International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 2, 2017

Original Article

A DESIGN OF EXPERIMENT APPROACH FOR OPTIMIZATION AND CHARACTERIZATION OF ETODOLAC TERNARY SYSTEM USING SPRAY DRYING

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Received: 08 Nov 2016 Revised and Accepted: 21 Dec 2016

ABSTRACT

Objective: The objective of the present investigation was to prepare and characterize Etodolac (ETO), Polyvinyl pyrrolidone K30 (PVP K30) and Hydroxypropyl β-cyclodextrin (HPB) ternary system in order to study the effect of complexation on solubility of ETO.

Methods: Physical mixtures of a drug and polymers in different weight ratios (1:1, 1:2, 1:4) were prepared to study the effect of individual polymers on solubility of ETO. Spray drying method was used to investigate the combined effect of PVP K30 and HPB on saturation solubility (SS), Dissolution efficiency (DE) and mean dissolution time (MDT) of ETO. Design of experiment (DoE) was used for preparation and optimization of ternary system. Drug polymer interactions were analyzed with Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM), Xray diffraction (XRD) and particle size analysis.

Results: Results of solubility study suggested that there was significant increase in solubility of ETO with increase in the concentration of PVP K30, Polyvinyl pyrrolidone K 90 (PVP K90) and HPB (*p<0.05). This might be due to the solubilizing effect of PVP K30, PVPK90 and complex formation of ETO with HPB. Various combinations of PVP K30 and HPB prepared using DoE approach by spray drying method showed greater solubility of ETO than its physical mixtures (*p<0.05). Results of FTIR, DSC, SEM, XRD and particle size analysis revealed the interaction between ETO, PVP K30 and HPB. This suggested formation of amorphous ternary system with mean particle diameter in the range of 763±1.35 nm.

Conclusion: Combine use of PVP K30 and HPB with DoE approach was an effective tool for formulating ternary system of ETO.

Keywords: Etodolac, Spray drying, Polyvinyl pyrrolidone K30, Hydroxypropyl β-cyclodextrin, Design of experiments, Ternary system

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i2.16087

INTRODUCTION

For improving drug dissolution rate, formulation of drugs with cyclodextrins (CDs) has demonstrated to be a powerful tool in the pharmaceutical field [1–3]. For improving drug dissolution by complexation, CDs have been extensively used in pharmaceuticals. CDs modifies physicochemical properties of the guest molecule such as solubility and stability by molecular encapsulation [4-6]. Hydrophilic exteriors of CDs imparts (or their complexes) water solubility and hydrophobic interior of it able to accommodate a guest molecule within the cavity [7]. Factors responsible for behavior of CDs in these complexes are proximity of charge to the CDs cavity, charge state of the CDs, steric factors, nature of the drug, co-solvent effects and temperature [8]. This strategy reduces the cost of a drug and enhances its bioavailability. This further reduces dose and side effects of the drug [9, 10].

Etodolac (ETO), 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid, is a non-steroidal anti-inflammatory drug (NSAID) used at relatively high dose, up to a maximum of 1200 mg/day for the treatment of acute pain, rheumatoid arthritis and osteoarthritis [11, 12]. ETO acts by the selective inhibition of cyclooxygenase enzyme-2 (COX-2), the synthesis of prostaglandin E2 and other prostaglandins (PGs) involved in mediating neural signals in pain pathways [13–15]. For rheumatologic as well as non-rheumatologic conditions, NSAIDs have now become the most widely prescribed and used drugs in the community which include biliary ureteric colic, acute and chronic pain, dysmenorrheal fever etc. In the United States nearly $2 billion are spent yearly on filling prescriptions of NSAIDs alone [16]. ETO is having low solubility and high permeability so it belongs to class II drugs of biopharmaceutical classification system (BCS). Therefore, the enhancement of its dissolution profile and solubility is expected to significantly improve its bioavailability and reduce its side effects. [17, 18]. The reason for choice of ETO as model drug is its less solubility in water and gastric damage mainly due to local effects. Systemic effects play only a marginal role [19, 20].

Spray drying is a unit operation capable of transforming solutions or suspensions into a solid product [21]. Tremendous development of the spray drying process with improved understanding of fluid dynamics and the refinement in the hardware equipment configuration has made spray drying a versatile technique. This technique is used in diverse industrial fields ranging from food and dairy processing, fertilizers, ceramics, detergents, paints and pharmaceutical industry [22]. Kinetic trapping of the API in the carrier matrix was achieved because of very fast solvent evaporation during spray drying which leads to rapid increase in viscosity of material. Generally, this method gives supersaturated molecular dispersion [23]. When poorly water soluble drugs are soluble in a volatile organic solvent or mixtures of solvents, it is possible to perform a spray drying of such compounds. Chemical nature of the drug substance decides solid state of the final product [24].

