

## Optimization And Characterization Of Rapidly Dissolving Films Of Cetirizine Hydrochloride Using Cyclodextrins For Taste Masking

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**Abstract:** Cyclodextrin and its derivatives were used as taste masking agents for the preparation of rapidly dissolving films of Cetirizine hydrochloride. The films were evaluated for drug content, thickness, tensile strength, % elongation and elastic modulus, *in-vitro* and *in-vivo* disintegration studies, *in-vitro* dissolution studies and surface morphology. The films were also tested for complex formation using Differential scanning calorimetry and X ray diffraction study. A 3<sup>2</sup> full factorial design was utilized to study the effect of 2 independent variables i.e. amount of HPMC E3 LV (X<sub>1</sub>) and amount of PEG 400 (X<sub>2</sub>) on responses *in-vitro* disintegration time and mechanical properties. Optimized batch A1 possessed *in-vitro* disintegration time 67.5 s, 17.7 N/mm<sup>2</sup> tensile strength, 50.2 % elongation and 274.2 N/mm<sup>2</sup> elastic modulus.

**Keywords:** Rapidly dissolving films, Cetirizine hydrochloride, Taste masking, Hydroxypropyl-β-cyclodextrin, Factorial design.

### Introduction

Rapidly dissolving dosage forms have acquired significant importance in the pharmaceutical industry due to their unique properties<sup>1,2</sup>. These dosage forms undergo disintegration in the salivary fluids of the oral cavity of the patient within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where absorption takes place in the gastrointestinal tract subsequently<sup>3,4</sup>. These dosage forms possess specific advantages like no requirement of water for disintegration, accurate dosing, faster onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance. These dosage forms were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form<sup>3-5</sup>. The lyophilized wafers, thin strips and films are newer types of rapidly dissolving dosage forms. Rapidly dissolving tablets are available in the market for a variety of drugs however; rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However these dosage forms have now also been introduced in the United States and European pharmaceutical markets for therapeutic benefits<sup>2,5-8</sup>. A film or strip comprises of water soluble and/or water swellable film forming polymer due to which the film or strip dissolves instantaneously when placed on the tongue in the oral cavity. The first oral strips were developed by the pharmaceutical company Pfizer (now taken over by Johnson & Johnson) who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films which contained benzocaine and were used for the treatment of sore throat<sup>8</sup>.

Solvent casting is the most common and traditional method of film casting<sup>2</sup>. Cetirizine hydrochloride (CTZ) is an orally active and selective H<sub>1</sub>-receptor antagonist used in seasonal allergic rhinitis, perennial allergic rhinitis

and chronic urticaria. CTZ is a white, crystalline water soluble drug possessing bitter taste properties<sup>9,10</sup>. Due to sore throat conditions, the patient experiences difficulty in swallowing a tablet type of dosage form. Thus, a RDF would serve as an ideal dosage form for the patients especially paediatric patients who find it difficult to swallow the tablet. Due to its ease of usage and high acceptability, RDF of CTZ were formulated in the present investigation.

Due to bitter taste of CTZ, taste masking was tried using cyclodextrins and its derivatives. Cyclodextrins are cyclic oligosaccharides containing at least 6D-(+) glucopyranose units attached by  $\alpha$ -(1-4) glucosidic bonds. Cyclodextrins with their lipophilic inner cavities and hydrophilic outer surfaces are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes. Cyclodextrins are found to possess taste masking property along with its solubility enhancement property<sup>11,12</sup>. Reduced bitter taste of carbetapentane citrate syrup was obtained by preparing its 1:1 complex with cyclodextrin<sup>13</sup>. Ibuprofen solution was prepared by forming inclusion complex with hydroxypropyl  $\beta$ -cyclodextrin using 1:11 to 1:15 ratio of ibuprofen to hydroxypropyl  $\beta$ -cyclodextrin<sup>14</sup>. Thus, cyclodextrin and its derivatives were selected for taste masking of CTZ.

## Materials

Cetirizine hydrochloride was received as a gift sample from Troikaa Pharmaceuticals Ltd., Ahmedabad, India. HPMC E3 LV was received as a gift sample from Colorcon Asia Pvt Limited, Goa, India.  $\beta$ -cyclodextrin and Hydroxypropyl  $\beta$ -cyclodextrin were received as a gift sample from Roquette Pharma through Signet Chemical Corporation Pvt Ltd, Mumbai, India. Crospovidone and Micro crystalline cellulose were received as gift samples from Signet Chemical Corporation, Mumbai, India. Sodium starch glycolate and Croscarmellose sodium were received as gift samples from Torrent Research Centre, Ahmedabad, India. Polyethylene glycol 400 and Glycerol were purchased from S.D.Fine Chem Ltd., Mumbai, India. All other chemicals used were of analytical grade and were used without further purification. Double distilled water was used for the study.

## Methods

### Preparation of the RDF

The RDF of CTZ using cyclodextrins and their derivative was prepared by solvent casting method<sup>7</sup>. An aqueous solution of the cyclodextrin was prepared in distilled water and CTZ was dissolved in it. This solution was stirred continuously for 4 hr. This was followed by the addition of film former HPMC E3 LV and stirring was continued to obtain homogenous solution. To the deaerated solution plasticizer was added. The solution was casted on a glass petridish (diameter 9 cm) and dried at room temperature for 24 hr. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose ( $2 \times 2 \text{ cm}^2$ ) per strip. The samples were stored in a dessicator at relative humidity 30-35 % until further analysis. Film samples with air bubbles, cuts or imperfections were excluded from the study.

### Drug content

The amount of drug present in the film was evaluated. RDF containing amount equivalent to 10 mg CTZ was dissolved in 900 ml 0.1 N HCl. The content of CTZ was estimated by UV-visible spectrophotometer (UV 2450 Shimadzu, Japan) at 231 nm.

### Thickness evaluation

The thickness of the RDF was evaluated using Dial thickness gage (Mitutoyo, Japan) with range 0-10 mm and resolution 0.01 mm. The RDF sample equivalent to dose of the drug was taken. Anvil of the thickness gage was lifted and the RDF was inserted after making sure that pointer was set to zero. The RDF was held on the anvil and the reading on the dial was noted down. The average of three readings was taken as mean thickness.

### Fourier transfer infra red spectroscopy (FTIR)

The identification of CTZ in RDF was done by Fourier Transfer Infra-Red Spectrophotometer, (Jasco, FTIR model 6100, Japan). The infra red (IR) spectra of the sample CTZ was compared with the IR spectra of the CTZ reference provided in Indian Pharmacopoeia.

### In-vitro disintegration studies<sup>2,6,15-17</sup>

Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. The film as per the dimensions ( $2 \times 2 \text{ cm}^2$ ) required for dose delivery was placed on a stainless steel

wire mesh placed in a petridish containing 10 ml distilled water. Time required for the film to break was noted as *in-vitro* disintegration time.

### **In-vivo disintegration studies**

The *in-vivo* disintegration time was measured in human volunteers (n=6). The RDF was placed on tongue of the volunteers and time required for disintegration in mouth was noted down.

### **In-vitro dissolution studies**<sup>6,16-17</sup>

The *in-vitro* dissolution studies were conducted using three dissolution media namely distilled water (500 ml), 0.1 N HCl (900 ml) and simulated saliva (500 ml). The dissolution studies (n=3) were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at  $37 \pm 0.5$  °C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm<sup>2</sup>) was placed on a stainless steel wire mesh with sieve opening 700 µm. The film sample was placed on the sieve and submerged into dissolution media. Samples were withdrawn at 2, 5, 10, 15 and 30 min time intervals and filtered through 0.45 µm Whatman filter paper and were analyzed spectrophotometrically by UV-visible spectrophotometer (UV 2450 Shimadzu, Japan) at 231 nm. To maintain the volume, an equal volume of fresh dissolution medium, maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment.

