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DEVELOPMENT AND OPTIMIZATION OF SPRAY DRIED AMORPHOUS TERNARY SYSTEM OF CELECOXIB USING DESIGN OF EXPERIMENTS

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Keywords:

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ABSTRACT: One of the major challenges in pharmaceutical development is the poor dissolution performance of drugs. Celecoxib (CLX) is a poorly water soluble drug with its bioavailability being limited by its poor dissolution. In this study spray drying method was employed to prepare CLX: PVP K30:HPB (hydroxypropyl β-cyclodextrin) amorphous ternary system (ATS). Statistical experimental design was employed to investigate the combined effect of two experimental factors, i.e., % of polyvinayl pyrrolidone (PVP) K30 and % of HPB on saturation solubility (SS), dissolution efficiency (DE) and mean dissolution time (MDT), considered as the responses to be optimized. Design of experiment was used in the context of quality by design, which requires a multivariate approach for understanding the multifactorial relationships among experimental factors. Central composite design allowed for defining a design space. Desirability function was used to attain simultaneous optimization of all responses. The desired goals were achieved for SS, DE and MDT. Experimental values obtained from the optimized formulations were very close to the predicted values, thus confirming the validity of the generated mathematical model. These results demonstrated the effectiveness of the proposed jointed use of PVP K30 and HPB, as well as the usefulness of the multivariate approach for the preparation of ATS. Validated optimum ATS were characterized by DSC, XRD, SEM and particle size analysis. Characterization results confirmed the formation of amorphous ternary system with average particle size 727.9±260.6nm.

INTRODUCTION: Celecoxib (CLX), 4-[5-(4-methylphenyl)-3-trifluromethyl-1H - pyrazol -1-yl} benzenesulfon- amide is a cycloxygenase-2 (COX-2) inhibitor and widely used as analgesic and anti-inflammatory (NSAID) in treatment of osteoarthritis, rheumatoid arthritis, familial adenomatous polyposis (FAP), primary dysmenorrhea and dental practice [1, 2, 3].

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It is also used against colon carcinogenesis as a chemopreventive agent [4]. It has potential role in the pathogenesis of non-small cell lung cancer (NSCLC) [5]. Moreover CLX offers unique therapeutic prospect of alternative pain and inflammation without gastric and other complication like conventional NSAIDs [6]. As CLX is having poor water solubility and high permeability, it belongs to class -2 drugs of biopharmaceutical classification system (BCS). Poor water soluble drugs are difficult to develop into therapeutically effective pharmaceutical formulations, as they usually exhibit poor and variable bioavailability because of poor aqueous solubility [7].

It has been reported that oral bioavailability of CLX is only 30% as per study in dogs and the amount of drug absorption is limited by the dissolution rate [8]. Therefore, increase in solubility and dissolution rate of CLX could result in increase in bioavailability. Moreover CLX exhibit poor pre-formulation properties such as poor flowability and low compatibility because of its long needle shape crystalline form. Thus, CLX is good drug candidate for enhancement of solubility and pre-formulation properties.

Increase in solubility and dissolution rate has several promising approaches such as particle size reduction which works by increase in surface area [9] and formation of amorphous form of the drug which is highly soluble than crystalline form because of the high free energy and weaker bonding between the molecules in the amorphous form of the drug as compared to its crystalline form [10]. Spray drying is unique and single step operation that transforms solution or suspension into solid amorphous nano / micro particles. This method produces very small particles as compared to other techniques. In addition, spray drying is routinely used in pharmaceutical industry for modification of particles and crystals of active pharmaceutical ingredients (API) and excipients [11, 12]. Thus, Literature has reported spray drying as the best technique for enhancement of solubility of poorly water soluble drugs.

Employing systematic design of experiments (DoE), are extensively practiced in the development of drug delivery devices. Such systematic approaches are far more advantageous, because they require fewer experiments to achieve an optimum formulation. Optimization using DoE represent effective and cost-effective analytical tools to yield the "best solution" to a particular "problem." through quantification of polymer, these approaches provide an ability to explore and defend ranges for formulation factors [13, 14].

Therefore, the aim of present study was to develop and optimize the spray dried amorphous ternary system (CLX-polyvinylpyrrolidone K30 - hydroxypropyl β cyclodextrin) by systematic DoE using central composite design (CCD) with the help of design expert software.

MATERIALS AND METHODS:

Materials: Celecoxib (CLX) (batch no: 225/KL/CLX/2014/062) and polyvinylpyrrolidone K30 (PVP K30) were obtained from Lupin research park, Pune, India, hydroxypropyl β cyclodextrin (HPB) was obtained from Roquette pharma (batch no: E0237). All other solvents and chemical used were of analytical grade.

Methods:

Design of Experiments (DoE): Design expert V10 software (DES) used for design of experiments. A CCD with α=1 was employed as per standard protocol.[13, 14] The amount of PVP (A) and HPB (B) were selected as experimental factors, studied at three level each the central point (0,0) was studied in quintuplicate. All other formulation and processing variable were kept invariant throughout the study. **Table 1** summarizes an account of the 13 experimental runs. Saturation solubility (SS), percent dissolution efficiency (%DE) and mean dissolution time (MDT) were taken as response variables.