Systematic design of experiment (DoE) approach is extensively practiced in the development of drug delivery devices. Advantage of this approach is that it requires few experimental trials to achieve an optimum formulation. Optimization using DoE is a cost-effective analytical tool, quick and best solution to a particular defined problem. This approach provides an ability to explore and determines ranges of polymer [25, 26].

Therefore, the aim of present study was to develop spray dried ternary system of ETO-polyvinylpyrrolidone K30 (PVP K30)-hydroxypropyl β cyclodextrin (HPB) by DoE approach, which ultimately improves dissolution profile and solubility of drug with reduction in side effects such as gastric irritation. Central composite design (CCD) was used for the preparation of spray dried ternary system with the help of a software, Design expert.

MATERIALS AND METHODS

Materials

Etodolac (ETO), polyvinylpyrrolidone K30 (PVP K30) and polyvinyl-pyrrolidone K90 (PVP K90) were obtained from Lupin research park, Pune, India, hydroxypropyl β cyclodextrin (HPB) was obtained from Roquette pharma, France. All other reagents and chemicals were of analytical grade.

Methods

Design of experiments (DoE)

For designing of experiments, Design expert V10 software was used. A CCD with α=1 was employed as per standard protocol [25, 26]. The amount of HPB (B) and PVP K30 (A) were selected as experimental factors and studied at three levels each. The central point (0, 0) was studied in quintuplicate. All other formulation ingredients and processing variable were kept constant throughout the study. Thirteen experimental runs with different combinations of factors were obtained by design expert software as depicted in table 1. Percent dissolution efficiency (%DE), saturation solubility (SS), and mean dissolution time (MDT) were taken as response variables.

Preparation of physical mixtures

Physical mixtures of ETO with different polymers i.e. PVP K30, HPB and PVP K90 in weight ratios of 1:1, 1:2 and 1:4 were prepared by passing ingredients through sieve (#60) separately and then mixing both solids by simple blending.

Table 1: Central composite design

Run	ETO 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

ETO: Etodolac; PVP: Polyvinylpyrrolidone; HPB: Hydroxypropyl β-cyclodextrin.

Preparation of spray dried ternary system

Accurate weight of ETO was added in 99.8% methanol. Required amounts of PVP K30 and HPB (as per DoE) were added in purified water. The solutions were further mixed and were kept for sonication for 20 min. and spray dried (Labultima LU-222). The drying conditions were as follows: inlet temperature 90 °C; outlet temperature 70 °C; aspirator 65%; feed rate 12%; atomization air pressure 1.75 Kg/cm^2.

In vitro drug release study

The dissolution studies were performed in USP dissolution test apparatus type II (rotating paddle type). Accurately weighed complexes equivalent to 100 mg of ETO were spread over 900 ml of dissolution medium (phosphate buffer pH 6.8). The temperature was maintained at 37 °C±0.5 °C and the stirring speed employed was 50 rpm. At various time intervals, 5 ml aliquots of dissolution media were withdrawn and replaced by 5 ml of fresh dissolution media maintained at the same temperature. The collected samples at different intervals were analysed spectrophotometrically at 279 nm. All the determinations were performed three times.

Solubility studies

Solubility studies were done on Plain ETO, spray dried (SD) ETO and different combinations of drug and polymers i.e. physical mixtures of ETO-PVP K30, ETO-HPB, ETO-PVP K90 and spray dried ETO-PVP-HPB ternary complex of all 13 runs. An excess amount of ETO was added to a 10 ml study fluid. Samples were rotated on an orbital shaker at 100 rpm (Biomedical BM-262-D) at 25 °C for 48 hr. The samples were filtered through Whatman filter paper no.42. The filtrates were analyzed for drug content using ultraviolet spectroscopy (UV) at 279 nm (Shimadzu Corporation, Japan-UV 1700). The saturation solubility, mean dissolution time and dissolution efficiency of each sample were determined using PCP disso software and the values are the mean and standard deviation of three observations.

Parameters for dissolution study

Dissolution efficiency (DE) is defined as the area under dissolution curve (y) up to certain time t, express as a percentage of the area of rectangle describe by 100% dissolution in the same time [27].

Mean dissolution time (MDT) is another parameter that describes the rate of dissolution of a drug. MDT value is used to compare release rate of different formulations and it represents the drug release retarding efficiency of polymers used. [28].

Statistical analysis

Saturation solubility, MDT and % DE were calculated using PCP Disso V3 software. Data of SS, MDT and % DE were inserted into the design of experiment software as response variables. Desirability function and response surface were used to find the optimum conditions and to define the design space. To generate various models, multivariate linear regression was used. For testing, the significance and validity of the model's analysis of variance (ANOVA) were applied.

Flow property measurement

Pure drug and prepared solid dispersions were evaluated for flow properties. Bulk density, tap density, angle of repose, compressibility index and Hausner's ratio were calculated to study flow properties of plain ETO and optimised ternary system of ETO, PVP K30 and HPB.

