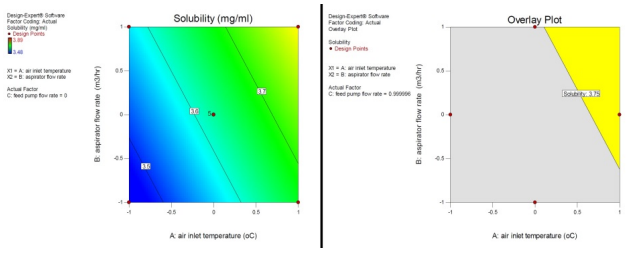

Figure 3: Contour plot and overlay plot for dependent response variable solubility.

Considering the correlation coefficient (R2=0.9851), response surface linear model was used plus an equation was built-in through response surface examination as specified in Table 3. As illustrated in Table 3, Solubility of the Cefixime decreased with increase in aspirator rate from 40 to 60% with particular air inlet temperature and feed pump low rate.

Response	Model	R2	P value	Reduced regression equation for the responses
Solubility of CFX	Linear	0.9851	0.0346	Y1=3.57118+0.0975 A-0.20125 B+0.17875 C
Process yield	Linear	0.9436	0.0146	Y2=32.38+3.53625 A-2.02625 B+0.9275 C
Total Cefixime Content	Quadratic	0.8257	0.0009	Y3=218.488+4.15 A-5.0375 B+1.9125 C+4.375 AB+3.725 AC-8.8 BC
Where, A: Air inlet temperature, B: Aspirator flow rate, C: Feed rate				

Table 3: Mathematical equation of parameters for responses according to Box–Behnken design.

The analysis of variance through the response surface linear model explained the increase in the air inlet temperature plus the lessen of aspirator flow rate influence the solubility (S) at 5.0% levels of significance whereas the process yield was increased through lessen in feed pump flow rate however the outcome was not significant. Though, the quadratic terms as well as the interactions among factors were not significant as linear model was recommended for solubility. The surface plot in Figure 2 demonstrates rising the air inlet temperature plus diminishing the aspirator flow rate showed significant augment in solubility of Cefixime. The augment in the solubility of Cefixime by means of cut of aspirator flow rate might be because of long residence moment in time of dispersed material inside the drying chamber resulting in added contact of dispersed system to increased temperature.

The positive as well as negative signs of the coefficient values in the equations acquired following statistical investigation correspond to the agonistic & antagonistic outcome of the self-determining variable whereas the degree of beta coefficient symbolizes the degree of effect of the analogous independent variables [29-31].

Process Yield (Py) Y2

The Py for 17 experiments supported on the factorial design was in between 24.41-36.84%. These outcomes were acceptable designed for a lab-scale spray drying apparatus since very lower yield (<50%) are generally given by them [32]. Considering the correlation coefficient (R2=0.9436), as well as response surface linear model's functionality

where an equation was fitted through response surface analysis like that specified.

The analysis of variance by the response surface linear model illustrated in Figures 4 and 5 the augment in the air inlet temperature plus the reduction of aspirator flow rate affected the Py at 5.0% levels of significance although there was augment in the method yield by means of raise in feed pump flow rate however the outcome was not significant (Table 3). Conversely, the quadratic terms as well as the interactions among factors were not significant since linear model was recommended in favour of process yield.

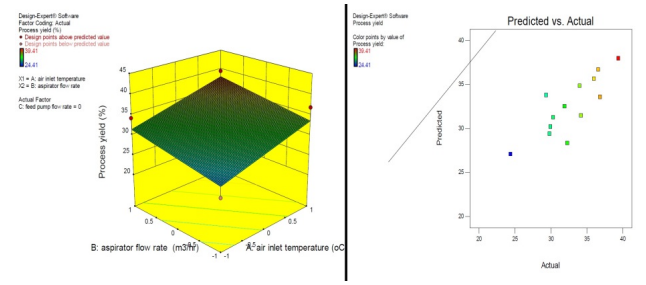

Figure 4: Response surface graph and predicted vs. actual graph for dependent response variable process yield.