### **Environment scanning electron microscopy (ESEM)**

The surface morphology of the film forming excipient HPMC E3 LV, Cetirizine hydrochloride, Hydroxypropyl -cyclodextrin and optimized film was observed using Environment scanning electron microscope (Philips, XL 30, The Netherlands) The film sample was placed in the sample holder and the photomicrographs were taken at 65x and 350x magnification using tungsten filament as an electron source.

### **Differential scanning calorimetry (DSC)**<sup>18,19</sup>

DSC scans were recorded by using Differential scanning calorimeter (Perkin- Elmer, Pyris-I, MA, USA). Samples weighing 5 mg were sealed in aluminium pans and heated to 250°C at rate 10°C/min. The equipment was calibrated using indium. Samples were heated from 50 to 250°C. If required it was cooled to -10°C and then heating was continued to 250°C.

### **X Ray Diffraction (XRD) study**<sup>18,19</sup>

XRD studies of powder samples and film was performed using X Ray Diffractometer (Philips, X'pert MPD, The Netherlands) having sensitivity 0.1 mg with 40 kV voltage, 30 mA current. The sample was placed vertically at an angle of 0° in the sample chamber. An X-Ray beam (Philips Cu target x-ray tube) of 2 KW was allowed to fall over the sample. The slide was moved at an angle of theta degree, a proportional detector detected the diffracted X-Rays at angle of 2-theta degrees. XRD patterns were recorded using Philips JPCD software.

### **Measurement of mechanical properties of the RDF**<sup>20,21</sup>

The RDF were evaluated for the measurement of mechanical properties using universal testing machine (Lloyd, UK model LR 100 K) with load cell 100 N. RDF of dimension 10 x 2.5 cm<sup>2</sup> were held between two clamps at a distance of 5 cm. The dimension of the film selected was 10 x 2.5 cm<sup>2</sup> as it was the minimum sample size required for the sample testing on the machine. The RDF were pulled by the clamp at the rate of 50 mm/min. Measurements of the mechanical properties of the film were done in triplicate for each batch. The mechanical properties like tensile strength, elastic modulus and % elongation were calculated for the RDF as described below.

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture as a mean of three measurements and the cross-sectional area of the fractured film as described in the equation (1)-

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the film (mm}^2\text{)}} \text{-----(1)}$$

Elastic modulus is the ratio of applied stress and corresponding strain in the region of approximately linear proportion of elastic deformation on the load displacement profile and calculated using the following equation (2)-

$$\text{Elastic modulus} = \frac{\text{Force at corresponding strain (N)}}{\text{cross-sectional area of the film}} \times \frac{1}{\text{corresponding strain}} \quad \text{-----(2)}$$

Percentage elongation was calculated by the following equation (3)-

$$= \frac{\text{Increase in length}}{\text{Original length}} \times 100 \quad \text{-----} \quad (3)$$

### Taste evaluation<sup>22</sup>

Taste acceptability was measured by a taste panel consisting of human volunteers (n=6) with 10 mg drug and subsequently film sample containing 10 mg drug held in mouth for 5-10 s, then spat out and the bitterness level was recorded. The volunteers were asked to gargle with distilled water between the drug and sample administration. Following scale was used for the indicating taste masking values:

- + = very bitter,
- ++ = moderate to bitter,
- +++ = slightly bitter,
- ++++ = tasteless/taste masked
- +++++ = excellent taste masking

## Results and Discussion

### Fourier transfer infra red spectroscopy (FTIR)

The FTIR spectra of the pure drug showed significant band at 3427, 2839, 2587, 1741 and 1600  $\text{cm}^{-1}$  which indicates the presence of hydroxyl, ether stretching, tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching respectively. The FTIR spectra of the drug was compared with spectra provided for the reference drug in Indian Pharmacopoeia 2010. The characteristic peaks of drug matched with the reference which confirms the purity of the drug.

The preliminary trials were undertaken for designing the RDF wherein the effects of cyclodextrins and their derivatives were studied as a taste masking agent on RDF containing HPMC E3 LV. The initial trials were taken to check the suitability of types of cyclodextrins for RDF containing HPMC E3 LV.

### Preliminary trial using $\beta$ -cyclodextrin

Various trials were undertaken using different CTZ to  $\beta$ -cyclodextrin molar ratio as 1:1, 1:2 and 1:4. Due to limited solubility of  $\beta$ -cyclodextrin in water (185 mg/10 ml water) the ratio could be varied for 1:1 and 1:2. Batches formulated using the 1:2 molar ratio of CTZ to  $\beta$ -cyclodextrin were partially taste masked. The films formed were brittle in nature, had unacceptably higher *in-vitro* disintegration time. Further trials using 1:4 molar ratio of CTZ to  $\beta$ -cyclodextrin could not be taken due to solubility limitation of  $\beta$ -cyclodextrin. Therefore, further trials were carried out using hydroxypropyl  $\beta$ -cyclodextrin which possesses higher solubility (>50 gm/100 ml). Complete film separation could not take place, further trials were designed to be taken using higher ratio of plasticizer PEG 400: polymer. Batches HPCD1 and HPCD2 containing 600 mg HPMC E3 LV, 160 mg Cetirizine hydrochloride and 961.6 mg Hydroxypropyl  $\beta$ -cyclodextrin along with PEG 400 in ratio 0.2:1 and 0.4:1 could not be separated from petridish. Batches HPCD3 and HPCD4 containing 1200 mg HPMC E3 LV, 160 mg Cetirizine hydrochloride and 961.6 mg Hydroxypropyl  $\beta$ -cyclodextrin along with PEG 400 in ratio 0.2:1 and 0.4:1 were very thick and possessed very high *in-vitro* disintegration time i.e.120 s. Taste masking was not achieved using 1:2 ratio of CTZ: Hydroxy propyl  $\beta$ -cyclodextrin in the above batches. Further trials were to be taken by reducing the amount of HPMC E3 LV in the batches.

## Experimental trials

### Trials using reduced amount of HPMC E3 LV

Trials were taken using reduced amount of HPMC E3 LV i.e. 800 mg along with 160 mg Cetirizine hydrochloride and 961.6 mg Hydroxypropyl  $\beta$ -cyclodextrin along with PEG 400 in ratio 0.2:1 and 0.4:1 in batches HPCD5 and HPCD6. As the film formed in batch HPCD6 had unacceptably high *in-vitro* disintegration time 90 s and were difficult to separate, teflon petridish was tried in next trials using lower amount of HPMC E3 LV. Trials were also taken using higher molar ratio of CTZ to Hydroxypropyl  $\beta$ -cyclodextrin by increasing the ratio from 1:2 to 1:4 to obtain desired taste masking.

It was observed that using 1:4 ratio of CTZ: hydroxypropyl  $\beta$ -cyclodextrin acceptable taste masking of the RDF was produced. Batches HPCD7 to HPCD10 were formulated using 400 mg HPMC E3 LV, 160 mg Cetirizine hydrochloride, 1923 mg Hydroxypropyl  $\beta$ -cyclodextrin and 938.6 mg PEG 400. Different superdisintegrants croscarmellose sodium, sodium starch glycolate, crospovidone and micro crystalline cellulose were added at 10% w/w concentration in batches HPCD7 to HPCD10. *In-vitro* disintegration time for batches HPCD7 to HPCD10 was between 80 s to 95 s. As none of the superdisintegrant was able to reduce the *in-vitro* disintegration time, it was concluded that superdisintegrants did not influence the *in-vitro* disintegration time of RDF containing hydroxypropyl  $\beta$ -cyclodextrin along with HPMC E3 LV. It was also concluded that amount of hydroxypropyl  $\beta$ -cyclodextrin also influenced the *in-vitro* disintegration time. As the *in-vitro* disintegration time was unacceptably higher, amount of hydroxypropyl  $\beta$ -cyclodextrin was varied in the batches to check its influence on *in-vitro* disintegration time.