Characterization of plain drug and prepared solid dispersion

Plain drug and prepared solid dispersion were characterised by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM) and particle size measurement.

a) Fourier transform infrared spectroscopy (FTIR)

FTIR spectrophotometer (Shimadzu IR affinity-1-8400S, Shimadzu, Japan) was used for determination of FTIR spectra of pure components and different samples. Potassium bromide disks were prepared by compressing the powders at a pressure of 5 tons for 5 min. in a hydraulic press. The scanning range was 4500–400 cm^{-1}.

b) Differential scanning calorimetry (DSC)

The thermal analysis of plain ETO and various samples of the ternary system were performed on Mettler-Toledo (Mettler-Toledo,

Switzerland) calibrated using indium standard and equipped with a refrigerated cooling system. The program temperature was set from 30-300˚C and increased at a rate of 10˚C/min. Flow rate of nitrogen gas was kept at 50 ml/min. Melting points of the samples and onset temperature were automatically calculated using the software provided (STARe Ver. 12.1 Mettler Toledo, Switzerland).

c) X-ray diffraction (XRD)

X-ray diffractometer (Bruker, D8 Advance, Germany) was used to determine powder X-ray diffraction patterns for all samples under the following conditions: voltage 35 kV; receiving slit 0.2 inches; current 30 mA; Ni-filtered Cu k (α) radiations as a source. For stability interpretation samples were analysed over 2θ range.

d) Scanning electron microscopy (SEM)

The surface characterizations of various samples were analysed with much higher resolution under a scanning electron microscope (JEOL, JSM-6360A Japan). The samples were coated with gold ion sputtering using auto fine coater JFC-1600 (JEOL, Japan). The sample was kept on the sample holder, and the scanning electron micrograph was taken.

e) Particle size measurement

Particle size measurement of the optimised ternary system of ETO-PVP K30-HPB 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

***In vitro* drug release study**

Dissolution behavior of a plain drug, physical mixtures and spray dried ternary systems were compared by plotting the graph of percentage drug release against time (fig.1-2). Due to hydrophobic nature and poor wetting, ETO floats on the surface of the dissolution medium which results in the slowest dissolution behavior of plain ETO at pH 6.8 [29].

Dissolution study revealed that all ETO formulations show two distinct phases of drug dissolution: an initial rapid phase in the first 10 min followed by a slower plateau phase. Moreover, the results in fig. 1-2 indicated that the amount of the drug released from spray dried formulations was greater in all 13 runs as compared to the amount released from corresponding physical mixtures and plain drug. As shown in fig. 2, run 3 gave 96% of drug release while its corresponding physical mixture (fig. 1, run 3) showed only 57.2% drug release in 10 min. Additionally, it was also noticed that the percentage of drug dissolved from physical mixtures and spray dried formulations was proportional to the concentration of carrier used.

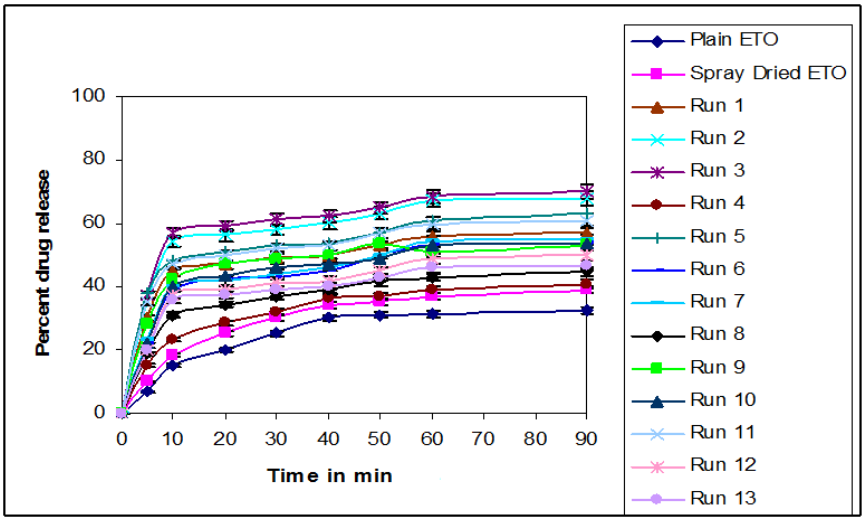

Fig. 1: Percent drug release from physical mixtures of ETO, Data given as mean±SD (n=3)

