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Formulation, Optimization and Evaluation of Orally Disintegrating Tablet of Non-Steroidal Anti-inflammatory Drug

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ABSTRACT

Piroxicam is a non steroidal anti-inflammatory drug with analgesic properties. The purpose of this study was to develop a taste masked orally disintegrating tablet of poorly soluble Piroxicam by direct compression technique with β-cyclodextrin (ß-CD) complexes using various superdisintegrants like sodium starch glycolate, crospovidone XL and croscarmellose sodium. Complex was characterized using infrared spectroscopy, differential scanning calorimetry, % drug release study, gustatory evaluation for taste masking. A 3^2 full factorial design was applied to systematically optimize the drug disintegration time. The concentration of Crospovidone (X1) and concentration of Croscarmellose (X2) were selected as independent variables. The Disintegration time (Y1) and Wetting time (Y2) were selected as dependent variables. The prepared tablets were evaluated for hardness, friability, disintegration time, wetting time and *In-vitro* drug release. FT-IR studies and physical compatibility study were conducted for drug, and drug excipient mixture for interactions if any. The different formulations showed disintegration time between 12 to 58 sec. The results indicated that concentration of Crospovidone (X1) and concentration of Croscarmellose (X2) significantly affected the Disintegration time (Y1) and Wetting time (Y2). Regression analysis and numerical optimization were performed to identify the best formulation. Formulation F10 prepared with croscarmellose (4.23%) & crospovidone (6.74%) was found to be the best formulation with disintegration time 16 sec, wetting time 21 sec and % drug release in 10 min 94.23%.

KEYWORDS

Piroxicam, Orally disintegrating tablet, ß-cyclodextrin, Crospovidone, Croscarmellose, Disintegration time, Wetting time.

INTRODUCTION

Recent developments in the technology have prompted scientists to develop orally disintegrating tablets with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules because pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. They are also suitable for bed-ridden, psychotics, developmentally disabled and the patients with persistent nausea during travelling or who have little access to water.[1,2] Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.[3] Moreover, drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability.[4,5] It provides good stability,

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accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.[6]

Piroxicam is a non-steroidal anti-inflammatory drugs (NSAIDs) act by blocking cyclo-oxygenase enzyme, a key enzyme of prostaglandin biosynthesis at the site of inflammation. Piroxicam was used to reduce the pain, inflammation, and stiffness caused by rheumatoid arthritis and osteoarthritis.[7] Its bioavailability is between 45- 75% after oral administration and half-life of about 40-50 hrs.[8] The usual daily dose is 20 mg. So in case of pain, osteoarthritis, gout it required immediate release of drug from the dosage form, which make piroxicam suitable candidate for the orally disintegrating tablets.

The Piroxicam has bad taste and solubility in water is low. Molecular complexation of Piroxicam with β -cyclodextrin improved drug solubility, and therefore it could be expected to hasten piroxicam absorption, resulting in a faster onset of action.

Full factorial experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Multiple regression analysis of results gives an equation that adequately describes the influence of the independent formulation variables on the selected responses.

MATERIALS AND METHODS

Piroxicam was gifted from Sifavittor Pvt Ltd, Italy. Mannitol SD 200, Microcrystalline cellulose pH 112 and sodium starch glycolate was purchased from Roquette Pharma Ltd, USA. Croscarmellose sodium was gifted from the FMC biopolymer, Philadelphia, USA. Crospovidone XL was gifted from the ISP petrochemicals. Betacyclodextrin was gifted from Signet Chemicals Pvt Ltd, Mumbai. Aspartame Fine grade was gifted from Nutra sweet, India. Sodium stearyl fumarate was gifted from Dr. Paul Lohman Pvt Ltd, USA. Aerosil was gifted from Xian Shunyichem Technology Co., Ltd, China and mango flavor was gifted from Symrise Pvt Ltd.

DRUG – EXCIPIENTS COMPATIBILITY STUDY

Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

Preparation of complex of Piroxicam with β-cyclodextrin by Kneading method

Amounts of the piroxicam and β-CD to give 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5 and 1:3 molar ratios were weighed and thoroughly mixed then triturated by addition of few drops of in mortar and pestle. The slurries were kneaded for 180 min, and dried at room temperature for 24 h. The dried complex was sieved through 80# and stored in airtight container.