TABLE 1: FACTOR COMBINATIONS AS PER CENTRAL COMPOSITE DESIGN

Run	CLX mg	PVP K30 (A) mg	HPB (B) mg
1	100	200	200
2	100	300	300
3	100	200	341.421
4	100	58.5786	200
5	100	341.421	200
6	100	200	200
7	100	200	200
8	100	100	100
9	100	200	200
10	100	200	200
11	100	100	300
12	100	200	58.5786
13	100	300	100

Preparation of spray dried amorphous ternary system (ATS): The spray drying operation was performed using a spray dryer (Labultima LU-222). Appropriate weights of CLX, PVP K30 and HPB as per DoE in all runs were added to 99.8% methanol. The spray drying was performed with the following conditions: inlet temperature of 90^0 C and outlet temperature 70^0 C, solution flow rate 5 ml/min at speed 5 ml/min and aspirator 65%; feed rate 12%; atomization air pressure 1.75 Kg/cm2. The spray dried particles were stored in a desiccator until used for further studies.

Solubility studies: Solubility studies were performed on raw CLX, spray dried (SD) CLX, physical mixtures of CLX-PVP K30, CLX-PVP K90, CLX-β CD, CLX-HPB, and spray dried CLX-PVP-HPB ternary complex of all 13 runs. An excess amount of sample was added to a 15 ml screw-capped glass vials containing 10ml double distilled water which was shaken at 100 rpm in an orbital shaker (Biomedica BM-262-D) at 25^0C for 48 hr. The resulting solution was filtered through whatman filter 42. The concentration of CLX was determined spectrophotometrically at 252 nm (Shimadzu corporation, Japan-UV 1700). The saturation solubility, dissolution efficiency and mean dissolution time of each sample was determined using PCP disso software and the values are the mean and standard deviation of three observations.

Dissolution parameters: Dissolution efficiency (DE) is defined as the area under dissolution curve (y) up to certain time t, express as a percentage of area of rectangle describe by 100% dissolution in the same time[15].

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

Another parameter that describes the rate of dissolution is the mean dissolution time (MDT); MDT is the statistical analysis that reflects to the mean time of dissolution. MDT is calculated by the following equations.

$$\mathrm{MDT} = \frac{\int_0^{\infty} t \, \mathrm{d}M(t)}{\int_0^{\infty} \mathrm{d}M(t)}$$

Where t is the midpoint of the time period during which the fraction of the drug has been released from sample [16].

Statistical analysis: Saturation solubility, dissolution efficiency, and mean dissolution time were calculated using PCP Disso V3 software. All data of SS, DE and MDT were inserted in to DES as response variables. Multivariate linear regression was used to generate the models. Response surface and desirability function were used to define the design space and find the optimum conditions. Analysis of variance (ANOVA) was applied for testing the significance and validity of the models.

Fourier transform infrared spectroscopy (FT-IR): The FT-IR spectra of samples were obtained using a Shimadzu IR affinity-1-8400S (Shimadzu, Japan). Sample were previously prepared with the potassium bromide (KBr) at 1:5 sample: KBr weight ratio. The KBr disks were prepared by compressing the powders at pressure of 5 tons for 5 min in a hydraulic press and scanned against a blank KBr disk at wave numbers ranging from 400 to 4000 cm^{-1}at resolution of 4 cm^{-1}.

X-ray diffraction: X-Ray diffraction patterns of selected sample, were obtained using a Bruker, D8 Advance, Germany diffractometer, using Ni filtered Cu K (α) radiations, a voltage of 35 kv, current of 30 mA and receiving slit of 0.2 In. Samples were analyzed over 2θ range of 5-70^0 and 5-50^0 for stability interpretation.

Differential scanning calorimetry (DSC): DSC thermograms of samples were recorded using a DSC 1 Mettler-Toledo (Mettler-Toledo, Switzerland) equipped with a refrigerated cooling system and calibrated using indium standard. Sample (4-5mg) of pure CLX and CLZ-PVP-HPB ternary system were placed in aluminum pans hermetically sealed with aluminum lids. The program temperature was set from 30-300˚C and increased at a rate of 10˚C/min. The nitrogen gas flow rate was adjusted to 50 ml/min. Onset temperature and melting points of the samples were automatically calculated using the software provided (STARe Ver. 12.1 Mettler Toledo, Switzerland).

Morphological analysis: Scanning electron microscopy has been used to study the surface topography, texture and to examine the morphology of nanoparticles. SEM studies were carried out by using scanning electron microscope (JEOL, JSM-6360A Japan). The samples were coated with gold ion sputtering using auto fine coater JFC-1600 (JEOL, Japan) and coating was done for 5-6 minutes. The sample was kept on the sample holder and the scanning electron micrographs were taken.

Particle size measurement: Particle size measurement of CLX-PVP-HPB optimize ternary system was done using particle sizer NICOMP 380 (PSS-NICOMP USA). Gaussian distribution plot

was obtained using particle sizing system Santa Barbara California USA.