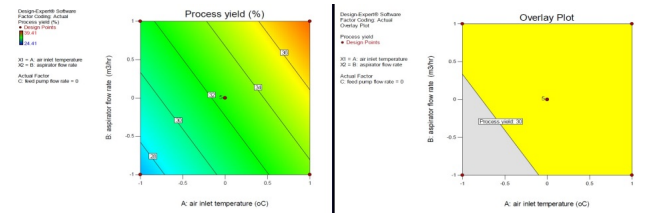

Figure 5: Contour plot and overlay plot for dependent response variable process yield.

The surface plot in Figure 3 explains so as to rising the air inlet temperature along with lessening the aspirator flow rate gave significant enhance in yield. This may perhaps be owing to an augment in drying rate, in so doing growing the likelihood to facilitate particle are dried out as soon as they arrive at the dryer walls moreover accordingly avoid sticking to the chamber. Whereas lessening the aspirator flow rate permit longer residence period of product in the drying chamber ensuing in the drier product along with moreover cut the probability of solid dispersion reaching away of the separators.

Total Cefixime Content (TCC) Y3

The TCC for the test was in between 202.9 to 233.6 mg/g. The statistical study illustrating that either the individual factors or their interactions terms were not able to affect the TCC significantly. Though, the squared expression of Fasp affected TCC at 5.0% level of significance. The surface plot in Figures 6 and 7 explains so as to the uppermost TCC take place on middle value of Fasp. In view of the correlation coefficient (R2=0.8257), response surface quadratic model was functional plus an equation was built-in via response surface analysis as given.

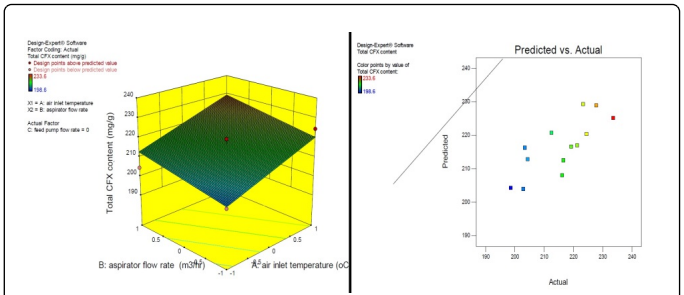

Figure 6: Response surface graph and predicted vs. actual graph for dependent response variable Total Cefixime Content (TCC).

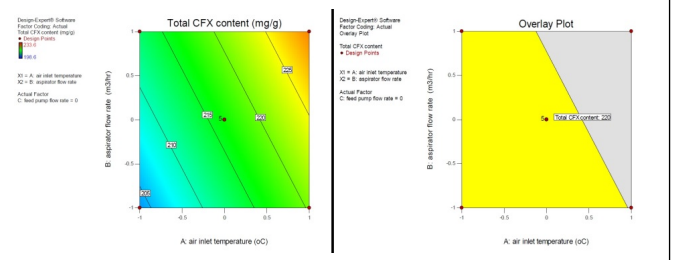

Figure 7: Contour plot and overlay plot for dependent response variable Total Cefixime Content (TCC).

Optimization outcome

The optimization was executed on the foundation of response surface modelling via the numerical optimization method (Table 3). Desirability is an objective function so as to ranging from zero outside the limits to one at the goal. The numerical optimization locates a point so as to maximize the desirability function. The sort of a goal could be changed through regulating the weight otherwise its importance. For some response and factors, all goals can be united into one desirability function. The optimization intends to locate a good set for setting the goal.

Experimental validation of design space

The multidimensional combination and interaction of independent variables and process parameters, that have been confirmed to offer assurance of quality, is term as the design space [3,33]. Design space may possibly be determined from the common region of doing well operational range designed for the two responses. Investigational justification of DOE trials was undertaken through producing optimized spray dried complex.

For spray dried complex, levels of factors which give Cefixime solubility (Y1) in 3.48 to 3.89 mg/ml range, process yield (Y2) in 24.41-36.84% and total Cefixime content in 202.9 to 233.6 mg/g ranges were monitor. Figure 8 show the superimpose plot viewing the optimized parameters recommended by DoE software to find the desired responses for spray dried complex. Model guess that spray dried complex (represented by flag in Figure 8) with Cefixime solubility of 3.95 mg/ml, process yield of 38.39% and drug content of 229.99 mg/g respectively.