From the formulation trial batches T1 to T3, it was decided that 400 mg HPMC E3 LV was the minimum quantity required for the film formation as film containing 300 mg HPMC E3 LV was sticky in nature. The films formed above were completely taste masked but had *in-vitro* disintegration time >60 s, addition of superdisintegrant was tried in the next formulation trial.

It was observed from Table 1 that as the amount of Hydroxypropyl  $\beta$ -cyclodextrin was increased from 961.3 mg in batch T4 to 1442 mg in batches T5 to T7, there was increase in *in-vitro* and *in-vivo* disintegration time. Batch T4 did not produce taste masking. Batch T5 was slightly brittle in nature. Batch T6 produced good taste masking effect with acceptable *in-vitro* and *in-vivo* disintegration time but was slightly sticky so complete film could not be removed. Batch T7 and T8 produced film with acceptable properties. CTZ content was estimated as 9.9 mg. Thus, 1:3 ratio of cetirizine hydrochloride: hydroxypropyl  $\beta$ -cyclodextrin produced acceptable taste masking along with acceptable *in-vitro* disintegration time of the rapidly dissolving films.

**Table 1. Effect of amount of Hydroxypropyl  $\beta$ -cyclodextrin on *in-vitro* disintegration time**

Ingredients(mg)/ Batch *	T4	T5	T6	T7	T8
HPMC E3 LV	400	400	400	400	500
Cetirizine HCl	160	160	160	160	180
Hydroxypropyl $\beta$ -cyclodextrin	961.3	1442	1442	1442	1622
PEG 400	608	600	700	800	691
Distilled water(ml)	10	10	10	10	10
Film separation	Yes	Yes, slight brittle	Yes	Yes	Yes
<i>In-vitro</i> Disintegration time (s)	55	70	72	70	68
<i>In-vivo</i> disintegration time (s)	30	40	40	37	38
Taste	+++	+++++	+++++	+++++	+++++

\*Batch size 16 strips, batch T8 18 strips

### Full Factorial design

To study the effect of 2 independent variables i.e. amount of HPMC E3 LV ( $X_1$ ) and amount of plasticizer to polymer ratio( $X_2$ ) on responses *in-vitro* disintegration time, *in-vitro* dissolution time and mechanical properties, a 3<sup>2</sup> full factorial design was developed.

A statistical model incorporating interactive and polynomial terms was used to evaluate the response using the equation (4)-

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2 \quad (4)$$

Where, Y is the dependent variable,  $b_0$  is the arithmetic mean response of the nine runs, and  $b_i$  is the estimated coefficient for the factor  $X_i$ . The main effects ( $X_1$  and  $X_2$ ) represent the average result of changing one factor at a time from its low to high value. The interaction terms ( $X_1X_2$ ) show how the response changes when 2 factors are simultaneously changed. The polynomial terms ( $X_1^2$  and  $X_2^2$ ) are included to investigate nonlinearity. The above equation indicates a coefficient with negative sign which shows there is increase in response when factor level is decreased from higher to lower level and the factor with higher absolute value of coefficient and lower value "p" has major effect on the response variables. A  $3^2$  randomized full factorial design was utilized to study systematically the effect of two independent factors on the characteristics of the film. In this design, two factors are evaluated, each at three levels and experimental trials were carried out at all nine possible combinations. High value of correlation coefficient ( $R^2$ ) indicates good fit. The result of full factorial design is depicted in the form of contour plot which represent relationship between *in-vitro* disintegration time as a function of  $X_1$  and  $X_2$ . The data of all the nine batches of factorial design were used for generating interpolated values using Design Expert software (Version 7.1.6).

The *in-vitro* disintegration time and mechanical properties namely tensile strength, % elongation and elastic modulus for the nine batches (A1 to A9) showed wide variation of 67.5 to 137.5 s, 6.5 to 24 N/mm<sup>2</sup>, 9.5 to 50.2, 75.1 to 408.2N/mm<sup>2</sup> respectively as indicated in Table 2. These data clearly indicates that  $X_1$  and  $X_2$  strongly effect *in-vitro* disintegration time and mechanical properties. The fitted polynomial equations (full model) relating the response to the transformed factors are shown in equation (5), (6), (7) and (8). The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative.

**Table 2. Composition and responses of full factorial batches A1 to A9**

Batch	Amount of HPMC E3 $X_1$	Amount of plasticizer PEG 400 $X_2$	<i>In-vitro</i> disintegration time (s)	Responses Mechanical properties			
				Tensile strength N/mm <sup>2</sup>	% Elongation	Elastic modulus N/mm <sup>2</sup>	
A1	-1	-1	67.5	17.7	50.2	274.2	
A2	-1	0	72.5	8.8	29.9	128.6	
A3	-1	+1	85	6.5	19.6	75.1	
A4	0	-1	70	19.2	29.9	393.7	
A5	0	0	90	17.5	28.1	187.2	
A6	0	+1	90	9.4	9.5	227.3	
A7	+1	-1	120	24.2	25.6	408.2	
A8	+1	0	125	14.3	15.3	323.1	
A9	+1	+1	137.5	15.5	19.3	304.8	
Coded values	Actual values						
	Amount of HPMC E3 LV ( $X_1$ )	Amount of plasticizer ( $X_2$ )					
	-1	500					30%
	0	600					35%
+1	700	40%					

### Statistical analysis of factorial design batches

#### 1) Summary of regression analysis and ANOVA for *in-vitro* disintegration time

The statistical analysis of the factorial batches was performed by multiple linear regression analysis using Microsoft Excel. The results of statistical analysis and ANOVA are shown in Table 3 and 4.

The critical value of F for  $\alpha=0.05$  is equal to 9.01. Since, the F calculated value (0.0068) is smaller than F critical value, it may be concluded that  $X_1$  and  $X_2$  do not contribute significantly to the prediction of *in-vitro*

disintegration time. The coefficients  $b_1(0.0013)$ ,  $b_2 ( 0.0248)$  and  $b_{12} ( 0.0179)$  were found to be significant at  $P < 0.05$ . Equation (4) for *in-vitro* disintegration time obtained using results from Table 3 is indicated as

$$Y = 83.88 + 26.25X_1 + 9.166X_2 - (6.4E-15)X_1X_2 + 17.92X_1^2 - 0.833X_2^2 \text{ -----(5)}$$

From the equation (5), it may be concluded that coefficient of  $X_1$  bears positive sign thus increase in concentration of HPMC E3 LV leads to increase in *in-vitro* disintegration time. The coefficient of  $X_2$ ,  $b_2$  bears positive sign thus increase in PEG 400 concentration leads to increase in *in-vitro* disintegration time. Interaction of  $X_1$  and  $X_2$  did not have significant effect. Interaction term  $X_1^2$  had significant effect on *in-vitro* disintegration time. The result of full factorial design is depicted in the form of contour plot which represents relationship between *in-vitro* disintegration time as a function of  $X_1$  and  $X_2$  as shown in Figure1(a).

