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Research Article

Solubility Enhancement of Etodolac Chewable Tablet Using Honey, and Evaluation with (Doe) Design of Experiment

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Abstract

Objective: Drug authentication, improve solubility of drug, Preparation and Evaluation of solid dispersion, Use of honey in formulation development, Preparation of chewable tablet and Stability study

Method: Drug and polymers in different ratios (1:1, 1:2 and 1:4) were prepared to study the effect of individual polymer on solubility of Etodolac. High pressure homogenizer and solvent evaporation method was used to investigate the combined effect of PVP K30 and BCD on saturation solubility, percent cumulative drug release (% CDR) of Etodolac. Design of experiment (DoE) was used for preparation and evaluation of solid dispersion. Drug polymer interaction were analyzed with Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) with all combination of solid dispersion, and selection of honey as an antiulcer (GI). Design of experiment (DoE) was used for preparation and evaluation of chewable tablet.

Result: Different combination of PVP K30 and BCD prepared using design of expert (DoE) approach by high pressure homogenizer and solvent evaporation method showed greater solubility of Etodolac than its physical mixtures. Result of FTIR, DSC and XRD revealed the interaction between Etodolac PVP K30 and BCD. Increase percent cumulative drug release (% CDR) of solid dispersion (SD). This suggested formation and evaluation of ETO chewable tablet. Increasing in percent cumulative drug release (% CDR) of Etodolac chewable tablet.

Conclusion: Design of experiment (DoE) was predicted combination of PVP K30 and BCD, it was a more effective combination for preparation of Etodolac chewable tablet.

Keywords: Etodolac; High Pressure Homogenizer; Solvent Evaporation; Polyvinyl Pyrrolidone K30; Hydroxypropyl B-Cyclodextrin; Design of Experiments; Chewable Tablet

Introduction

Cyclodextrin (CD) inclusion complexation, which is the formation of host-guest inclusion complexes by weak intermolecular interaction, has been shown to be a promising technique in enhancing solubility and bioavailability of poorly water-soluble drugs [1]. Cyclodextrin and its derivatives are widely used as pharmaceutical materials for preparing inclusion complexes due to its non-toxic, high biodegradability and various other advantages, it has a hydrophilic outer surface and a hydrophobic central cavity that can be used to solubilize compounds with less polarity. Therefore, CD is widely used to improve the dissolution of less polar compound and drugs. In addition, CD is nontoxic and has good stability [2]. They can be used to improve the water-solubility, chemical stability and bioavailability of insoluble drug, as well as reducing drug toxicity. Among three types of cyclodextrin, β-CD is the least soluble, making it the easiest to be crystallized from water. Thus, β-CD is the most commonly used cyclodextrin. HP-β-CD is the ether derivative of β-CD. Compared with β-CD, HP-β-CD is more soluble and less toxic. When administered via injection, HP-β-CD has almost no stimulation to muscle and mucosal. It has been approved by the United State Food and Drug Administration (FDA) to be used as a drug solubility agent and penetration enhancer. Thus, HP-β-CD has great potential applied in pharmaceutical excipients [3].

Etodolac is act as an analgesic (selective COX-2 inhibitor) and anti-inflammatory drug especially for the treatment of arthritis and analgesic also [4]. The anti-inflammatory activity of Etodolac has been reported to be mainly due to the inhibition of prostaglandin biosynthesis. A white or almost white, crystalline power practically insoluble in water freely soluble the spectrum obtains with Etodolac, dose 300 - 600 mg daily. This drug has a very poor solubility in water and its use to solid dosage form forms for oral administration. The major drawbacks associated with the NSAIDs are local gastrointestinal toxicity and ulceration [5]. It is under the class II biopharmaceutical classification system (BCS), low solubility and high permeability. The side effect of NSAIDs include the risk of digestive tract disorder, kidney function impairment [6].

Mechanical homogenization was defined as the capability of producing a homogeneous size distribution of particles suspended in a liquid, by forcing the liquid under the effect of high pressure through a disruption valve [7]. High pressure homogenizers are widely used in the pharmaceutical, chemical, and food industries

[8]. Homogenization makes physicochemical changes that effect on product solubility (easy dissolve). Homogenization is the mechanical process which reduces the particle size of drug via high pressure and decrease dissolution rate of drug [9].

Solvent evaporation method

The solvent evaporation technique has widely been used for preparation of microspheres for controlled release of drug. The preparation method consists basically of three it major steps: (i) dissolution or dispersion of the bioactive compound often in an organic solvent containing the matrix forming material, (ii) emulsification of this organic phase in a second continuous phase immiscible with the first one, (iii) extraction of the solvent from the dispersed phase by the continuous phase, which is optionally accompanied by solvent evaporation, either one transforming the droplet into solid microspheres, (iv) harvesting drying pf the microspheres [10].

Materials and Methods

Material: Etodolac and PVP K30 from Lupin research park, Pune, India, hydroxypropyle β cyclodextrin (HPB) from Roquette pharma, France. All other reagents and chemical was used analytical grade.

Methods Design of experiments (DoE)

For designing of experiments, Design expert V10 software was used. The amount of the BCD(A) and PVP K30 (B) both are selected as experimental factors and studied. Software was gives thirteen experimental runs with different combination of factors were obtained by design expert software as depicted in percent Cumulative drug release and anti-inflammatory activity were taken as response variables.

Preparation mixture of Etodolac and PVP K30 in weight ratios of 1:1, 1:2 and 1:14 were prepared by passing ingredients through sieve (#60) separately and then mixing both solids by simple blending, same treatment with BCD.

Preparation of Solid Dispersion

High pressure homogenization

The sample of drug, and the another sample prepared for homogenization, 1L sample was subjected to high pressure homogenization at 0 to 300 MPa at 100 MPa increments using a high pressure valve homogenizer. The homogenizing chamber was cool to 1°C using a controlled temperature water bath. The temperature of the sample prior to homogenization was approximately 20°C. Since the temperature increased linearly from 20° to 75°C corresponding to 0 ~300 MPa of homogenization pressure, a tubular heat exchanger was connected immediately after the homogenization valve to cool down the sample to room temperature. After processing, the sample were kept at 40°C for further analysis [11].