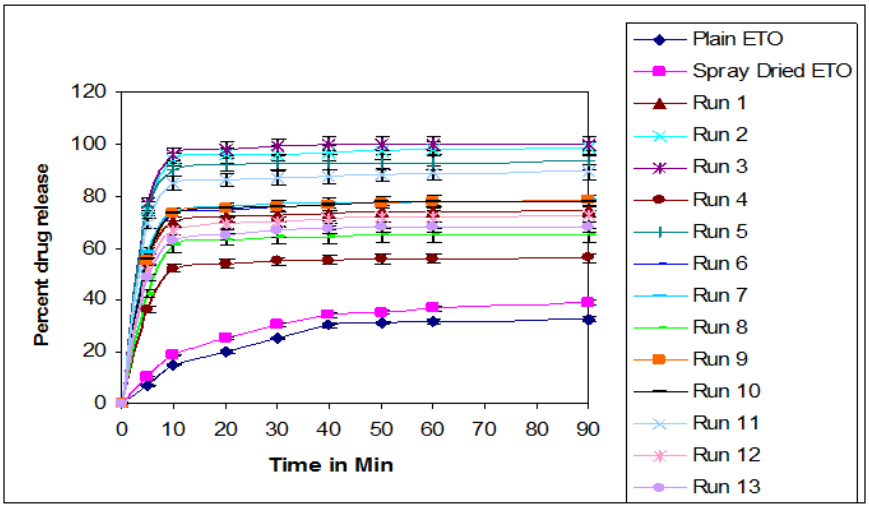

Fig. 2: Percent drug release from spray dried formulations of ETO, Data given as mean±SD (n=3)

Solubility studies

The solubility of ETO dramatically increases at pH values above its p*K*a [30, 31]. SS of plain ETO and its physical mixtures in simulated gastric fluid (SGF) pH 1.2 and phosphate buffer system (PBS) pH 6.8 with different carriers in the different selected ratios are depicted in table 2. The solubility of plain ETO in SGF was found 0.112 mg/ml. The solubility of ETO was greater in PBS pH 6.8 (6.08 mg/ml) as compared to SGF pH 1.2.

The higher solubility of ETO in the basic media of intestine might be due to the acidic nature of ETO (indole acetic acid derivative) with a p*K*a value of 4.65 [30]. The same results were obtained in various ratios of physical mixtures. From the obtained results, it can also be noted that ETO solubility increases with increase in carrier ratio. In comparison with plain ETO, the spray dried ETO showed very small improvement in the saturation solubility (*p<0.05). However, in physical mixtures, the presence of PVP K30, PVP K90 and HPB increased the solubility of ETO (*p<0.05). Results of ANOVA test showed that there was no significant difference between the solubility values of plain ETO and physical mixtures (ETO: PVP K30, ETO: PVP K90) in 1:1 weight ratio. Significant increase in solubility was observed (*p<0.05) when the concentration of PVP K30, PVP K90 and HPB were further increased (1:2 and 1:4 weight ratio). This might be due to the solubilizing effect of PVP K30, PVPK90 and complex formation of ETO with HPB as reported by Gupta *et al.* [32]. Data obtained from binary systems were used in the design of experiments for the development of the ternary system. Spray drying technique was selected because of its widespread use in various fields with different applications, as it is a method in which particle morphology and particle size can be controlled [33]. As PVP K90 produces a very sticky dispersion, it was not used for spray drying. A study was carried out in PBS 6.8 using PVP K30 and HPB as it produces a non-sticky free flowing fine powder. ETO, PVP K30 and HPB ternary systems were formulated by performing thirteen runs as per central composite design for spray drying. Results of SS, % DE and MDT were considered for optimisation of above runs.

Table 2: Saturation solubility (SS) in SGF (pH= 1.2) and PBS (pH =6.8) of plain ETO, spray dried ETO and physical mixtures of ETO and carriers

ETO-carrier PM	ETO: carrier ratio	Saturation solubility at pH 1.2 (mg/ml)	Saturation solubility at pH 6.8 (mg/ml)
Plain ETO	--	0.112±0.10	6.08±0.14
SD ETO	--	0.134±0.21	6.98±0.25
	1:1	0.201±0.33	10.24±0.29
PVP K30	1:2	0.281±0.25	11.78±0.28
	1:4	0.292±0.80	11.97±0.71
	1:1	0.211±0.54	12.52±0.44
PVP K90	1:2	0.311±0.58	13.22±0.52
	1:4	0.324±0.14	13.54±0.10
	1:1	0.923±0.54	18.79±0.34
HPB	1:2	1.612±0.22	22.20±0.18
	1:4	1.793±0.18	22.97±0.15

Data given as mean±SD (n=3) ETO: Etodolac; PVP: Polyvinyl pyrrolidone; HPB: Hydroxypropyl β-cyclodextrin.

Table 3 depicts saturation solubility, Overall dissolution efficiency at 90 min. and mean dissolution time of spray dried and physical mixture samples at pH 6.8. These results revealed that spray dried ETO products in the presence of various combinations of PVP K30 and HPB shows greater solubility as compared to physical mixtures of ETO. The results were analysed by ANOVA (*p<0.05). Run 5 showed maximum saturation solubility of 84 mg/ml; however, results of dissolution efficiency (92%) and mean dissolution time (10 min) were not satisfactory. It may be because of high concentration of PVP K30 which increases saturation solubility but delays release of a drug. Saturation solubility, dissolution efficiency and mean dissolution time of physical mixture (run 3) were found to be 42 mg/ml, 70% and 6 min, respectively. Whereas these parameters for spray dried product (run 3) were found to be 82 mg/ml, 100% and 3 min respectively; which is possibly due to the highest concentration of HPB that forms a complex with ETO. DSC and XRD results confirmed the formation of the amorphous ternary system.