**Table 3. Results of regression analysis for *in-vitro* disintegration time**

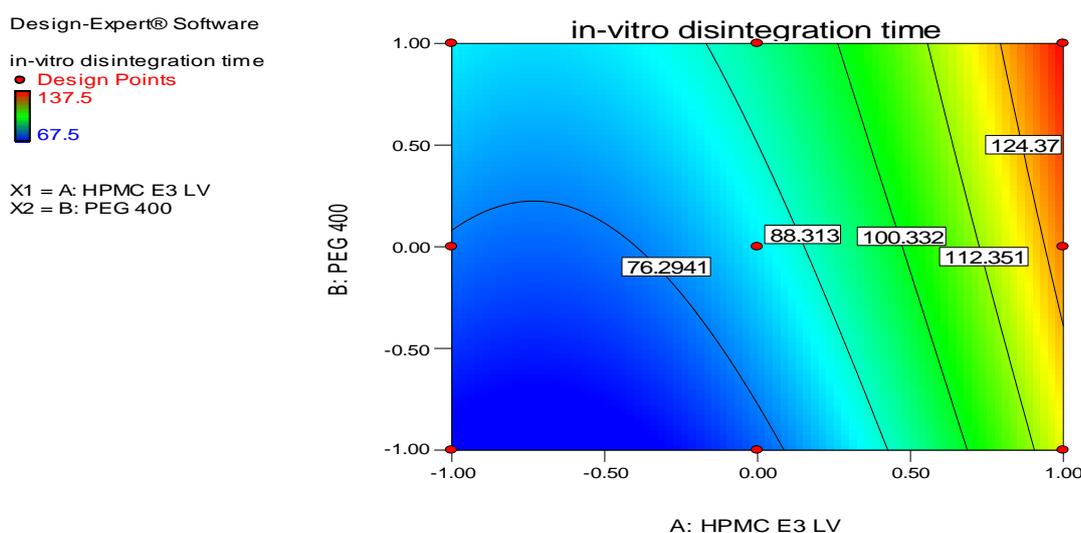
Response							
<i>In-vitro</i> disintegration time(s)							
	$b_0$	$b_1$	$b_2$	$b_{11}$	$b_{22}$	$b_{12}$	$R^2$
Full model (FM)	83.88	26.25	9.16	17.92	-0.833	-6.45E-15	0.984

**Table 4. ANOVA result for *in-vitro* disintegration time**

For <i>in-vitro</i> disintegration time (s)					
	DF	SS	MS	F	
Regression	5	5281.944	1056.389	36.80323	Fcal=0.0068 F critical=9.01 DF=(5,3)
Residual	3	86.11111	28.7037		
Total	8	5368.056			

\*DF indicates degree of freedom,SS, sum of squares; MS, mean of squares; F, Fischer's ratio

**Figure 1(a). Contour plot for *in-vitro* disintegration time**



To validate statistical model, check point batch was prepared where  $X_1 = -0.5$  and  $X_2 = -0.5$ . The results reveal the close match of the predicted (70.44) and observed value (73). Thus, we can conclude that statistical model is mathematically valid.

## 2) Summary of regression analysis and ANOVA for tensile strength study

The statistical analysis of the factorial batches was performed by multiple linear regression analysis using Microsoft Excel. The results of statistical analysis and ANOVA are shown in Table 5 and 6.

The critical value of F for  $\alpha=0.05$  is equal to 9.01. Since, the F calculated value (0.368) is smaller than F critical value, it may be concluded that  $X_1$  and  $X_2$  do not contribute significantly to the prediction of tensile strength. The coefficient  $b_2$  (0.0028) was found to be significant at  $P < 0.05$ . Equation (6) for tensile strength obtained using results from Table 5 is indicated as

$$Y = 14.11 + 3.5X_1 - 4.95X_2 + 0.625X_1X_2 - 0.87X_1^2 + 1.88X_2^2 \text{-----(6)}$$

From the equation (6), it may be concluded that high level of  $X_1$  (amount of HPMC E3 LV) increases tensile strength, level of  $X_2$  (amount of PEG 400) shows more significant effect on tensile strength compared to  $X_1$ . Tensile strength decreases with increase in plasticizer amount Interaction of  $X_1$  and  $X_2$  did not have significant effect.

The coefficient of  $X_1$ ,  $b_1$  bears a positive sign thus increase in HPMC E3 LV concentration leads to increase in tensile strength. The coefficient of  $X_2$ ,  $b_2$  bears a negative sign thus increase in PEG 400 concentration leads to decrease in tensile strength. Interaction of  $X_1$  and  $X_2$  did not have significant effect. The result of full factorial design is depicted in the form of contour plot which represent relationship between tensile strength as a function of  $X_1$  and  $X_2$  as shown in Figure 1(b).

**Table 5. Result of Regression analysis for tensile strength**

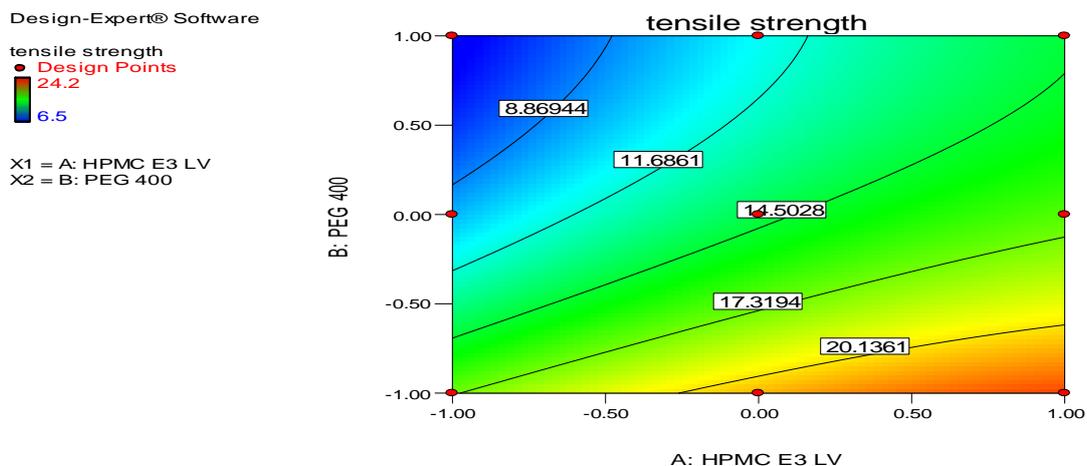
Response								
Tensile strength								
	$b_0$	$b_1$	$b_2$	$b_{11}$	$b_{22}$	$b_{12}$	$R^2$	R
Full model (FM)	14.11	3.5	-4.95	-0.86	1.88	0.625	0.893	0.945

**Table 6. ANOVA result for tensile strength**

Results of ANOVA						
Response	DF	SS	MS	F	$R^2$	F
Tensile strength						
Regression						
Full model	5	230.6736	46.13472	5.026431	0.893	0.107109
Error						
Full model	3	27.53528	9.178426			Fcal=0.368
						F critical=9.01
						DF=(5,3)

\*DF indicates degree of freedom, SS, sum of squares; MS, mean of squares; F, Fischer's ratio

**Figure 1(b). Contour plot for tensile strength**



**3) Summary of regression analysis and ANOVA for % elongation**

The statistical analysis of the factorial batches was performed by multiple linear regression analysis using Microsoft Excel. The results of statistical analysis and ANOVA are shown in Table 7 and 8.