RESULT AND DISCUSSION:

Solubility studies: Table 2 shows the saturation solubility of raw CLX, spray dried (SD) CLX, and various physical mixture at different ratios of CLX:PVP K30, CLX:PVP K90, CLX:BCD, and CLX:HPB. The solubility study of raw CLX indicated a very low solubility in water (2.23±0.14 µg/ml) which is slightly lower than literature data (~3 µg/ml) [17]. As shown in **Table 2** in comparison with raw CLX, the spray dried CLX did not show any improvement in the saturation solubility ($p > 0.05$), however the presence of PVP K30, PVP K90, BCD, and HPB in physical mixture samples increased the solubility of CLX (ANOVA test, $p < 0.05$). ANOVA test showed that there was no significant difference between the solubility of untreated CLX, physical mixtures containing 1:1 weight ratio of CLX and PVP K30, PVP K90, BCD, and HPB ($p > 0.05$). When the concentration of PVP K30, PVP K90, BCD and HPB, were further increased to 1:2 and 1:3 weight ratio, the solubility of the drug was significantly increased ($p < 0.05$). This could be due to the solubilizing effect of PVP K30, PVPK90, and complex formation of CLX with BCD and HPB which was discussed earlier [18, 19]. These data were used in design of experiments in for development of amorphous ternary system. Spray dried technique was adopted for development of amorphous ternary system. PVP K90 and β – CD were rejected for spray drying technique as PVP K90 produced very sticky dispersion and β – CD not formed molecular dispersion for effective spray drying. However PVP K30 and HPB produced free flowing non sticky fine powder. Thirteen runs were prepared as per central composite design for spray drying. These runs were evaluated and optimized on the basis of results of saturation solubility (SS), % dissolution efficiency (DE) and mean dissolution time (MDT).

TABLE 2: SATURATION SOLUBILITY IN DISTILLED WATER OF RAW CLX, SPRAY DRIED CLX AND PHYSICAL MIXTURE (PM) OF CLX AND CARRIERS.

CLX-carrier PM	CLX: carrier ratio	Saturation solubility µg/ml
Raw CLX	--	2.23±0.14
SD CLX	- -	2.45±0.27
PVP K30	1:1	5.96±0.43
	1:3	12.58±0.21
	1:5	14.87±0.95
PVP K90	1:1	7.34±0.53
	1:3	13.93±0.62
	1:5	16.05±0.16
β - CD	1:1	6.76±0.27
	1:3	14.21±0.31
	1:5	17.86±0.73
HPB	1:1	11.57±0.85
	1:3	18.94±0.38
	1:5	21.63±0.15

The results in **Table 3** shows that the spray dried CLX obtained in the presence of different ratios of PVP K30 and HPB combinations presented greater solubility than when CLX was physically mixed with the same polymers. This was confirmed by ANOVA ($p < 0.05$). The presence of PVP K30 and HPB in spray dried samples increased the solubility of CLX significantly. Run 5 shows maximum saturation solubility 82±0.22 but dissolution efficiency and mean dissolution time was not to the mark 92% and 10 min respectively. It may be because of high concentration of PVP K30. As concentration of PVP K30 increases saturation solubility was increased; whereas it retarded drug release. Run 3 shows 79±0.16 saturation solubility, 100% dissolution efficiency and 3 min mean dissolution time it is because run 3 contains highest concentration of HPB. It reveals that HPB formed complex with CLX and formation amorphous ternary system. DSC and XRD results also implies the same. Optimization was done by response surface methodology. Optimized amorphous ternary system (ATS) was evaluated for solubility studies.

It was found that optimized ATS shows maximum apparent equilibrium solubility of 80.80±0.17 µg/ml, dissolution efficiency 100.85% and MDT was minimum i.e. 2.98 min. It is because of particle size is significantly reduced, CLX converts in amorphous form, PVP K30 forms hydrophilic layer over all particles and HPB form inclusion complex with CLX.

TABLE 3: SATURATION SOLUBILITY (SS), DISSOLUTION EFFICCINECY (DE) AND MEAN DISSOLUTION TIME (MDT)

Run	SS (µg/ml)	DE (%)	MDT (min)
SD CLX	2.45±0.27	43	21
1	65±0.19	71	12
2	78±0.34	98	3
3	79±0.16	100	3
4	54±0.12	54	19
5	82±0.22	92	10
6	66±0.45	76	11
7	66±0.18	78	11
8	53±0.29	64	14
9	67±0.57	78	10
10	67±0.16	77	11
11	72±0.58	87	9
12	59±0.25	71	16
13	62±0.37	67	14

RSM Optimization Results:

Mathematical Modeling:

Mathematical relationship generated using MLRA for the studied response variables are expressed as following equation.

$SS= 66.20++6.82*A+7.91*B-0.75* AB+0.34* A^2+0.84* B^2$….(1)

$DE=76.00+8.47* A+11.88* B+2.00* AB-1.56* A^2+4.69* B^2$…(2)

$MDT=11-2.34* A-4.30* B-1.5* AB+1.25* A^2-1.25* B^2$….(3)

A: PVP K30, B: HPB. All the polynomial equations were found to be statistically significant ($p<0.05$), as determined using ANOVA, as per the provision of Design expert software.

The polynomial equations comprise the coefficient for intercept, first order main effects. The sign and magnitude of main effects signify the relative influence of each factor on the response. The values obtained for main effects of each factor in equation 1 to 3 revels that HPB has more effect on all three responses (SS, DE and MDT) compared to PVP.