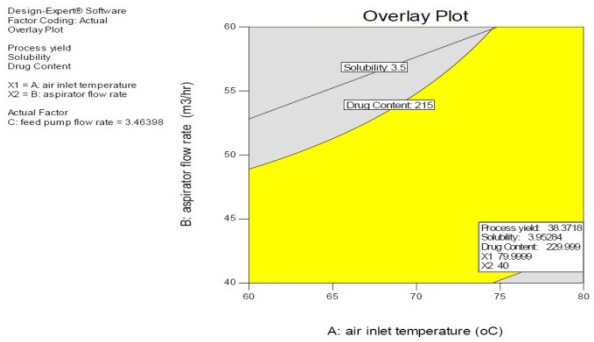

Figure 8: Overlay plot for optimized parameters of spray dried Cefixime.

Subsequent to calculation by software, the spray dried complex was organized with amount of excipients recommended by model and characterized. Cefixime solubility in spray dried complex was found to be 3.89 mg/ml.

As revealed in Figure 9, SEM analysis exposed that spray dried complex give way approximately spherical shaped particles.

As shown in Table 4 expects as well as experimentally determined values for Y1, Y2 and Y3 were analogous. These values were in very close conformity along with recognized dependability of the optimization method.

Response	Predicted	Observed
Y1 (Solubility of CRM)	3.95286 mg/ml	3.89 mg/ml
Y2 (Process yield)	38.37%	39.20%
Y3 (Drug Content)	229.999 mg/g	233.6 mg/g

Table 4: Assessment among predicted as well as experimental values for IC.

SEM

The morphology of the CFX and IC was examined using SEM and the photographs are shown in Figure 9.

SEM of pure CFX appeared as flat-broken needle-shaped crystals of varying sizes with well-developed edges. Whereas its surface was modified after inclusion complexation preparation with carrier HPBCD and by spray drying method [34].

The topography of pure Cefixime and spray dried IC was looked under a scanning electron microscope (SEM; JEOL model JSM-6390LV) operating at an excitation voltage of 15 kV.

As revealed in Figure 9, SEM analysis exposed that spray dried complex give way approximately spherical shaped particles.

However, CFX-HPβCD inclusion complex was appeared as spherical shaped particles of varying sizes with smooth surface though the topography of the original drug crystals was unlike than this prepared spray dried IC.

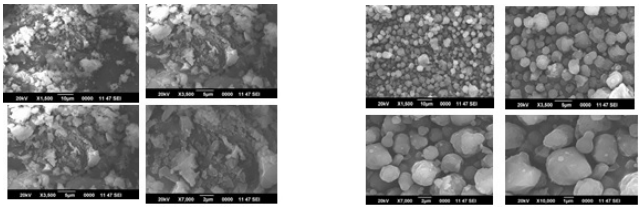

Figure 9: SEM micrographs. A. Pure Cefixime. B. Solid complex.

FTIR

The FTIR spectra of pure components along with prepared inclusion complex are given in Figure 10. Pure Cefixime showed-NH2 primary amine peak at 3392 cm^{-1}, C-H stretch at 2996.7 cm^{-1}, C=O peak at 1774.39 cm^{-1}, C=O stretching at 1666.33 cm^{-1} and 1635.2cm^{-1}, C-N stretching 1533.45 cm^{-1}, N-O stretching at 1390 cm^{-1}, 1334 cm^{-1}. It was found that the inclusion complex give an idea about the O-H stretching at wavenumber of 3386.77 cm^{-1}, C-H stretch at 2925.81 cm^{-1}, C-O at 1155.28 cm^{-1}, C-N stretch at 1080.06 cm^{-1}, 1031.85 cm^{-1}. Hydrogen bond is likely to occur among Hydroxyl groups of HPBCD & the carbonyl group of Cefixime as of the elemental configuration [35]. Widening as well as fading of a few peaks was experiential in FTIR spectrum of complexation explaining the peak's abridged intensity. A few peaks of Cefixime were gone signifying configuration of included complex in solid phase. The stretch vibrations of functional groups were instituted in the range inclusion demonstrating nonexistence of whichever noteworthy elemental interaction during configuration of complex.

The spectrum of SDs showed that a weak-OH stretching vibration peak was observed at 3410.01 cm^{-1}, while Carbonyl stretching at 1761.16 cm^{-1} of drug was absent and only the C=O peak at 1634.23 cm^{-1} was present. This finding suggested that CFX interacted with Kollidon 64, presumably by hydrogen bonding.