Response surface methodology was used for optimization. The optimized ternary system of spray dried ETO: PVP K30: HPB was evaluated for SS, %DE and MDT. Significant increase in apparent equilibrium solubility (81.80 mg/ml) and DE (100.45%) was observed; while MDT was reduced i.e. 2.96 min significantly. This may be due to a reduction in drug particle size, the formation of a hydrophilic layer over drug particles by PVP K30 and formation of inclusion complex by HPB with the drug.

Table 3: Saturation solubility (SS), Dissolution efficiency (DE) and Mean dissolution time (MDT) of spray dried products in pH 6.8

Run	Spray dried products			Physical mixtures		
	SS (mg/ml)	DE (%)	MDT (min)	SS (mg/ml)	DE (%)	MDT (min)
1	68±0.21	74.45	13	30±0.24	51	16
2	80±0.36	98.54	04	40±0.32	68	07
3	82±0.12	100	03	42±0.15	70	06
4	58±0.15	56.23	18	25±0.25	41	21
5	84±0.26	93.12	09	45±0.40	63	13
6	66±0.39	78.12	12	28±0.21	54	15
7	66±0.11	78.58	12	28±0.14	55	15
8	57±0.21	65.15	13	23±0.47	45	16
9	68±0.49	78.20	11	30±0.21	53	14
10	68±0.14	77.98	11	30±0.26	54	14
11	74±0.42	89.21	08	34±0.34	61	11
12	60±0.15	72.54	17	25±0.14	50	20
13	64±0.32	68.24	14	26±0.10	47	17
SD ETO	6.98±0.25	39.24	23	-	-	-

Data given as mean±SD (n=3) SS: Saturation solubility; DE: Dissolution efficiency; MDT: Mean dissolution time.

Mathematical modeling using response surface methodology

Following equation expresses mathematical relationship generated using MLRA for the studied response variables

SS= 67.20+6.22*A+8.01*B-0.25* AB+1.34* A^2+1.34* B^2….(Equation: 1)

DE=77.47+8.07* A+11.65* B+1.56* AB-1.44* A^2+4.36* B^2….(Equation: 2)

MDT=11.80-1.97* A-4.35* B-1.25* AB+0.35* A^2-1.40* B^2….(Equation: 3)

Where, A: PVP K30, B: HPB.

As per ANOVA results, all the polynomial equations were found statistically significant (*p<0.05). The polynomial equations comprise the coefficient for intercept, first order main effects. Relative influence of each factor on the response was signified by sign and magnitude of main effects. The values obtained for main effects of each factor in equation 1 to 3 showed HPB has more effect on all three responses (SS, %DE and MDT) compared to PVP K30.

Response surface analysis

Fig. 3A, 4A and 5A represents the 3-dimentional response surface plots, while 3B, 4B and 5B are the corresponding counter plots for each response (SS, %DE, and MDT). Fig. 3A and 3B represent linear trend of saturation solubility in ascending order, with augmentation of PVP and HPB levels. This may be explained on the basis of the mathematical model generated for the response variable saturation solubility (Equation 1). From the model, it can be noted that high level of PVP, HPB and their combinations show a positive effect on saturation solubility.

Fig. 4A and 4B exhibited that dissolution efficiency vary in ascending order but in a non-linear manner with an increase in the amount of each polymer. The counterplot showed that HPB has a comparatively greater influence on dissolution efficiency than PVP K30 (fig. 4B).

Effect of PVP K30 and HPB on MDT is depicted in fig. 5A and 5B. An inverse relation was observed on mean dissolution time by use of PVP K30 and HPB. As represented in equation 3, HPB was more effective than PVP K30. High concentration of HPB showed minimum MDT of 3-4 min (fig. 5B); whereas a high level of PVP K30 increased MDT slightly.

Flow property measurement

The preparation of essentially all dosage forms involves the handling of solid materials. The flow properties of solids have a great impact on various steps in pharmaceutical operations like sieving, micronizing, pouring, mixing, grinding, pneumatic conveying, drying compaction, etc. Hence, this study was carried out on ETO and optimized ternary system of ETO, PVP K30 and HPB. The result of the study revealed that there was marked improvement in flow properties of ETO in the optimized ternary system as compared to plain ETO [table 4].