Response Surface Analysis: (Fig. 1A to 3A) portray the 3-dimentional response surface plots, while **(Fig. 1B** to **3B**) are the corresponding counter plots for studied response properties viz SS, DE, and MDT (**Fig. 1A** and **1B)** nonlinear trends of saturation solubility in an ascending order, with augmentation of PVP and HPB levels. This may be explained on the basis of mathematical models generated for the response variable saturation solubility **(Equation 1**). It can be deduced from the model that at high level of PVP, HPB and their combinations shows positive effect on saturation solubility.

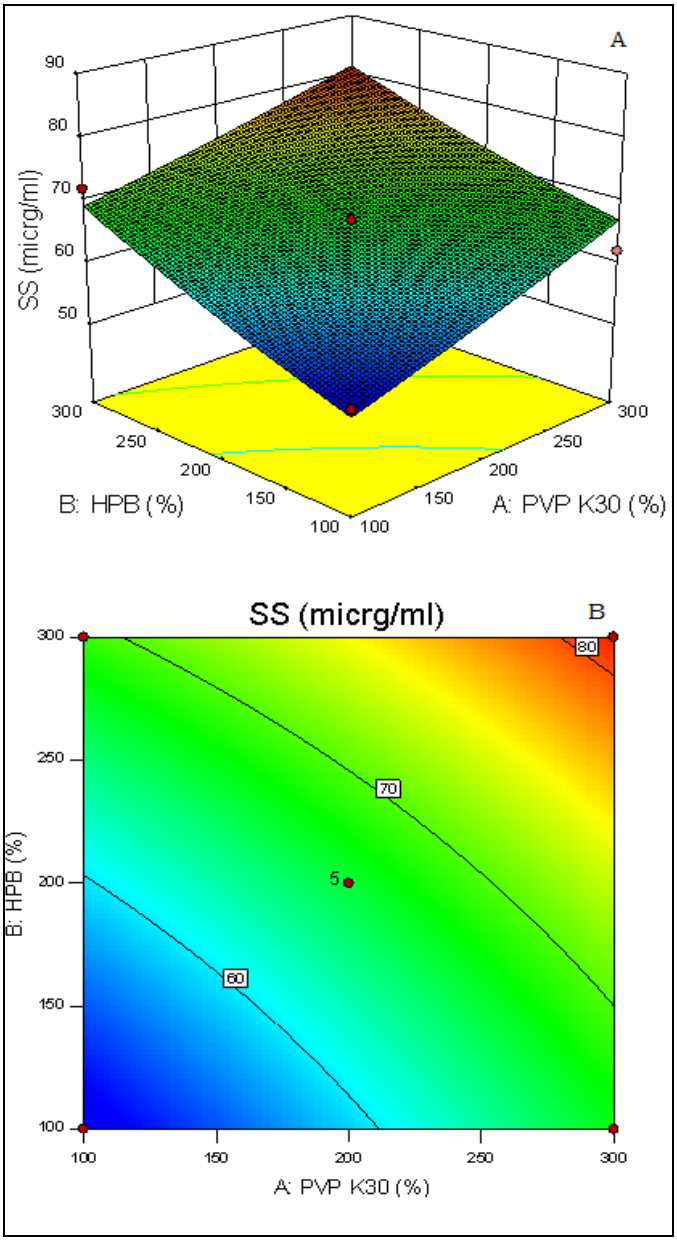

FIG. 1: EFFECT OF PVP AND HPB ON SS A. 3D GRAPH B. CONTOUR GRAPH

(Fig. 2A and B) also exhibited that dissolution efficiency vary in a non linear manner, but in an ascending pattern with an increase in amount of each polymer and its combinations. Except high level of PVP K30 this decline trend was observed at highest level of PVP K30. The counter plot Figure 2B shows that HPB has comparatively greater influence on dissolution efficiency than PVP K30.