Solvent evaporation method

Preparation of solid dispersion by using solvent evaporation method: organic solvent (ethyl acetate), stirring speed (700 rpm) and organic to aqueous ratio (1:10). Ethyl cellulose was taken in a crucible is dissolved in ethyl acetate to form a homogenous solution. Drug was added to the homogenous solution and mixed thoroughly. Dispersion was then added as a thin stream to 100 ml of aqueous mucilage of 0.5% sodium cmc contained in a 250 ml beaker while being stirred at 700 rpm to emulsify the added dispersion as fine droplets.

The solvent removal was achieved by continuous stirring at room temperature for three hours to produce homogenized powder. The homogenized powder formed was collect. The product was then air dried [10].

Evaluation of solid dispersion

Angle of repose

The angle of repose of powder was determined by the funnel method. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured, and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Hence, $\theta = \tan\text{-}1h/r$

Where, θ = angle of repose

h = height of the cone

r = radius of the cone base

Angle of Repose (°)	Flow Ability
< 20	Excellent
20 - 30	Good
30 - 40	Passable
> 40	Very poor

Table 1: Relationship between angle of repose ($^{\theta}$) and flow ability.

Bulk density

Both bulk density (BD) and tapped density (TD) were determined. A quality of 2g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height nearly of 2.5 cm. The tapping was continued until no further change in volume was noted.

Tap density

A sample powder was filled in 100 ml graduated cylinder. The mechanical tapping was carried out and the volume V^f was noted.

$\rho t = M/V^f$

Where, ρt = tapped density

M = weight of the sample powder

V^f = tapped volume of the powder

BD and TD were calculated using the following formulas.

BD = Weight of the powder/Volume of the packing

TD = Weight of the powder/Tapped of the packing

Hausner ratio

Hausner ratio was calculated using the formula;

Hausner ratio = $\rho t/\rho_{\circ}$

Where,

ρt = tapped density

$\rho_{\circ}$ = bulk density

Hausner Ratio	Flow Ability
1.05 - 1.18	Excellent
1.14 - 1.20	Good
1.22 - 1.26	Fair to passable
1.30 - 1.54	Poor
1.50 - 1.61	Very poor
> 1.67	Very, very poor

Table 2: Relationship Between Ration and Flow Ability.

Carr's Compressibility Index

The compressibility of the granules was determined by Carr's Compressibility Index

Carr's compressibility index (%) = [(TD-BD) × TD]/100

% Compressibility	Flow Ability
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair to passable
23 - 35	Poor
33 - 38	Very poor
> 40	Very, very poor

Table 3: Relationship Between % Compressibility and Flow Ability.

Optimized Formulation of Solid Dispersion

Designed formulation (Run 7: BCD – 200 mg and PVP K30 - 100 mg) of solid dispersion select and this formulation was used for tablet formulation. Selected formulation of solid dispersion treats with solvent evaporation method and high pressure homogenizer, this selected formulation was studied anti-inflammatory activity.

Run	BCD	PVP K30
1	200	100
2	200	170.711
3	200	100
4	150	150
5	129.289	100
6	150	50
7	200	100
8	200	100
9	270.711	100
10	200	100
11	250	50
12	250	150
13	200	29.2893

Table 4: Central Composite Design for Solid Dispersion.

In Vitro Drug Release Study

Drug release studies were performed by employing USP apparatus II. The Spray Dried powder equivalent to 200 mg of ETO were inserted in dissolution vessel containing 900 ml of dissolution medium maintained at 37 ± 0.50°C and stirred at 50 rpm. 5 ml of Samples were collected periodically and replaced same amount by fresh dissolution medium. Withdrawn samples were filtered through Whatman filter paper no.41, concentration of ETO was determined spectrophotometrically at 279 nm. The dissolution study was repeated 3 times.

Optimized Formulation of Tablets

Designed formulation (F9) was select and this formulation composition used in tablet formulation. Selected formulation (F9) composition is greater percentage drug release and (F4) formulation was greater anti-inflammatory activity.

Run	Factor 1A. Honey	Factor 2B. CCs
1	80	40
2	100	30
3	100	30
4	100	15.8579
5	120	40
6	100	44.1421
7	100	30
8	120	20
9	100	30
10	128.284	30
11	71.7157	30
12	80	20
13	100	30

Table 5: Optimized Formulations of Tablets.

Chewable Tablet Formula

Formula of chewable tablet used optimized formulation of solid dispersion, solid dispersion equivalent to 500 mg (Etodolac - 200 mg, BCD - 200 mg and PVP K30 - 100 mg). Designed formulation of honey and CCS was used in tablet formulation.

Ingredient	Quantity in mg
Solid dispersion	Equivalent to 500
Honey	100
Aerosil 200	100
Sodium bicarbonate	100
Mannitol	110
Magnesium stearate	40
Croscarmellose Sodium	30
Menthol	3
Sodium saccharin	6
Raspberry Flavor	10
Red color	1
Total weight of tablet = 1000	

Table 6: Chewable Tablet Formula.

Preparation of tablet

Preparation of tablet by using designed formulation (high pressure homogenizer). Dry granulation method was use for chewable tablet, and 16 mm punch was used.

Procedure for tablet

From that ETO equivalent to 500 mg for one tablet, Sodium Saccharin, Aerosil, Honey, magnesium stearate, Mannitol, Menthol, Sodium bicarbonate, flavor, color and CCS were weighed accurately. All the materials were passed through 60 # screen prior to mixing. All the materials were transferred to glass mortar and triturated till it mixed uniformly. Honey and Aerosil separate and then added in tablet ingredients. The resulting powder mixture was compressed into tablets using single punch tablet machine.