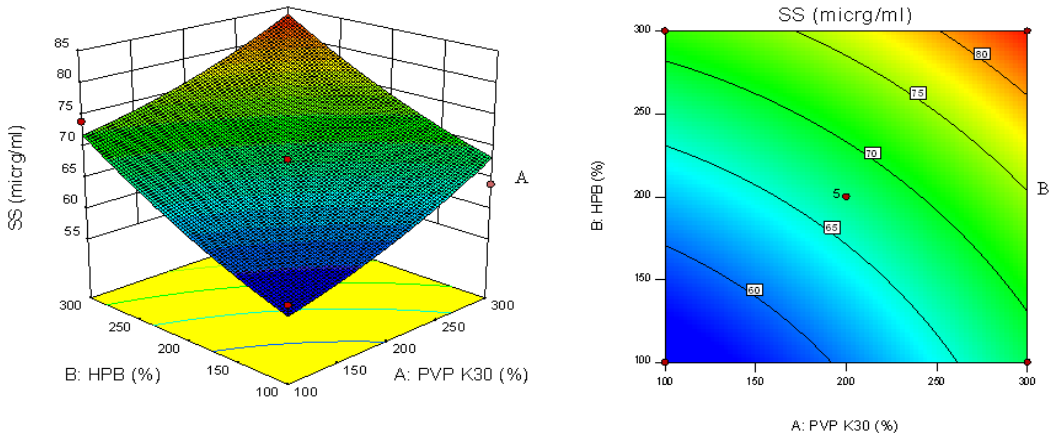

Fig. 3: Effect of PVP K30 and HPB on SS, A) 3D Graph, B) contour graph, PVP: polyvinyl pyrrolidone; HPB: Hydroxypropyl β-cyclodextrin; SS: saturation solubility

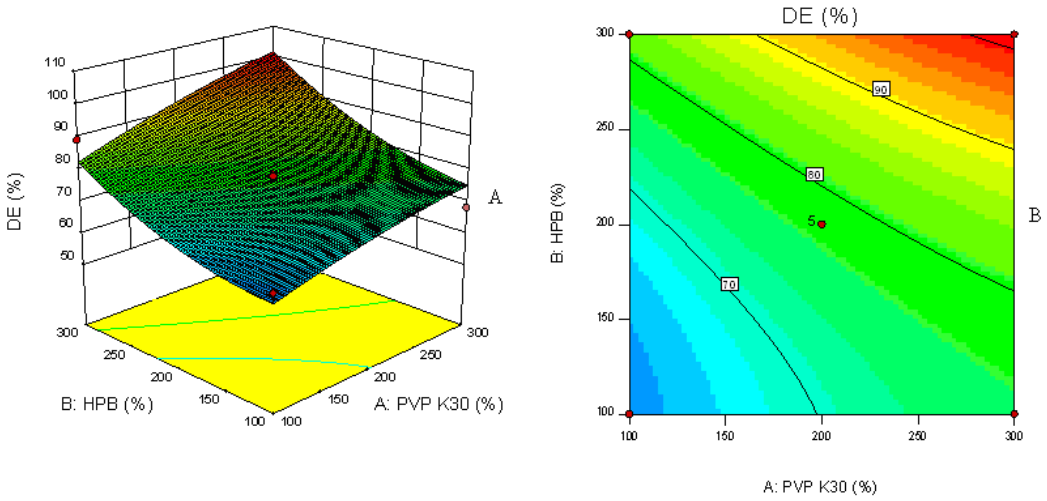

Fig. 4: Effect of PVP K30 and HPB on DE, A) 3D Graph, B) Contour graph, PVP: polyvinyl pyrrolidone; HPB: hydroxypropyl β-cyclodextrin; DE: dissolution efficiency

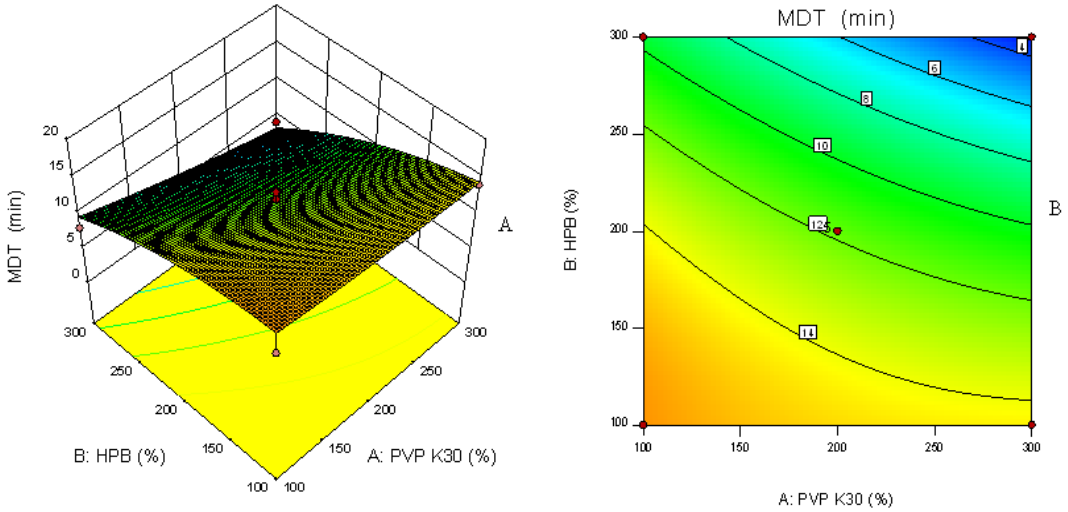

Fig. 5: Effect of PVP K30 and HPB on MDT, A) 3D Graph, B) Contour graph, PVP: Polyvinylpyrrolidone; HPB: Hydroxypropyl β-cyclodextrin; MDT: mean dissolution time