The critical value of F for  $\alpha=0.05$  is equal to 9.01. Since, the F calculated value (-2.31) is smaller than F critical value it may be concluded that  $X_1$  and  $X_2$  do not contribute significantly to the prediction of % elongation. The coefficient  $b_2$  (0.026) was found to be significant at  $P < 0.05$ . Equation (7) for % elongation obtained using results from Table 7 is indicated as

$$Y = 21.66 - 6.58X_1 - 9.55X_2 + 6.075X_1X_2 + 4.15X_1^2 + 1.25X_2^2 \text{-----(7)}$$

From the above equation it may be concluded that the coefficient of  $X_1$ ,  $b_1$  bears a negative sign thus increase in HPMC E3 LV concentration leads to decrease in % elongation. High level of  $X_1$ (amount of HPMC E3 LV) decreases % elongation, the coefficient of  $X_2$ ,  $b_2$  bears a negative sign thus increase in PEG 400 leads to decrease in % elongation level of  $X_2$  (amount of PEG 400).  $X_2$  shows more significant inverse effect on % elongation compared to  $X_1$ . Interaction of  $X_1$  and  $X_2$  have significant effect. The result of full factorial design is depicted in the form of contour plot which represent relationship between % elongation as a function of  $X_1$  and  $X_2$  as shown in Figure 1(c).

**Table 7. Result of regression analysis for % elongation**

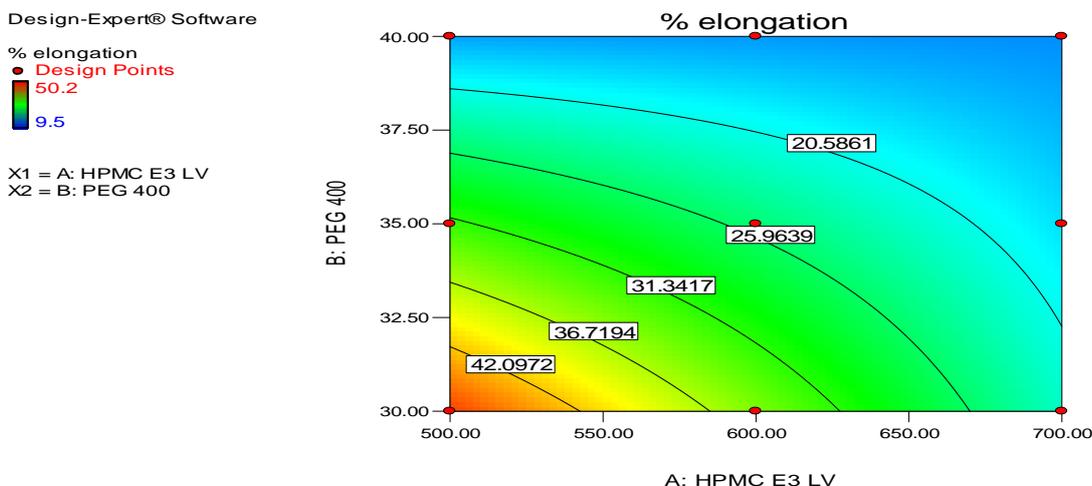
Response								
% elongation								
	$b_0$	$b_1$	$b_2$	$b_{11}$	$b_{22}$	$b_{12}$	$R^2$	R
Full model (FM)	21.66	-6.58	-9.55	4.15	1.25	6.075	0.911	0.955

**Table 8. ANOVA result for % elongation**

Results of ANOVA						
Response	DF	SS	MS	F	$R^2$	F
% elongation						
Regression						
Full model	5	992.4492	198.4898	6.207	0.912	0.081912
Error						
Full model	3	95.93083	31.97694			Fcal=-2.138
						F critical=9.01
						DF=(5,3)

\*DF indicates degree of freedom, SS, sum of squares; MS, mean of squares; F, Fischer's ratio

**Figure 1(c). Contour plot for % elongation**



**4) Summary of regression analysis and ANOVA for elastic modulus**

The statistical analysis of the factorial batches was performed by multiple linear regression analysis using Microsoft Excel. The results of statistical analysis and ANOVA are shown in Table 9 and 10.

The critical value of F for  $\alpha=0.05$  is equal to 9.01. Since, the F calculated value (-3.712) is smaller than F critical value it may be concluded that  $X_1$  and  $X_2$  do not contribute significantly to the prediction of elastic modulus. The coefficient  $b_1$  (0.006),  $b_2$  (0.01) were found to be significant at  $P < 0.05$ . Equation (8) for elastic modulus obtained using results from Table 9 is indicated as

$$Y = 224.3 + 93.03X_1 - 78.15X_2 + 23.93X_1X_2 - 17.07X_1^2 + 67.58X_2^2 \text{-----(8)}$$

From the above equation it may be concluded that the coefficient of  $X_1$ ,  $b_1$  bears a positive sign thus increase in HPMC E3 LV concentration leads to increase in elastic modulus. The coefficient of  $X_2$ ,  $b_2$  bears a negative sign thus increase in PEG 400 concentration leads to decrease in elastic modulus. Interaction of  $X_1$  and  $X_2$  have significant effect.

The result of full factorial design is depicted in the form of contour plot which represent relationship between *in-vitro* disintegration time as a function of  $X_1$  and  $X_2$  as shown in Figure 1(d).

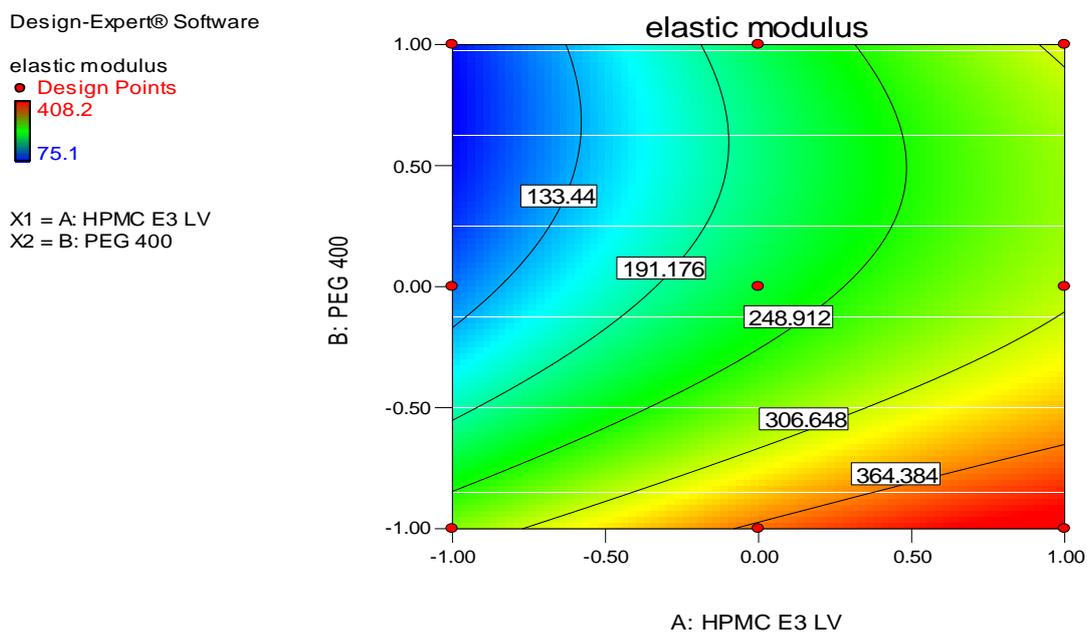
**Table 9. Result of regression analysis for elastic modulus**

Response								
Elastic modulus								
	$b_0$	$b_1$	$b_2$	$b_{11}$	$b_{22}$	$b_{12}$	$R^{21}$	R
Full model (FM)	224.34	93.03	-78.15	-17.07	67.58	23.93	0.968	0.984

**Table 10. ANOVA result for elastic modulus**

Results of ANOVA						
Response	DF	SS	MS	F	$R^2$	F
Elastic modulus						
Regression						
Full model	5	100582.9	20116.58	18.659	0.968	0.01815
Error						
Full model	3	3234.195	1078.065			Fcal=-3.712
						F critical=9.01
						DF=(5,3)

\*DF indicates degree of freedom,SS, sum of squares; MS, mean of squares; F, Fischer's ratio

**Figure 1(d). Contour plot for elastic modulus**

To validate statistical model, check point batch was prepared where  $X_1 = -0.5$  and  $X_2 = -0.5$ . The results are revealed in Table 11.