Evaluation of Tablet

Thickness

Thickness of tablets was determined using Vernier caliper. Ten tablets from each batch were used, and average values were calculated.

Weight variation

Weight variation was carried out to ensure that, each of tablets contains the proper amount of drug. The test was carried out by weighing the 10 tablets individually using analytical balance, then calculating the average weight, and comparing the individual tablet weight to the average.

Sr. no.	Average weight of tablets (mg)	Maximum percentage difference allowed
1	130 or less	± 10.0
2	130 - 324	± 7.50
3	More than 324	± 5.0

Table 7: Weight Variation Limits for Tablets (I.P).

Drug content

Six tablets were weighed individually and these tablets were crushed in mortar. From which drug equivalent to 10 mg of powder was taken, to this 100 ml of methanol was added. The drug content was determined at 279 nm by UV spectrophotometer.

Hardness

For each formulation, the hardness of 6 tablets was determined using the Pfizer hardness tester.

Friability

For each formulation, the friability of 10 tablets was determined using the friabilator. This test subjects a number of tablet to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm. A sample of preweighed 10 tablets was placed in friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 0.5 – 1% in weight in generally considered acceptable. Percent friability (%F) was calculated as follows,

$$F = 100 \times \left(1 - \frac{wo}{w}\right)$$

Where,
W = Average weight of 10 tablets
W0 = after testing tablets

Disintegration

The disintegration time for dispersible tablet was carried using USP disintegration apparatus. The limit for disintegration was not more than 3 minutes, at a temperature 37°C. For study three tablets of each batch were tested. Tablets were placed individually in each tube of disintegration test apparatus and the disc were placed. The water was maintained at 37°C. Mean of three reading were considered as disintegration time of each batch.

In vitro dissolution study of chewable tablet

Drug release studies were performed by employing USP apparatus II. The spray dried powder equivalent to 200 mg of Etodolac were inserted in dissolution vessel containing 900 ml of dissolution medium maintained at 37 ± 0.50°C and stirred at 50 rpm. 5 ml of sample were collected periodically and replaced same amount by fresh dissolution medium. Withdrawn sample were filtered through Whatman filter paper concentration of

Etodolac was determined spectrophotometrically at 279 nm. The dissolution study was done triplicate.

Accelerated Stability Studies

The stability of tablets was monitored up to 3 months at accelerated stability conditions of temperature and relative humidity (40°C/75% RH). Sample were withdrawn after one month and characterized by dissolution study and anti-inflammatory activity.

Results and Discussion

Drug characterization

Organoleptic properties

a) Color: White or almost white, crystalline powder

b) Taste: Bitter

c) Melting point: Melting point of drug was found to be 145°C

Flow Property of drug

Parameter	Result	Flowability
Carr's Compressibility index	14	Good
Hausners ratio	1.16	Good
Angle of repose	21	Good

Table 8: Flow Property Result of Drug.

IR Spectroscopy

IR spectrum showed dominant characteristic peaks of Etodolac. Biggest and sharp peak indicates N-H may be present, broad peak indicate OH may be present, 1412.6 this value indicate benzene ring may be present and 1748.16 this value indicates double bond may be present. Especially N-H, O-H, and C = O stretching vibrations at 3343.96, 2970.27, 1748.16 and 1412.6, which confirms drug sample was authentic one.

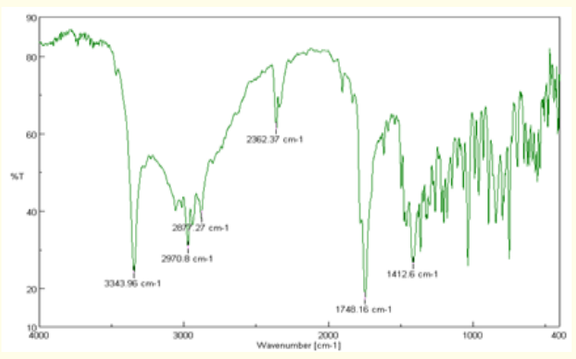

Figure 1: Graph IR Spectrum of Etodolac.

Functional Group	Peak Positions	Types of Vibration
N-H	3343.96	Stretching
O-H	2970.8,2877.27	Stretching
C=O	2362.37,1748.6	Stretching
C-H	1412.6	Bending

Table 9: Authentication of drug by IR Spectroscopy.

UV spectrum

Maximum absorbance of Etodolac was found to be at 229 and 279 nm. This is characteristic property of Etodolac in its pure form. The result complies with specification of Etodolac in USP. This confirms that the drug is authentic.

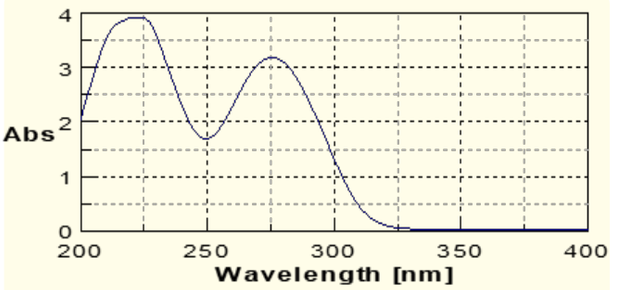

Figure 2: Graph UV Spectrum of ETO.

Solid Dispersion Methods

Prepared solid dispersion powder of by using high pressure homogenizer and solvent evaporation method.

Optimization study of solid dispersion (BCD and PVP K30)

Optimization formulas of solid dispersion was fixed with the help of Design expert version 10 (trial). The optimized formula of two factor which will use for tablet formulation. Software gives 13 optimized formulation, this studied with two activity one is % CDR and second is anti-inflammatory activity.

- **% CDR:** % CDR of all formulation was studied with the help of dissolution apparatus (USP II). All formulations % CDR was fill in the optimized formulation table (refer table 8).
- **Anti-inflammatory activity:** Anti-inflammatory activity of all formulation was studied with the help of dissolution apparatus (USP II). All formulations % activities was fill in the optimized formulation table (refer table 8).