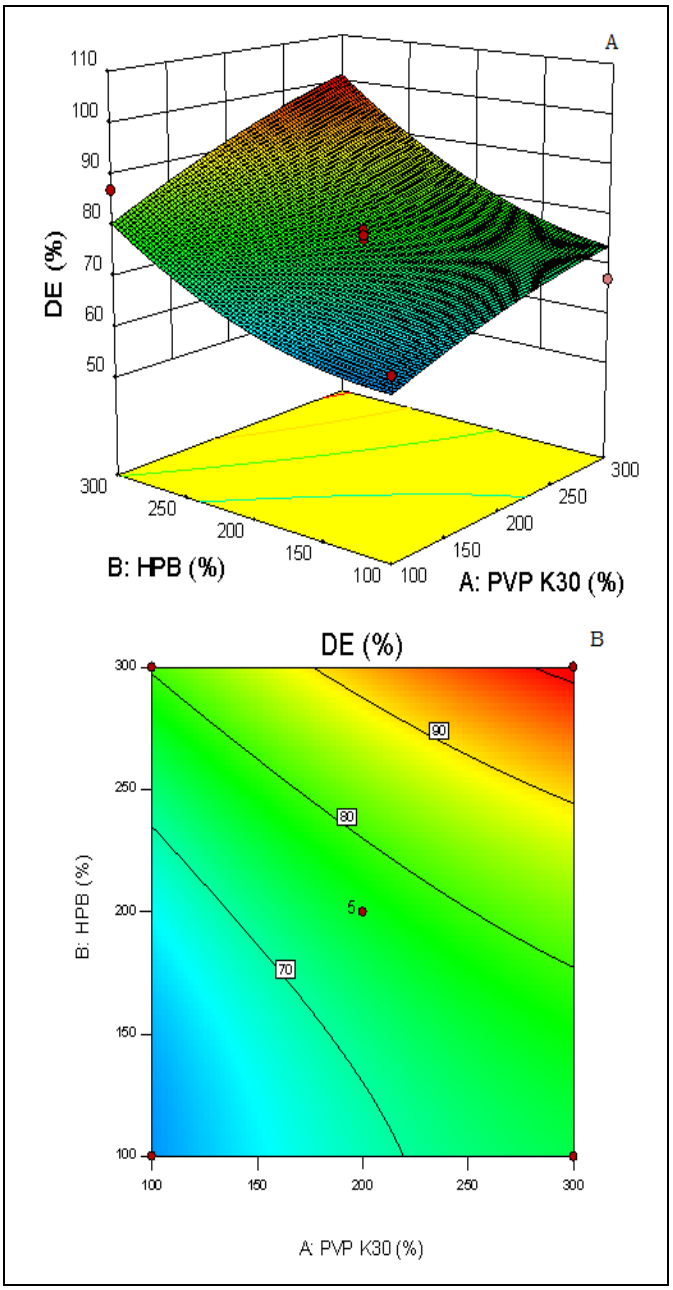

FIG. 2: EFFECT OF PVP AND HPB ON DE A. 3D GRAPH B. CONTOUR GRAPH

(Fig. 3A and B) shows an effect on PVP K30 and HPB on third response mean dissolution time PVP K30 and HPB shows inverse relation with the mean dissolution time. As per the equation 3, HPB is more effective than PVP K30. Figure 3B counter plot shows minimum MDT (3- 4 min) at high concentration of HPB whereas at high level of PVP K30 MDT was slightly increased.

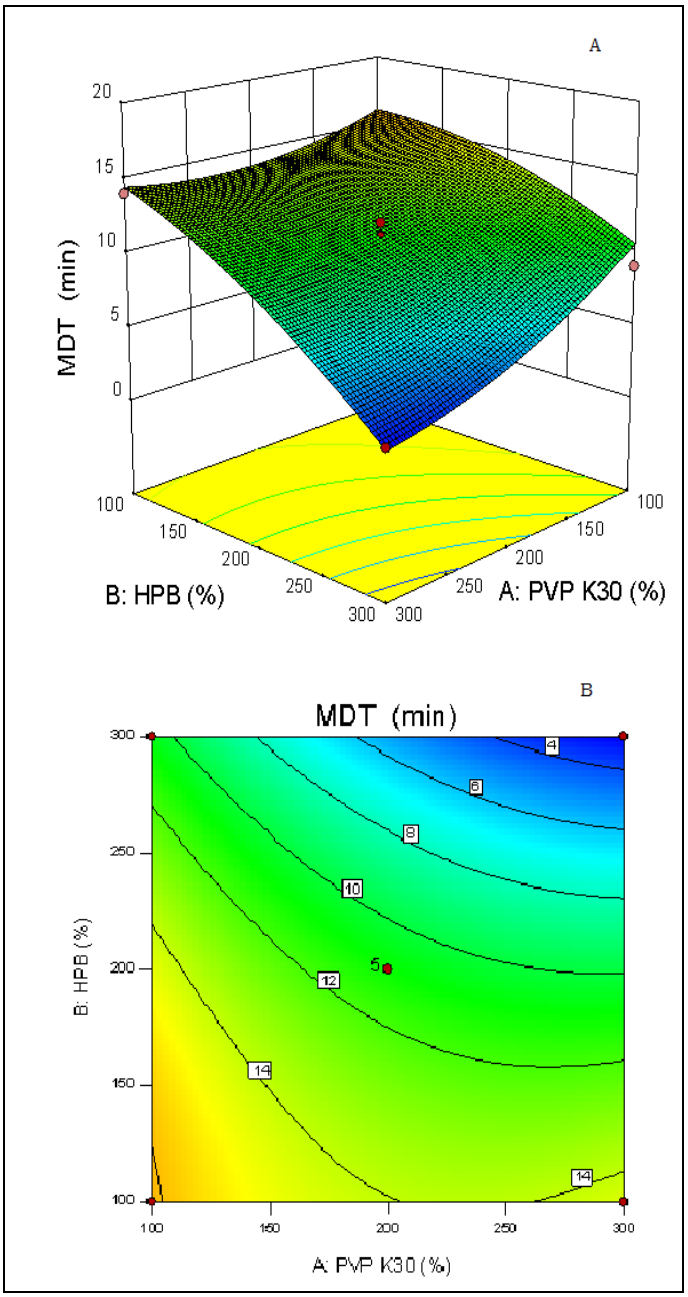

FIG. 3: EFFECT OF PVP AND HPB ON MDT A. 3D GRAPH B.CONTOUR GRAPH

Characterization of Optimum CLX-PVP-HPB Ternary System: The solid CLX-PVP-HPB ternary system obtained by spray drying was characterized by DSC and X-ray powder diffractometery, to confirm the formation of the solid complex.