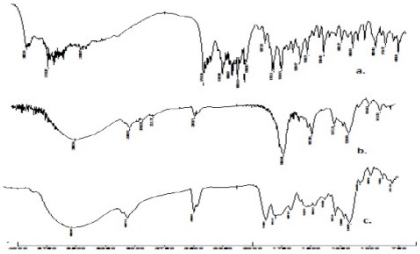

Figure 10: FTIR spectra of (A) Cefixime, (B) Hydroxypropyl beta cyclodextrin, (C) Inclusion complex.

Dissolution of both marketed and optimized formulation

The dissolution profile of spray dried complex, pure drug, optimized formulation, &marketed preparation are displayed in Figure 11. The pure cefixime exhibited 51.37% drug release after 45 min with lower Cefixime discharge whereas optimized spray dried product displayed 98.53% discharge of Cefixime after 45 min. This increment in Cefixime

release is attributed to its inclusion complex formation as well as improved wetting by Hydroxypropyl beta cyclodextrin.

The enhancement of solubility as well as dissolution of poorly soluble Cefixime by use of hydrophiles have been studied and demonstrated using other hydrophilic polymeric carriers [36,37]. The compressed tablets of optimized formulation were then compared to marketed tablets for dissolution profile Figure 12. Tablets containing inclusion complex exhibited comparable dissolution profile than commercial tablets. Thus, the inclusion complexation by spray drying technique can be successfully used for improvement of dissolution of Cefixime.

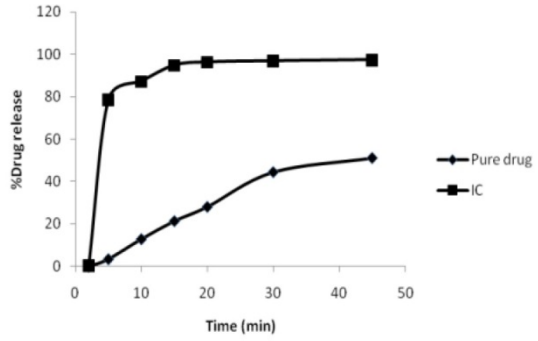

Figure 11: Dissolution profile of the pure Cefixime and optimized formulation.

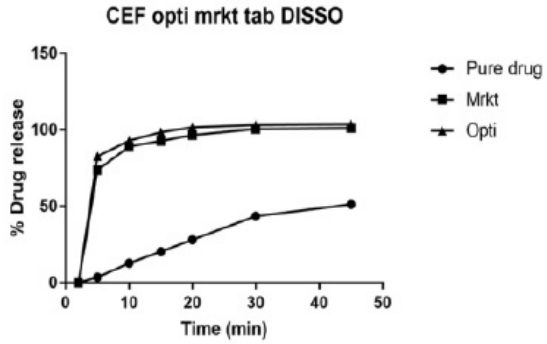

Figure 12: Dissolution profile of the marketed and optimized formulation.

Stability studies

After subjecting the optimized CFX-HPβCD spray dried sample to stability studies for 6 months at 40°C and 75% RH and ambient conditions showed that there was no change in physical appearance as well as saturated solubility and Percentage dissolution of the samples indicating its stability.

Conclusion

Characteristics of spray dried Cefixime were explained by design of experiments. The investigated process parameters were air inlet temperature, aspirator flow rate and feed pump flow rate. Inlet air temperature was found to be the most important parameter for the spray dried material characteristics, followed by the aspirator flow rate whereas Feed flow rate was found less significant. The results indicate that formulation parameters are at least important than process parameters when spray drying inclusion complex. In particular, parameters affecting the response variables are important when designing a proper process for spray drying inclusion complex. Design of experiments proved to be useful tools for QBD and was able to identify important parameters and variable correlations.

Different approaches are available for increasing the solubility, dissolution rate and thereby bioavailability of BCS class II and IV drugs. No approach is universally applicable to all drugs and subsequently a prudent determination about technique is required for each drug candidate. Some, not all, criteria for determination for suitableness of technique can be selected based on the compound's physical-chemical properties, the projected dose, and the desired release profile.

For CFX, spray drying with HPβCD proved to be most effective in achieving the desired increase in solubility and bioavailability. It might additionally be considered the simplest and most cost-effective methods among other approaches.

Acknowledgements

I am grateful to the Glenmark pharmaceutical, Nasik for providing the samples needed for the research work.

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