**Table 11. Predicted and observed values of check point batches on mechanical properties.**

Mechanical properties	Predicted value	Observed value
Tensile strength (N/mm <sup>2</sup> )	15.24	18
% elongation	32.59	34
Elastic modulus (N/mm <sup>2</sup> )	235.32	241

The close match of the predicted and observed values of mechanical properties indicate that statistical model is mathematically valid.

### Selection of best batch

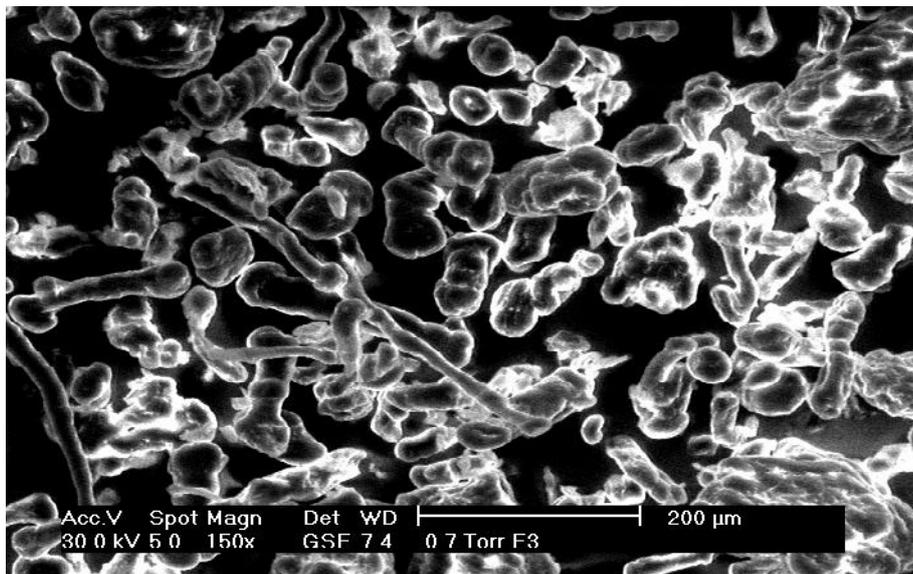
**Table 2 indicates batch A1** possesses least *in-vitro* disintegration time 67.5 s. It also possess toughness characterized by 17.7 N/mm<sup>2</sup> tensile strength, high % elongation 50.2 indicating ductile nature and moderate elastic modulus 274.2 N/mm<sup>2</sup> which indicates stiff nature of polymers. Thus, batch A1 was considered as optimized batch. *In-vivo* disintegration time of batch A1 was 38 s indicating comparatively faster disintegration in mouth. *In-vitro* dissolution study indicates 72% drug released in 2 min using 0.1 HCl as dissolution medium.

### Drug content

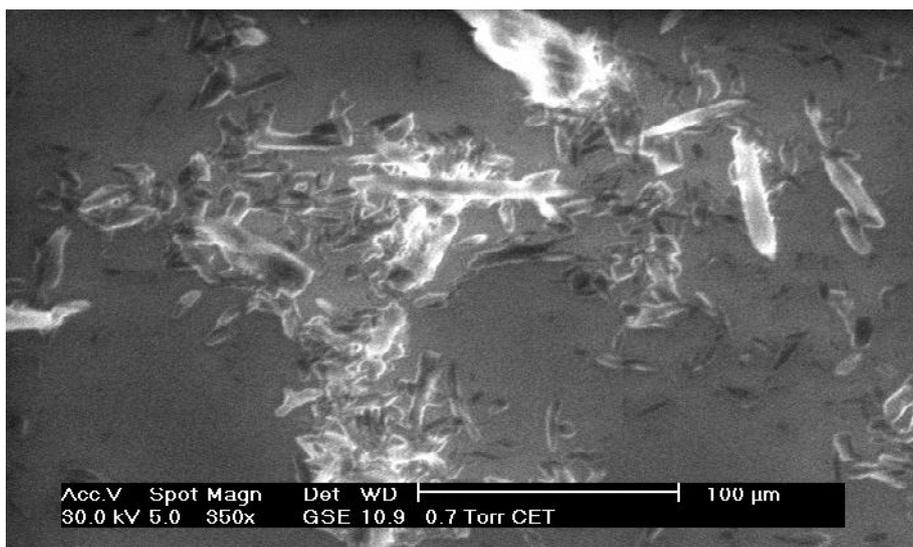
The drug content of batch A1 was found to be 9.9 mg. It can be concluded that drug was uniformly distributed in the film.

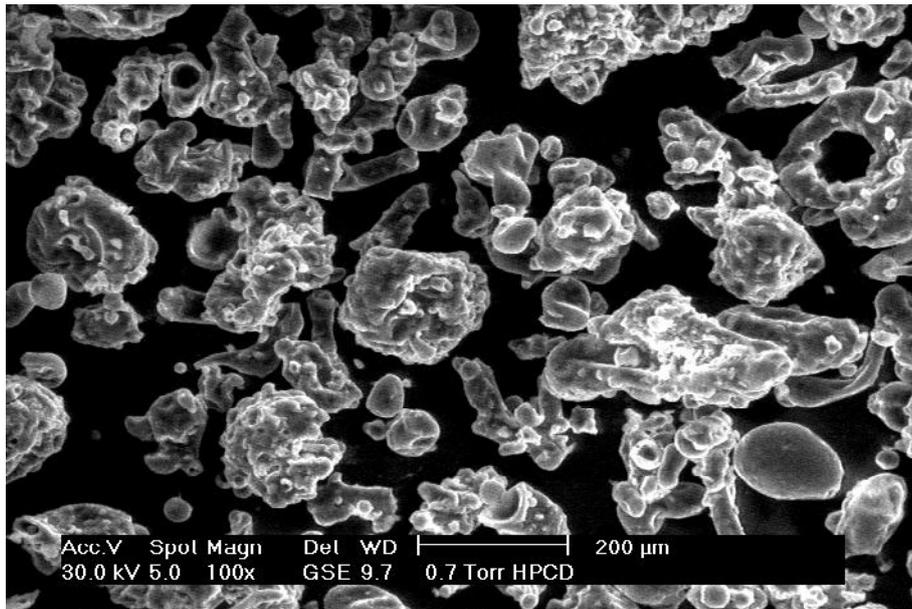
**Environment scanning electron microscopy(ESEM)**

**Figure 2(a). ESEM of HPMC E3 LV at 150x magnification**



**Figure 2(b). ESEM of Cetirizine hydrochloride at 350x magnification**



**Figure 2(c). ESEM of Hydroxy propyl -cyclodextrin at 100x magnification****Figure 2(d). ESEM of batch A1 at 100x magnification**

The ESEM of HPMC E3 LV at 150x magnification as shown in Figure 2(a) indicated the presence of long cylindrical fibres of HPMC E3 LV. Cetirizine hydrochloride particles could not be seen distinct as such. On dispersing it in acetone cylindrical distinct particles could be observed at 350x magnification as shown in Figure 2(b). The ESEM of Hydroxy propyl beta cyclodextrins shown in Figure 2(c) indicated irregular round shaped particles at 100x magnification. The optimized film A1 at 100x magnification shown in Figure 2(d) indicated uniform film with few pores and striations.