Dissolution Studies of Piroicam-β-CD complex [9]

Dissolution experiments were performed in triplicate with an Electrolab dissolution tester in 900 ml of phosphate buffer pH 6.8 at 37±0.5 °C using the paddle at a rotation speed of 50 rpm. Powdered samples of each preparation equivalent to 20 mg of piroxicam were added to the dissolution medium. At appropriate time intervals, 10 ml aliquots were withdrawn and filtered through 0.45 µ filter. Fresh media (10 ml), which was pre-warmed at 37 °C, was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. The removed samples were assayed for piroxicam content at 354 nm.

Gustatory evaluation of Piroxicam-β-CD complex [10]

A voluntarily signed informed consent form was obtained from each subject before carrying out the test (n=9). Each individual was given weighed equivalent to 20 mg of piroxicam-β-CD the complex. Before testing, the volunteers were asked to retain the reference solutions in their mouths for 10 s, and the taste perceived by each volunteer was noted.

Fourier transform infrared (FTIR) spectroscopic analysis

The Fourier transform infrared spectrum of moisture free powdered sample of piroxicam, β-CD and kneaded complex recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The scanning range was 400 to 4000 cm^{-1}.

Differential scanning calorimetry (DSC) analysis:

DSC scans of the powdered samples were recorded using DSC-Shimadzu 60 with a TDA trend line software. The thermal traces were obtained by heating the complex from 40 to 350 °C at heating rate of 10 °C under inert nitrogen dynamic atmosphere (100 ml/min) in open aluminum crucibles.

3^2 full factorial design

A 3^2 full factorial design was used in order to investigate the joint influence of 2 formulation variables. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations.[11] The amounts of crospovidone (X1), and amount of croscarmellose (X2), were selected as independent variables. The disintegration time and wetting time were selected as dependent variables. Checkpoint batch was also prepared to prove the validity of the evolved mathematical model. In addition, contour plots were used to graphically represent the effect of the independent variables.

Preparation of Orally disintegrating tablets

Orally disintegrating tablets were prepared using direct compression method according to formula given in table 2. All the ingredients (without SSF and aerosil) were passed through #40 mesh separately. Required quantity of each excipient was weighed accurately and blend was mixed thourouly. Lubricants i.e. aerosil and sodium stearyl fumarate were passed through 80# and mixed them to above blend. Powder blend was compressed using 12/32 (9.53 mm) concave punch on 8 stations "D" tooling rotary tablet machine. Then the compressed tablets were evaluated for tablet evaluation tests such as weight variation, hardness, friability, thickness, disintegration time, wetting time, % drug content and *In-vitro* dissolution study.

Evaluation parameters of powder blends

Orally disintegrating tablets are manufactured by several processes but for all of them, first a blend of various ingredients (APIs and excipients) is made. The quality of tablet, formulated is generally depending upon the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested are as given below.

Bulk density

Apparent bulk density was determined by pouring 10 gm of powder blend into graduated cylinder and measuring the volume.

Bulk density =Weight of the powder / Volume of the packing

Tapped Density [12]

Weighed quantity of powder blend was taken into a graduated cylinder and volume occupied by powder blend was noted down. Then cylinder was subjected to 500, 750 and 1250 taps in tap density tester

According to USP the blend was subjected to 500 taps. The %volume variation was calculated and subjected for additional 750 taps and %volume variation is calculated.

Tapped density= Weight of the powder / volume of the tapped packing

Carr's compressibility index

The compressibility index of the blends will be determined by Carr's compressibility index.

$$\text{Carr's compressibility index (\%)} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Table: 1 3^2 Full Factorial Design Layout*

BATCHES	TRANSFORMED VALUES		DISINTEGRATION TIME(sec) ± SD	WETTING TIME(sec) ± SD
	X1	X2		
F1	-1	-1	46± 1	51± 2
F2	-1	0	41± 1	46± 1
F3	-1	1	34± 1	39± 1
F4	0	-1	29± 2	34± 3
F5	0	0	24± 1	30± 1
F6	0	1	21± 1	26± 2
F7	1	-1	17± 1	22± 3
F8	1	0	15± 2	19± 2
F9	1	1	12± 2	17± 2

Levels	Coded values	Actual values	
		X1	X2
Low	-1	0	1
Intermediate	0	4	3
High	+1	8	5