Response 1 Drug release

Contour plot: This contour plot is indicates that with increasing quantity of BCD increases % CDR. PVP K30 increasing effect on % CDR but less. Prediction point shown the percent drug release is 82.64% and coposition of solid despersion is BCD- 200 mg and PVP K30- 100 mg.

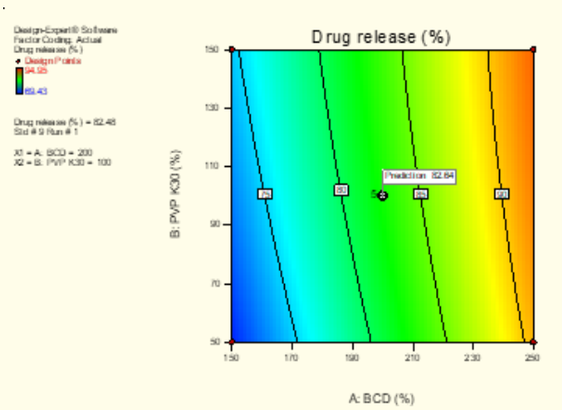

Figure 3: % CDR Contour Plot of Solid Dispersion.

3D graph: This 3D graph is indicates that with increasing the quantity of BCD, increases in percente drug release than PVP K30. Prediction point shown the percent drug release is 82.64 % (F7) and coposition of of solid despersion is BCD - 200 mg and PVP K30 - 100 mg.

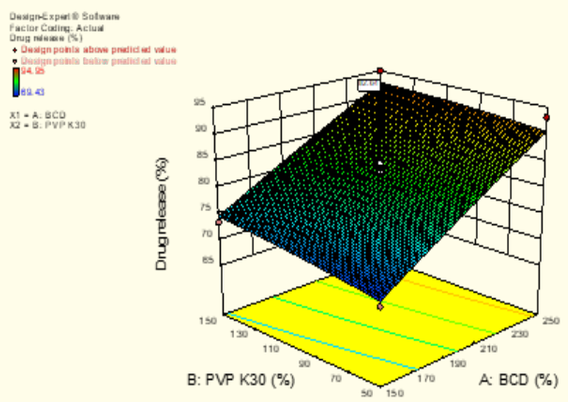

Figure 4: 3D surface plot of % CDR (solid dispersion).

Anti-inflammatory Activity

Response 2 Anti-inflammatory activity

Contour plot: This contour plot is indicates that with increasing quantity of BCD, increases antiinflammatory activity than PVP K30. Prediction point shown the percent drug release is 84.64% and coposition of solid despersion is BCD - 200 mg and PVP K30 - 100 mg.

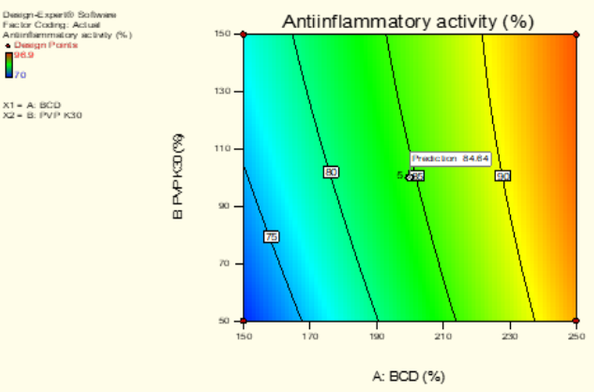

Figure 5: Contour Plot of Anti-Inflammatory Activity.

3D graph: This 3D is indicate increasing the quantity of BCD increasing in antiinflammatory activity than PVP K30. Prediction point shown the antiinflammatory activity is 84.64 % and coposition of solid despersion is BCD-200 mg and PVP K30- 100 mg (F7).

Desirability

Desirability=1 means formulation is perfect. This graph give the perfect limit of composition for perfect formulation. Percent drug release is 82.64% and antiinflammatory activity is 84.64%. Coposition of solid despersion is BCD-200 mg and PVP K30- 100 mg (F7).

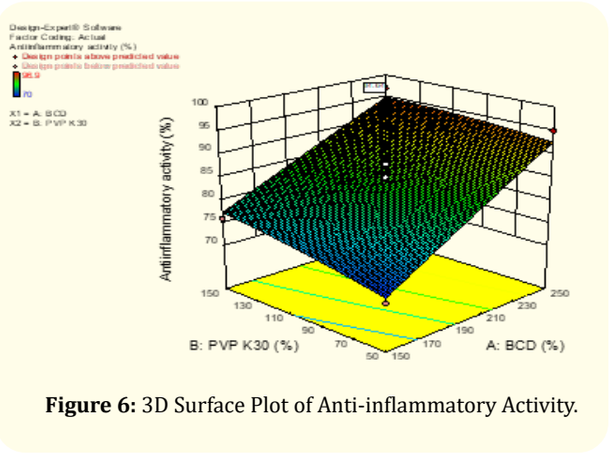

Figure 6: 3D Surface Plot of Anti-inflammatory Activity.

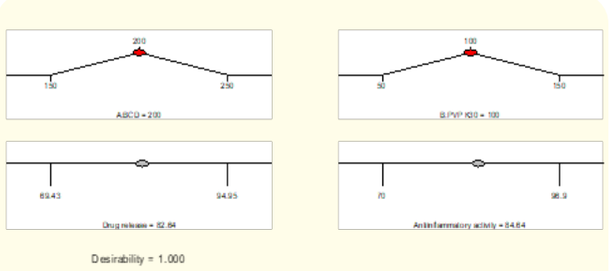

Figure 7: Numerical Graph..

Evaluation solid dispersion

Characterization of solid dispersion Powder Design formula

The flow property of Solid dispersion is good, show following table 10.