## DSC study

**Figure 3. DSC study of various samples**

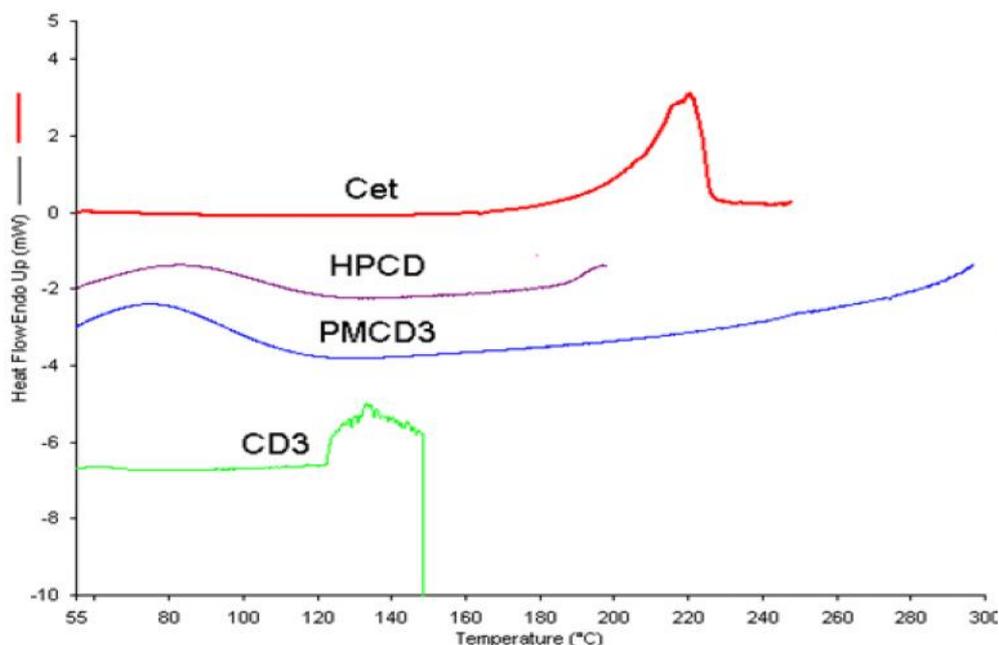
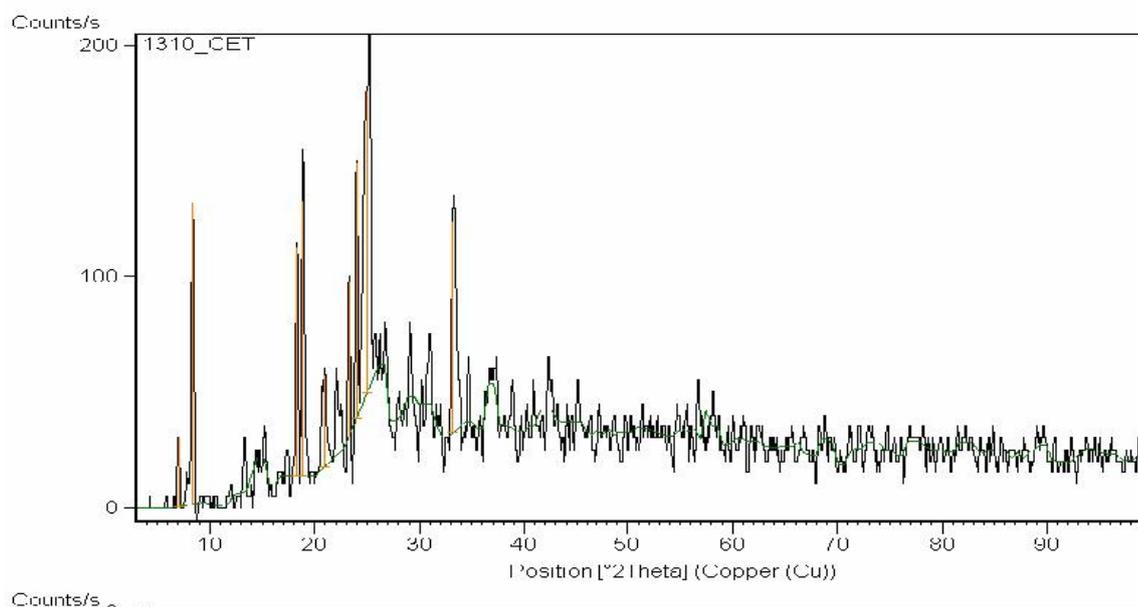


Figure 3 shows DSC scan of cetirizine hydrochloride (Cet) indicated sharp endothermic peak indicating melting at 220.4°C. DSC scan of Hydroxypropyl -cyclodextrin (HPCD) indicated endothermic peak at 77.5°C. The DSC scan of physical mixture (PMCD3) indicated endothermic peak at 83.7°C followed by further decomposition. The endothermic peak corresponding to cetirizine hydrochloride was absent in PMCD3 and CD3. Batch A1 indicated as CD3 was prepared by inclusion complexation showed peak at 61.1°C which indicates inherent change of appearance of amorphous state in the compound which is followed by further decomposition in the DSC scan.

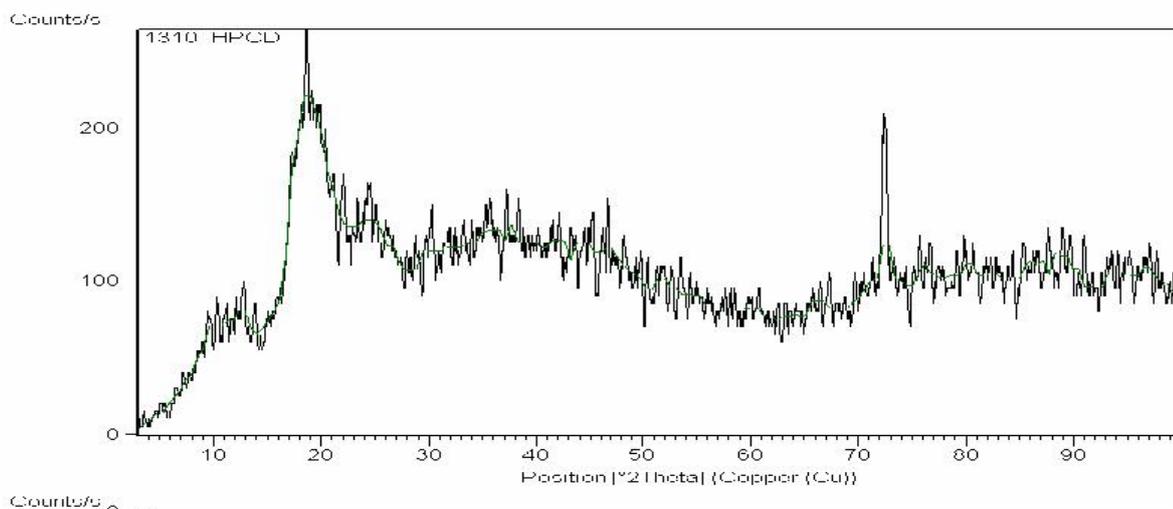
## X ray diffraction (XRD)

XRD study was performed to confirm the results of DSC studies. X ray diffraction (XRD) is a useful method for determination of complexation in powder or microcrystalline state.