Differential Scanning Calorimetry (DSC):

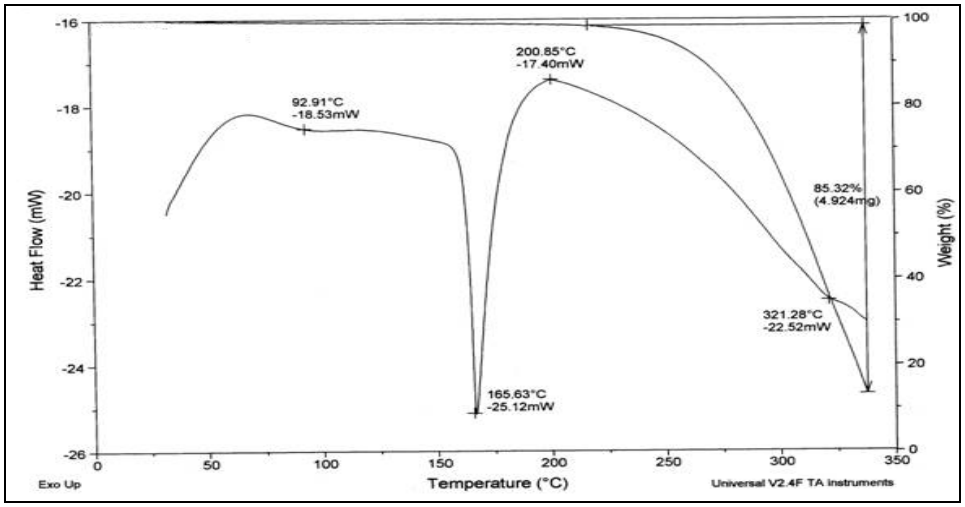

FIG. 4: DSC THERMOGRAM OF RAW CLX

The thermal curve of CXB was typical of a pure anhydrous crystalline substance, exhibiting a sharp fusion peak at 165.63^{0}C indicating melting point of drug as shown in **(Fig. 4**). The endothermic peak of CLX which appeared at 165.63^{0}C in case of the ATS was absent shown in **(Fig. 5).** This may be ascribed to the formation of inclusion complex.

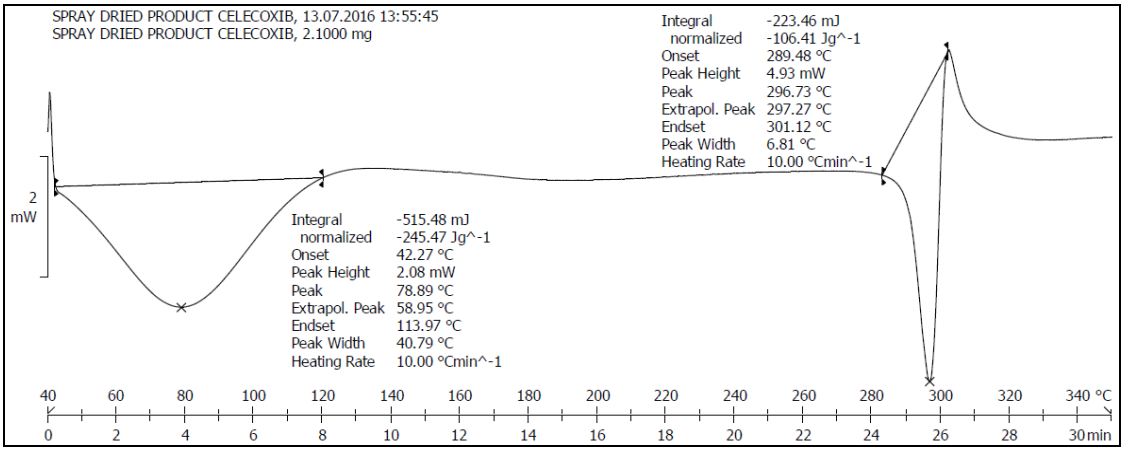

FIG 5: DSC THERMOGRAM OF OPTIMUM ATS

X-Ray diffraction:

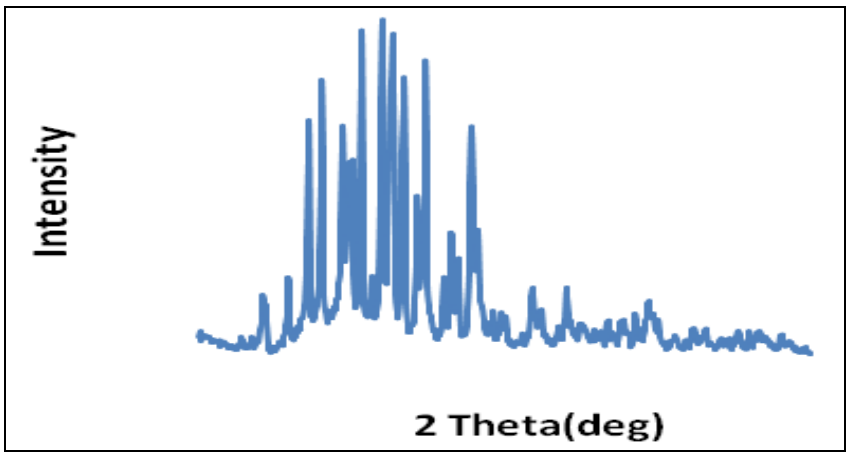

FIG. 6: X-RAY DIFFRACTION OF CLX

The X-ray diffraction pattern of the drug was characterized by the presence of several intense and sharp peaks as shown **(Fig. 6)** confirming its crystalline nature, while they totally disappeared in the corresponding CLX-PVP –HPB complex shown in **(Fig. 7)**, indicating its complete amorphization in agreement with DSC results. Dissolution rate studies demonstrated very better dissolution properties of the ternary spray dried product.