Parameter	Result	Flowability
Carr's Compressibility index	12	Good
Hausners ratio	1.20	Good
Angle of repose	19.36	Good

Table 10: Flow Property of Solid Dispersion (powder).

Infrared Spectroscopy

Consideration of the structure of ETO illustrate that can only act as proton acceptor (through either O or N atoms of pyrrole ring) and ETO has both proton donor (OH group, NH) and acceptor sites (C = O group) in structure. PVPK-30 has only accepter sites (C = O).

Drug and all the polymers show characteristic spectrum of their functional groups. Although formulation HMEE9 shows characteristic peaks of drug corresponding to N-H, O-H, C=O functional groups.

FTIR spectrum of PVP K-30 showed broad peaks at about 3050 - 3720 $cm^{-1.}$ The spectrum of PVP-K30 showed, among others, important bands at 2925 $cm^{-1.}$ (C-H stretch) and 1652 $cm^{-1.}$ (C = O). A very broad band at 3300 $cm^{-1.}$, which was attributed to the presence of water, was also visible.

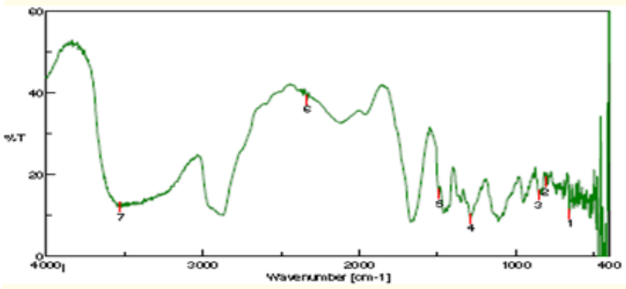

Figure 8: Graph Infrared Spectra of ETO.

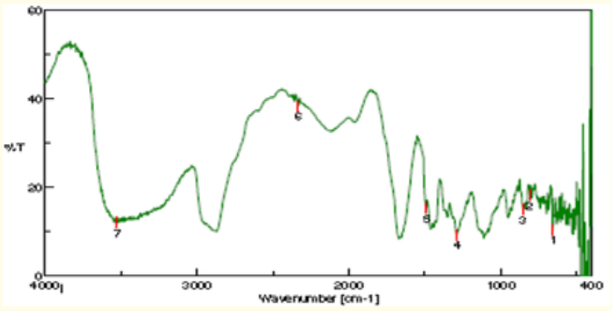

Figure 9: Graph Infrared Spectra of ETO + PVP K30

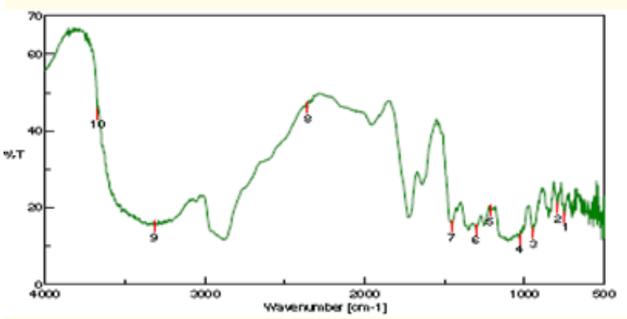

Figure 10: Graph Infrared Spectra of ETO + β-Cyclodextrin.

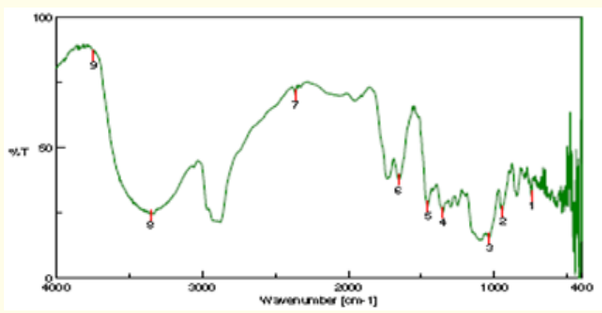

Figure 11: Graph Infrared Spectra of ETO+HP-β-Cyclodextrin.

HP-β-CD spectrum exhibited absorption bands of hydroxyl group at 3405 cm^{-1} and vibration bands of C - O and O-H groups at 1083 cm^{-1} and 1032 cm^{-1} respectively.

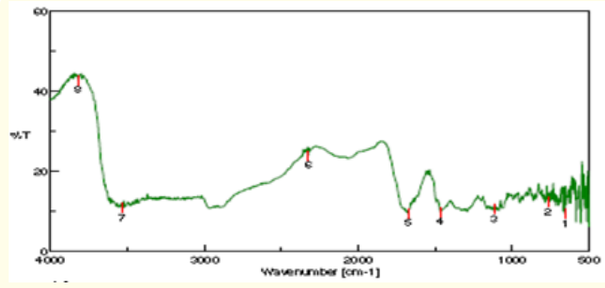

Figure 12: Graph Infrared Spectra of High Pressure Homogenizer (HPH F 7).

The Infrared Spectra of optimized formulation Hot Pressure Homogenizer (HPH F7). The Spectrum Exhibit absorption bands of hydroxyl group at 3600 cm^{-1} and vibration bands of C-O and O-H group at cm^{-1} and 1045 cm^{-1} and 1450 cm^{-1} respectively.

X-ray diffraction study

X ray diffraction study of pure ETO and HPH F7 showed high intensity peaks between 8 and 28, prove its crystalline nature. For the calculation of disorderness of formulations the term relative degree of crystallinity (RDC) was used, this can be calculated as.

$$RDC = \frac{\text{Highest peak intensity of formulation}}{\text{Highest peak intensity of drug}}$$

Diffraction pattern of (HPH F1) sample, exhibits diffraction peaks still at 2θ angles expected for ETO but with significant differences in their relative intensities (Figure). This effect could be the result of slight changes in molecular conformation. Such an effect does not affect parameters and symmetry of the unit cell. Peaks are slightly wider than in pure ETO, indicating narrower crystalline size and/or presence of disorder.