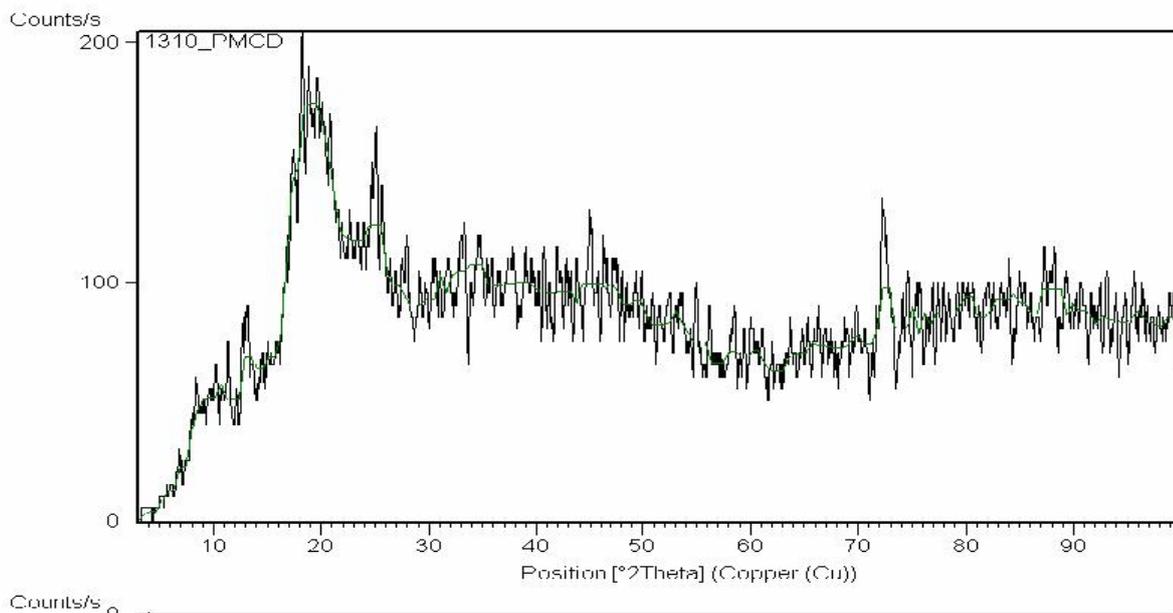
**Figure 4(a). XRD of Cetirizine hydrochloride**

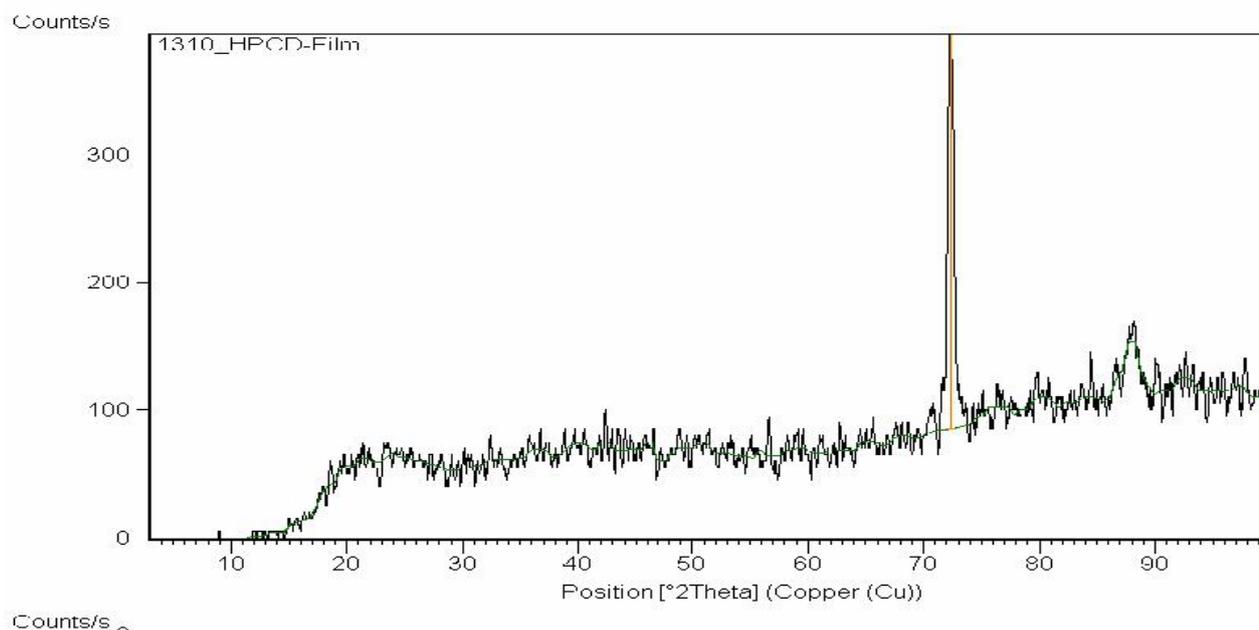


**Figure 4(b). XRD of Hydroxy propyl -cyclodextrin**



**Figure 4(c). XRD of physical mixture**



**Figure 4(d). XRD of batch A1**

XRD of Cetirizine hydrochloride (CTZ) in Figure 4(a) showed sharp peaks at  $8.3^\circ$ ,  $18.29^\circ$ ,  $18.79^\circ$ ,  $23.97^\circ$ ,  $25^\circ$  and  $33.16^\circ$   $2\theta$  positions with height 130.59, 99.15, 119.24, 130.9 and 91.93 cps indicating crystalline nature of the drug. XRD scan of Hydroxypropyl  $\beta$ -cyclodextrin (HPCD) as shown in Figure 4(b) did not show crystalline nature with peak at  $18.72^\circ$   $2\theta$  positions with height 250 and 200 cps. Figure 4(c) indicates the physical mixture (PMCD) with significant decrease in intensity of peaks of cetirizine hydrochloride indicating transformation to amorphous state. Batch A1 film shown in Figure 4(d) as HPCD film indicated complete absence of sharp peaks of cetirizine hydrochloride which indicated transformation to amorphous state of cetirizine hydrochloride and inclusion complex formation which is responsible for taste masking of cetirizine hydrochloride. The XRD patterns of CET, HPCD and PMCD, HPCD-Film showed a total 9, 1, 5, and 1 peaks respectively. The XRD of batch A1 exhibits only 1 peak. This suggests that crystallinity of cetirizine hydrochloride is reduced in the film. Decrease in crystallinity of the cetirizine hydrochloride may contribute to taste masking of cetirizine hydrochloride.

### Stability study

The stability study of batch A1 was carried out at  $25^\circ\text{C}/40\%\text{RH}$  using HDPE container in a sealed zip lock bag. The samples were found to be stable for 3 months.

The *in-vitro* disintegration time for 3 months old sample was 68 s, *in-vivo* disintegration time 38 and 70% *in-vitro* dissolution in 2 min compared to initial time where the *in-vitro* disintegration time for 3 months old sample was 68 s, *in-vivo* disintegration time 38 and 72% *in-vitro* dissolution in 2 min. Drug content did not vary significantly from 9.9 mg for initial batch to 9.8 mg for the 3 month old stability batch.

### Conclusion

Rapidly dissolving films were prepared using HPMC E3 LV as a film forming polymer. Taste masking of Cetirizine hydrochloride was done using Hydroxypropyl  $\beta$ -cyclodextrin as a taste masking agent. It was found out that at optimized ratio of 1:3 of Cetirizine hydrochloride to Hydroxypropyl  $\beta$ -cyclodextrin desired taste masking could be obtained. As amount of HPMC E3 LV and plasticizer PEG 400 had critical role in film properties, a  $3^2$  full factorial design was applied in the study. Excellent taste masking was achieved using cyclodextrins as complexing agent. The *in-vitro* disintegration time was slightly higher on storage and the films were found to be stable for 3 months.

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