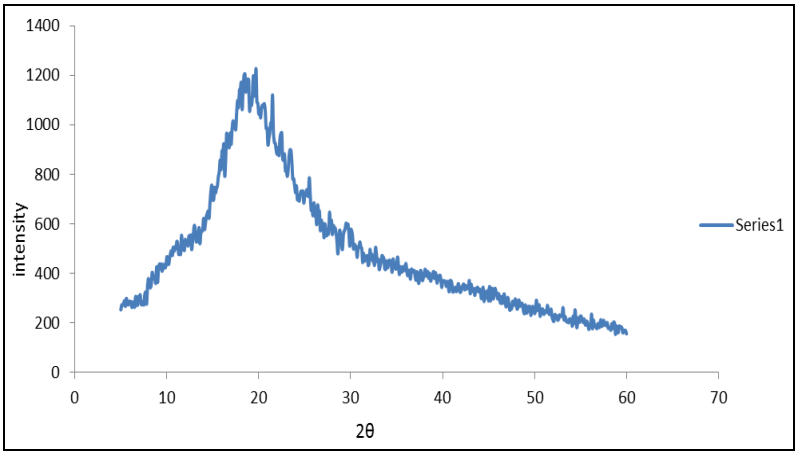

FIG. 7: X-RAY DIFFRACTION OF ATS

Morphological analysis: The scanning electron microphotograph of CLX-PVP-HPB amorphous ternary complex was obtained as depicted in **(Fig. 8)**. Pure CLX exhibited typical crystalline pattern as per DSC and XRD study. The SEM of amorphous complex was observed. Free drug crystals were also not observed. The original morphology of CLX, PVP K30 and HPB disappeared and it was not possible to differentiate the three components. Spray dried system (ATS) showed amorphous and homogenous aggregates of flake like structure. The drastic change in the surface morphology of the spray-dried complexes was indicative of the presence of a new solid phase, which may be due to the molecular encapsulation of drug in the HPB. XRD patterns of ATS also indicated formation of amorphous complex. This indicated the presence of strong interaction between the CLX, PVP K30 and HPB.

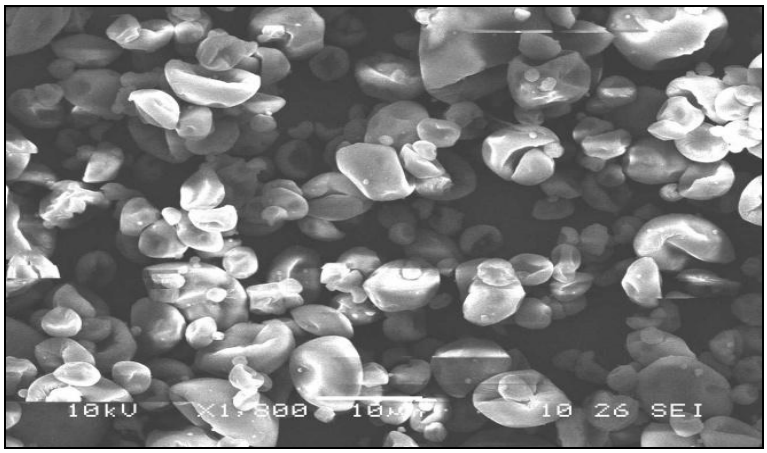

FIG 8: SEM OF ATS

Particle size measurement: Fig. 9 shows the optimum ATS of spray dried product had a mean particle diameter between 727.9±1.5 nm. Gaussian distribution plot of optimum ATS shows that particle size of the spray dried product was ranged between 200-2000 nm and average particle size was found to be 727.9±260.6 nm. Particle size range of 500 to 800 nm contained maximum number of particles. This indicates that particle size of CLX was significantly reduced.

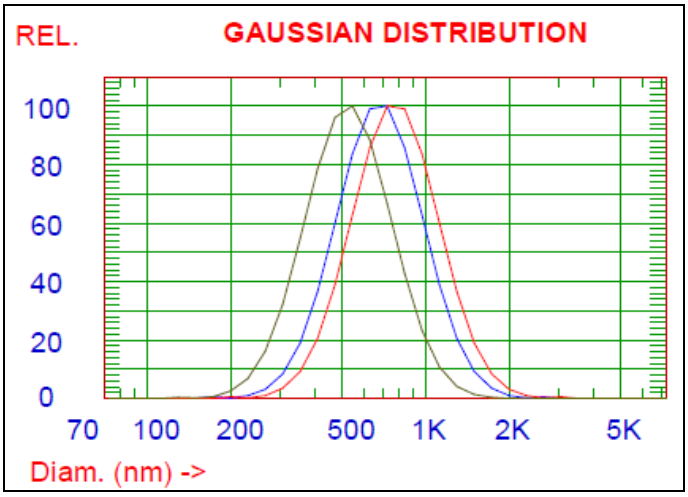

FIG. 9: PARTICLE SIZE ANALYSIS OF ATS

CONCLUSION: Present study showed that DoE approach can be successfully used in the development of amorphous ternary system of CLX with predictable dissolution properties. In particular, DoE allowed the simultaneous evaluation, by a response surface study. The effects of the selected variables, i.e., PVP K30 and HPB on the saturation solubility, dissolution efficiency and mean dissolution time were optimized. The use of desirability function was necessary to find the best compromise which allowed simultaneous optimization of all considered responses. It can be expected that this application of the DoE tools in QbD approach could be useful for further formulation studies. The results conclude that PVP-K30 and HPB are potential carrier in developing amorphous ternary system of CLX for the dissolution improvement.