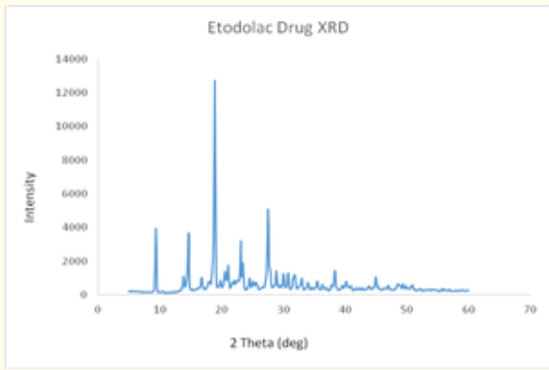

Figure 13: Graph XRD spectrum of ETO.

Differential scanning Calorimetry

DSC thermo grams of ETO, HPH F1 were presented in figure. The thermo gram of ETO showed a sharp melting event at 155.20 with enthalpy of fusion between -30.00 to -40.00 Mw. While HSH

E... formulations were showed melting endothermic event at 143.2 with enthalpy of fusion at -15.00 reveals drug in crystalline state.

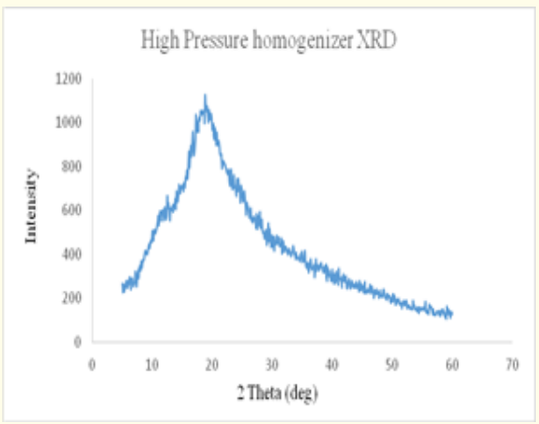

Figure 14: Graph XRD Spectrum of (E) High Pressure Homogenizer.

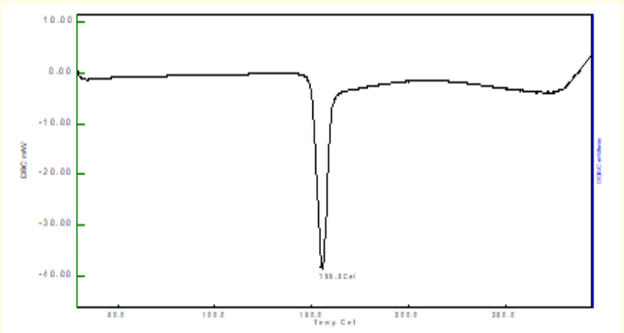

Figure 15: Graph: DSC thermos gram of Etodolac.

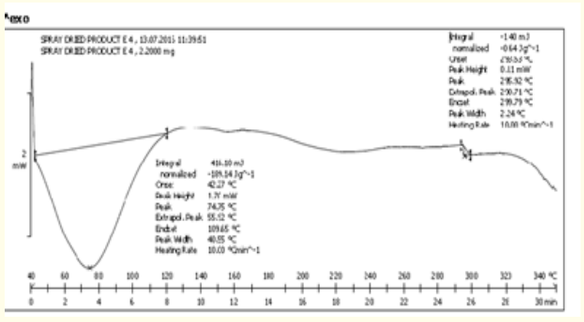

Figure 16: Graph DSC Thermo Gram of (F7) High Pressure Homogenizer.

DSC thermo gram of HPH F1 displayed an endothermic peak at 150°C. The endothermic peak of Etodolac (160°C) was absent in this case, which may be described to the formation of inclusion complexes. The presence of drug peak indicated that Etodolac was dispersed in the Free State between inclusion complexes.

In vitro dissolution study of solid dispersion

In vitro dissolution study of various solid dispersion formulations are represented in graph. All the formulations show a good release pattern for 90 minutes in dissolution studies for the composition of BCD and PVP K30. Increasing concentration of BCD % CDR also increased, and PVP K30 also help for drug release. Both polymer is used for solubility enhancement. Hence the combination of BCD and PVP K30 showing a good release pattern because of increased solubility of drug.

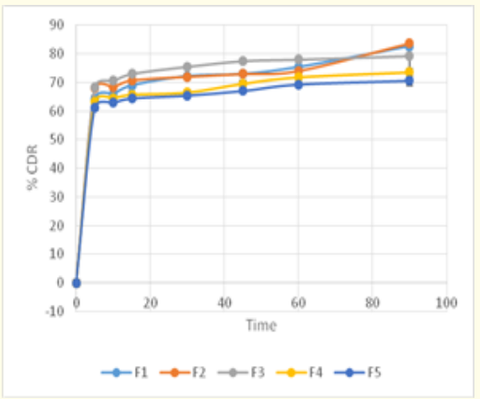

Figure 17: Graph % Cumulative drug release of solid dispersion F1-F5.

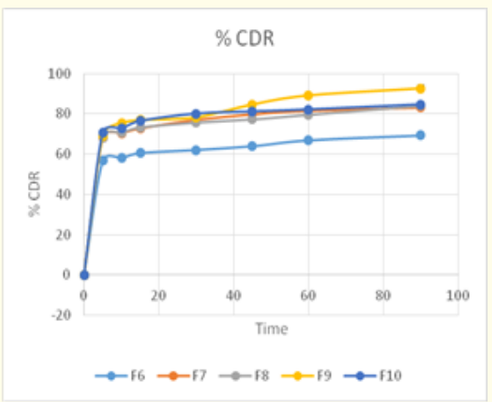

Figure 18: Graph % Cumulative drug release of solid dispersion F6-F10.