Table 4: Study of flow properties

S. No.	Parameters	ETO	Optimized ternary system
01	Bulk density (gm/cm3)	0.310	0.305
02	Tapped density (gm/cm3)	0.482	0.341
03	Compressibility index (%)	34.94	22.25
04	Hausner's ratio	01.55	01.11
05	Angle of repose (°)	36.30	17.40

ETO: Etodolac.

Characterization of optimized ternary system

To confirm the formation of solid complex and its amorphous nature, the ternary system of ETO-PVP-HPB obtained by spray drying process was characterised by FTIR, DSC, XRD and particle size analysis.

a) FTIR spectroscopy

FTIR spectrum of plain ETO showed C=O stretching region at 1748 cm-1(carboxyl carbonyl band). Strong carbonyl bond of pure ETO was significantly reduced, broadened, and shifted to a lower wavenumber (around1714 cm-1) in FTIR spectra of the optimized ternary system [fig. 6]. This represents the existence of interactions involving hydrogen bonds between ETO, PVP K30 and HPB in the optimized ternary system. Obtained results suggest the formation of new solid phase by spray drying process. This conclusion is consistent with the results of solubility study,

b) Differential scanning calorimetry (DSC)

The sharp endothermic peak at 153 °C in plain ETO sample indicated the melting point of the drug as shown in fig. 7. DSC thermogram of ETO-PVP-HPB complex did not show any peak at ETO's melting point (153 °C). This represents that drug is enclosed in HPB cavity to form inclusion complex, and it has converted into the amorphous state [34].

c) X-ray diffraction (XRD)

The powder X-ray diffractogram of ETO exhibited intense peaks and confirmed high crystallinity [fig. 8B]. ETO-PVP K30-HPB complex was found amorphous in nature [fig. 8A]. Very few peaks were observed in the case of the complex which indicated loss of crystallinity. The difference in number and shape of peaks in these two diffractograms confirmed complex formation.

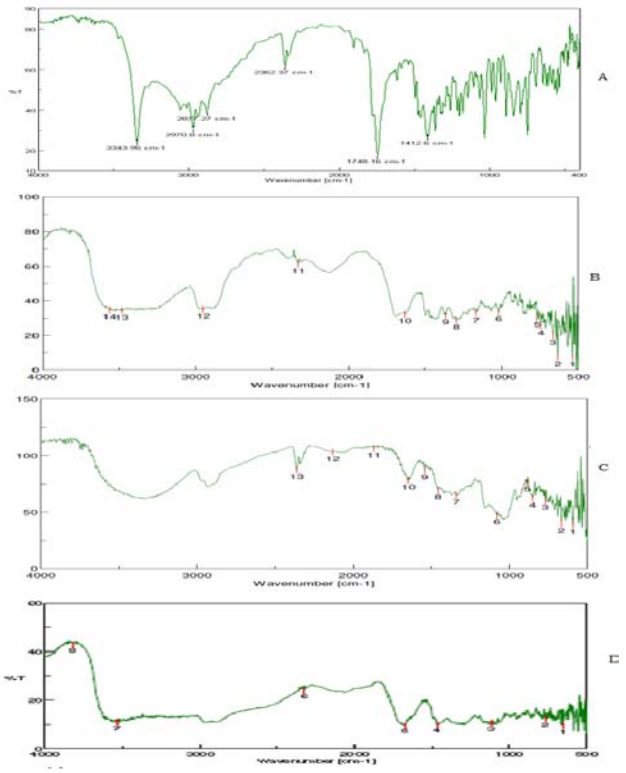

Fig. 6: FTIR spectra of A: pure ETO, B: PVP K30, C: HPB, D: optimized ternary system