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CONFLICT OF INTEREST: Authors explicitly declare that, there is no conflict of interest.

REFERENCES:

1. Kawaguchi I, Kamae I, Soen S, and Sakamoto C: Cost-Effectiveness analysis of celecoxib in the treatment of patients with chronic pain in Japan. Value Health 2014; 08:1697.
2. Nolfo F, Rametta S, Marventano S, Grosso G, Mistretta A, Drago F, Gangi S, Basile F, and Biondi A: Pharmacological and dietary prevention for colorectal cancer. BMC Surgery 2013; 13 (2):S16.
3. Paudel U, Lee YH, Kwon TH, Park NH, Yun BS, Hwang PH, and Yi H: Eckols reduce dental pulp inflammation through the ERK1/2 pathway independent of COX-2 inhibition. Oral Diseases 2014; 20(8):827-832.
4. Wang H, Ke F, and Zheng J: Hedgehog-glioma-associated oncogene homolog-1 signaling in colon cancer cells and its role in the celecoxib-mediated anti-cancer effect. Oncology Letters 2014; 8(5):2203-2208.
5. Liu S, Jiang M, Zhao Q, Li S, Peng Y, Zhang P, and Han M: Vascular endothelial growth factor plays a critical role in the formation of the pre-metastatic niche via prostaglandin E2. Oncology Reports 2014; 32(6):2477-2484.
6. Huang F, Gu J, Liu Y, Zhu P, Zheng Y, Fu J, Pan S, and Le S:Efficacy and safety of celecoxib in chinese patients with ankylosing spondylitis: a 6-week randomized, double-blinded study with 6-week open-label extension treatment. Current Therapeutic Research, Clinical Experimental 2014; 5(76):126-133.
7. Zhu W, Zhao Q, Sun C, Zhang Z, Jiang T, Sun J, Li Y, and Wang S: Mesoporous carbon with spherical pores as a carrier for celecoxib with needle-like crystallinity: improve dissolution rate and bioavailability. Material Science Engineering C Mater Biol Applications 2014;1(39):13-20.
8. Nguyen TH, Tan A, Santos L, Ngo D, Edwards GA, Porter CJ, Prestidge CA, and Boyd BJ: Silica-lipid hybrid (SLH) formulations enhance the oral bioavailability and efficacy of celecoxib: An in vivo evaluation. Journal of Control Release 2013; 10; 167(1):85-91.
9. Chen H, Khemtong C, Yang X, Chang X, and Gao J: Nanonization strategies for poorly water-soluble drugs, Drug Discovery Today 2011; 16:354–360.
10. Kawabata Y, Wada K, Nakatani M, Yamada S, and Onoue S: Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications, International Journal of Pharmaceutics 2011; 420: 1–10.
11. Paudel A, Worku ZA, Meeus J, Guns S, and Van den Mooter G: Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations, International Journal of Pharmaceutics 2013; 453:253–284.
12. Vehring R; Pharmaceutical particle engineering via spray drying, Pharmaceutical Research 2008; 25: 999–1022.
13. Singh B, Kumar R, and Ahuja N: Optimizing drug delivery systems using systematic “design of experiments” part I: fundamental aspects Critical reviews™ in Therapeutic Drug Carrier Systems, 2004; 22(1):27–105.
14. Singh B, Dahiya M, Saharan V, and Ahuja N: Optimizing drug delivery systems using systematic “design of experiments” part II: retrospect and prospects Critical Reviews™ in Therapeutic Drug Carrier Systems, 2005; 22:215–293.
15. Al-Hamidi H, Edward AA, Mohammad MA and Nokhodchi A: To enhance dissolution rate of poorly water soluble drugs: glucosamine hydrochloride as potential carrier in solid dispersion formulations. Colloids surface B 2010; 76: 170-178.
16. Costa FO, Souse JJ, Pais AA, and Fomosinho SJ: Comparison of dissolution profile of ibuprofen pellets, Journal of Control Release 2003; 89:199-212.
17. Chawla G, Gupta P, Thilagavathi R, Chakraborti AK, and Bansal AK: Characterization of solid-state forms of celecoxib, European Journal Pharmaceutical Science 2003; 20:305–317.
18. Gupta VR, Mutalik S, Patel MM, and Jani GK: Spherical crystals of celecoxib to improve solubility, dissolution rate

and micromeritic properties, Acta Pharmaceutica 2007; 57:173–184.

19. Mennini N, Furlanetto S, Cirri M, and Mura P: Quality by design approach for developing chitosan-Ca-alginate microspheres for colon delivery of celecoxib-hydroxypropyl-b-cyclodextrin-PVP complex. European Journal of Pharmaceutics and Biopharmaceutics 2012; 80:67–75.

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