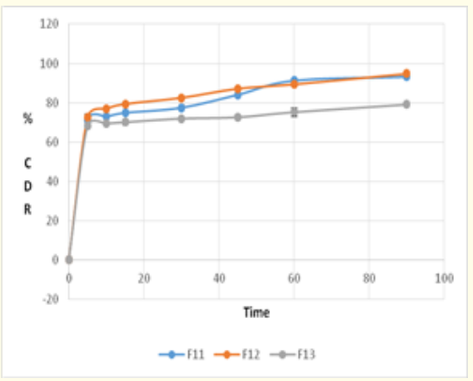

Figure 19: Graph % Cumulative drug release of solid dispersion F11-F13.

Optimization study of tablet (Honey and CCS)

Optimization formulas of solid dispersion were fixed with the help of Design expert version 10 (trial). The optimized formula of two factors which will use for tablet formulation. Software gives 13 optimized formulations, this studied with two activity one is % CDR and second is anti-inflammatory activity.

- **% CDR:** % CDR of all formulation was studied with the help of dissolution apparatus (USP II). All formulations % CDR was fill in the optimized formulation table.
- **Anti-inflammatory activity:** Anti-inflammatory activity of all formulation was studied with the help of dissolution apparatus (USP II). All formulations % activities was fill in the optimized formulation table.

Response 1% CDR

Contour plot : This contour plot is indicates less quantity of CCS increasing in percent drug release than honey. Because honey is adhere to other excipient, therefor the drug release is less. But this formulation is Predicted (Run 9) because the limited amount of CCS than honey, point shown the percent drug release is 85.00 % and coposition is honey- 100 mg and CCS 30 mg.

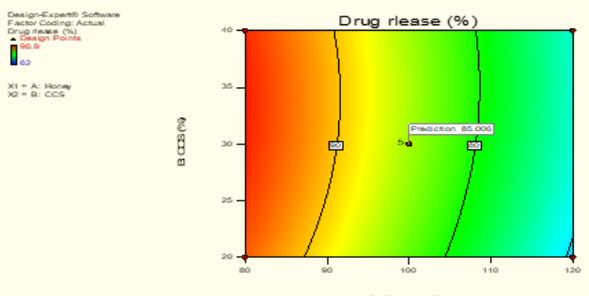

Figure 20: Contour plot of % CDR.

This 3D contour plot indicates less quantity of CCS increasing in percente drug release than honey. Because honey is adhere to other excipient, therefor the drug release is less. But this formulation is Predicted (F9) because the limited amount of CCS than honey, point shown the percent drug release is 85.00% and coposition is honey – 100 mg and CCS 30 mg.

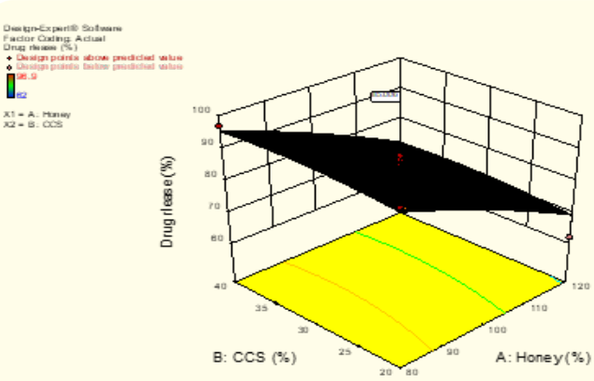

Figure 21: 3D surface plot for % CDR.

Response 2: Anti-inflammatory activity

Contour plot : This contour plot indicates that with increasingthe quantity of honey, increases percent drug release than CCS. Because honey has antiinflammatory activity, therefor the drug release more than CCS. CCS is desintegrant not antiinflammatory agent.Predicted point of formulation is shown the anti-inflammatory activity 86.96% (Run 9) and coposition is honey-100 mg and CCS 15.85 mg.

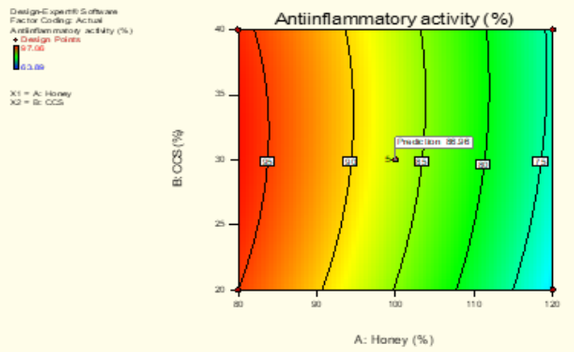

Figure 22: Contour plot of anti-inflammatory activity.

This 3D graph indicates that with increasing the quantity of honey, increases percent drug release than CCS. Because honey has antiinflammatory activity, therefor the drug release more than CCS. CCS is desintegrant not antiinflammatory agent. Predicted point of formulation is shown the antiinflammatory activity 86.96% (Run 9) and coposition is honey- 100 mg and CCS 15.85 mg.

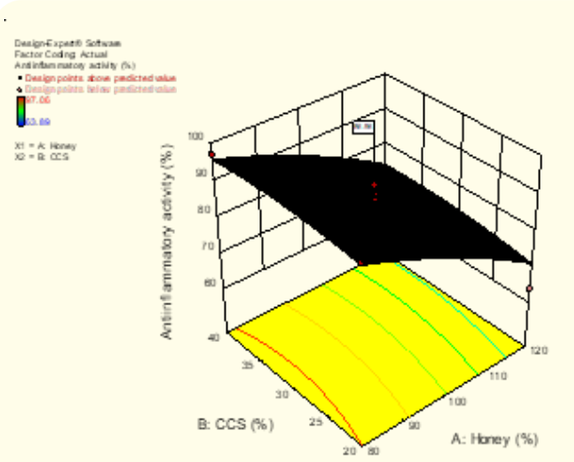

Figure 23: 3D surface plot of anti-inflammatory activity.

Desirability

Desirability = 1 means formulation is perfect. This graph give the perfect limit of composition for perfect formulation. Percent drug release is 85.00% (F9) and antiinflammatory activity is 86.96% (F9). Coposition of honey and CCS for tablet formulation is honey = 100 and CCS = 30 mg.