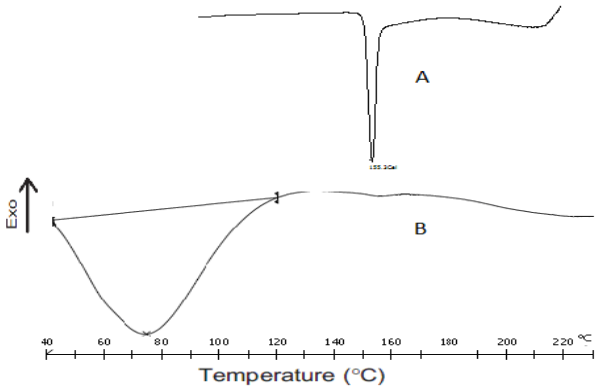

Fig. 7: DSC thermogram of A: pure ETO, B: optimized ternary system

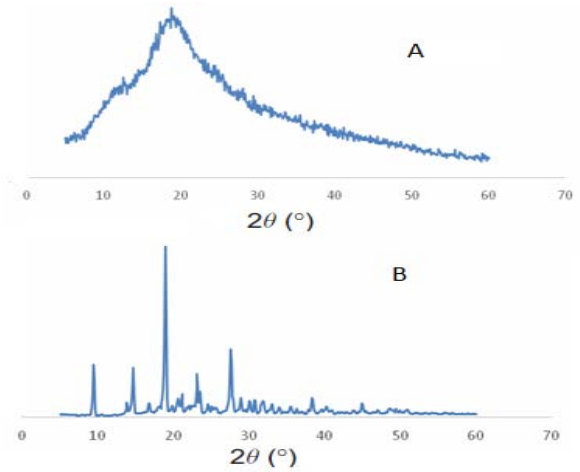

Fig. 8: X-RAY diffraction of A: optimized ternary system, B: Pure ETO

d) Scanning electron microscopy (SEM)

The scanning electron microphotograph (SEM) of ETO-PVP-HPB ternary complex was depicted in fig. 9. As per results obtained from DSC and XRD study, Pure ETO exhibited the typical crystalline pattern. In the SEM of the complex it was difficult to differentiate amongst drug, HPB and PVP K30 particles. This demonstrated that the drug particles greatly loose crystallinity. Drastic change in the surface morphology was observed which is indicative of the presence of a new solid phase. This might be due to the molecular encapsulation of a drug into the HPB. This suggested the presence of strong interaction between the ETO, PVP K30 and HPB. Same results were observed in the XRD patterns as well.

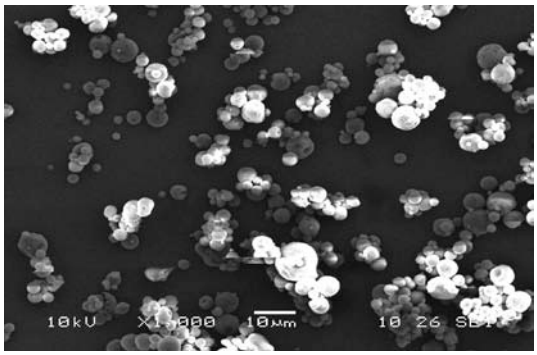

Fig. 9: SEM of optimized complex (ETO-PVP K30-HPB)

e) Particle size analysis

Analysis of particle size was performed on an optimized ternary system (ETO: PVP K30: HPB). The mean particle diameter was found in the range of 763±1.35 nm (fig. 10). Gaussian distribution plot of the optimized spray dried product showed that the particle size was in the range between 200-2000 nm and the average particle size was found 763.8±294.8 nm. A maximum number of particles were present in the range of 400 to 900 nm.

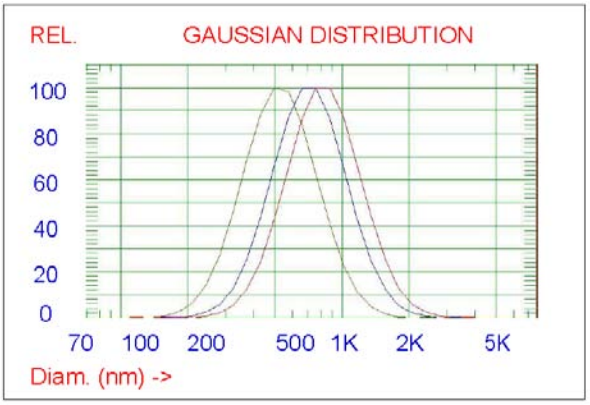

Fig. 10: Particle size analysis of optimized ternary system

CONCLUSION

Predictable dissolution attribute for ETO can be successfully achieved by DoE approach in the ternary system. Effects of PVP K30 and HPB, on the SS, DE and MDT of ETO can be evaluated and optimized effectively using DoE approach. Simultaneous optimisation of all the responses was performed using desirability function. Results of the present study concluded that combined use of PVP K30 and HPB with the multivariate approach is an effective method for formulating a ternary system of ETO by spray drying technique.

ACKNOWLEDGEMENT

The authors are thankful to the SCES's, Indira College of pharmacy, Pune for providing necessary facility and infrastructure to conduct this research work. The authors are grateful to Lupin Research Park, Pune and Roquette pharma, France for providing the gift samples.

CONFLICT OF INTERESTS

Authors explicitly declare that there is no conflict of interest.

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How to cite this article

- Amir A Shaikh, Praveen D Chaudhari, Sagar S Holkar. A design of experiment approach for optimisation and characterization of etodolac ternary system using spray drying. Int J Pharm Pharm Sci 2017;9(2)233-240