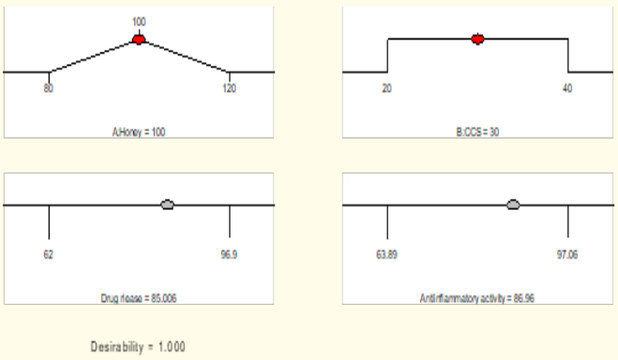

Figure 24: Numerical Graph.

Chewable Tablet of Etodolac

Prepared chewable tablet of Etodolac, by direct compression.

Evaluation of chewable tablets (F9)

Parameter	Evaluation
Hardness	4.21 Kg/cm^2
Friability (%)	0.6
Disintegration time	11:26 minutes
Weight variation	2%
Drug Content	96.12%
Thickness	5.68 mm

Table 11: Evaluation of chewable tablets (f9).

In vitro dissolution study of tablet

In vitro dissolution study of various tablet formulations are shown in graph. All the formulations show a good release pattern for 90 minutes in dissolution studies for the composition of honey and CCS. With increasing concentration of CCS % CDR also increased. Also, the addition of honey showing good % CDR up to certain limit, then decreases because honey bind with excipient and increase the hardness. Hence drug release is little bit slowly. CCS is a disinterant, Hence CCS is showing a good release pattern because of increased solubility of drug.

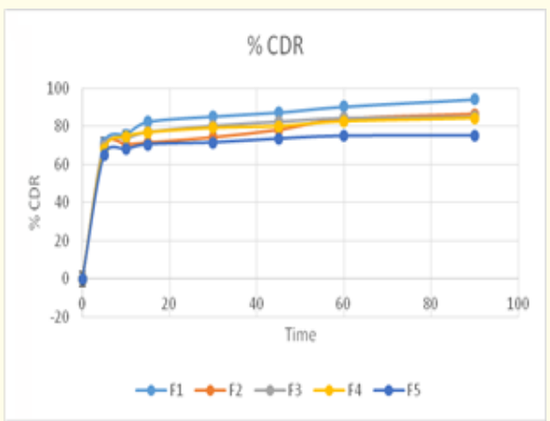

Figure 25: Graph % Cumulative drug release of tablet F1-F5.

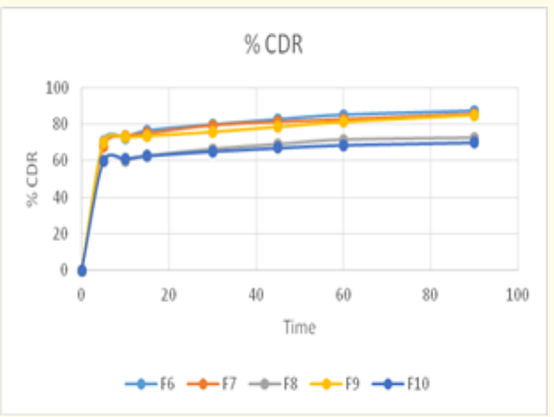

Figure 26: Graph % Cumulative drug release of F6-F10.

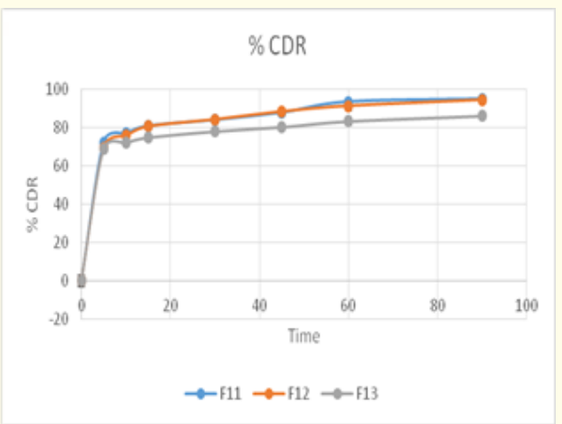

Figure 27: Graph % Cumulative drug release of tablet F11-F13.

Accelerated Stability Study

Parameters	Accelerated Stability Study		
	Initial	2 Month	3 Month
% CDR	94.87	94.82	94.70
Anti-inflammatory activity study (%)	97.06	97.04	96.98

Table 12: Accelerated stability study of F9, at conditions (40C/75% RH).

The design formulation was kept in stability chamber for 3 months at (40°C/75% RH) according to ICH guidelines. Initially checked the physical parameter of tablet, calculate % anti-inflammatory activity and % CDR. Then after 3 months interval sample was removed and checked same parameter. The stability study data indicates that there is no instability in the formulation as there is no significant change in the % drug release and % anti-inflammatory activity. No change in the % anti-inflammatory activity and % CDR of the sample, this indicates the formulation was stable.

Conclusion

High pressure homogenizer method was effectively applied to increase the solubility of Etodolac. In this study, Etodolac drug was complexed with HPB and PVP K30 which was subsequently formulated with and without honey. Complexation increases the solubility of Etodolac in gastric simulated fluid and increase availability of the drug for anti-inflammatory action and percent drug release. Results of HRBC membrane stabilization and protein denaturation method showed that all the formulations showed greater anti-inflammatory and antibacterial activity as compared to pure Honey. Addition of honey played a significant role in increasing the anti-inflammatory activity of all formulations. Hence from this study, it can be concluded that use of PVP K30 and HPB in combination with honey was an effective approach to enhance the anti-inflammatory activity and percent drug release of Etodolac drug.

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