*X1 indicates amount of crospovidone (%); X2, amount of croscarmellose (%)

Table: 2 Formulations using 3^2 Factorial Design

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Piroxicam-ß-CD complex	191.45	191.45	191.45	191.45	191.45	191.45	191.45	191.45	191.45
Crospovidone XL	-	-	-	12	12	12	24	24	24
Croscarmellose sodium	3	9	15	3	9	15	3	9	15
Microcrystalline cellulose pH 112	45	45	45	45	45	45	45	45	45
Mannitol SD 200	50.55	44.55	38.55	38.55	32.55	26.55	26.55	20.55	14.55
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mango flavor	1	1	1	1	1	1	1	1	1
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
sodium steryl fumarate	6	6	6	6	6	6	6	6	6
Total wt (mg)	300	300	300	300	300	300	300	300	300

Hausner's ratio

Hausner's ratio is an index of ease of powder flow. It is calculated by following formula.

Hausner's ratio = Tapped density / Bulk density

Table: 1 3^2 Full Factorial Design Layout*

Angle of repose

Angle of repose (θ) is a measure of flowability of material. It was determined using fixed height funnel method. A glass funnel was placed with its tip positioned at a fixed height (h) above a graph paper on a horizontal surface. The blend was poured through a funnel until the apex of conical pile touched the tip of the funnel. The radius of the pile (r) was measured and angle of repose was calculated as follows.

$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose

h = height of the pile

r = average radius of the powder cone

Evaluation parameters of ODT

Hardness

Hardness was measured using the Monsanto hardness tester. Measure the pressure required to break diametrically placed matrix tablet, by a coiled spring.

Thickness

The thickness of the tablets was determined using a vernier caliper.

Weight variation[13]

It was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Friability[12]

Friability of Tablets was performed in a Roche Friabilator. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weigh them accurately. A maximum loss of weight not greater than 1.0 per cent is acceptable for most tablets.

$$\text{Friability} = [(W1-W2)100]/W1$$

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

Disintegration test[12]

The USP device to test disintegration has six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 °C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. The time required to obtain complete disintegration of all the tablets will be noted.

Wetting time

A small piece of tissue paper folded twice will be placed in a small petridish containing 6ml of water. A tablet will be put on the paper and the time required for complete wetting was measured.

% Drug content[14]

Three tablets were accurately weighed and finely powdered. A quantity equivalent to 20 mg of piroxicam was transferred to a 100 ml volumetric flask. To it, 50 ml of methanol was added and shaken for 1 hour to dissolve drug. The solution was filtered and residue was washed with 25 ml of methanol. The washing obtained was added to initial filtrate and volume was made up to 100 ml with methanol. From above solution 1 ml of stock solution was

diluted to 100 ml of phosphate buffer pH 6.8. The drug content was determined spectrophotometrically at 354nm.

Dissolution Studies[15,16]

Dissolution studies were carried out for all the formulation combinations in triplicate, employing USP XXIII paddle method (Apparatus 2) using phosphate buffer pH 6.8, as the dissolution medium (900 ml) at 50 rpm and 37 ± 0.5ºC. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plane dissolution medium. The samples were analyzed spectrophotometrically at 354 nm.

Data analysis[17]

Response surface model factorial design with 2 independent formulation variables at 3 different levels were used to study the effects on dependent variables. All batches of ODT were statically (confidence level 95 % or $P < 0.05$) evaluated with regard to disintegrating time and wetting time using multiple regression analysis in MS-Excel. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

Optimization of formulation ingredients[17]

From overlay plot of responses, optimized formulation was selected as check point to validate RSM. Optimization was performed to obtain value of X1 and X2, which targeted disintegration time (DT) <20 sec; wetting time <25 sec. The tablets were formulated using the chosen optimal composition and evaluated for disintegration time and wetting time. The observed and predicted responses were critically compared.

Comparison of Optimized formulation with market product using similarity factor (f_2) [18]

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profiles of products were compared using f_2. This similarity factor is calculated by following formula,

$$f_2 = 50 \times \log \{[1+(1/n) \sum_{j=1}^{n} | R_j - T_j |^2]^{-0.5} \times 100\}$$

Where,

n = number of time points

R_j = Dissolution value of the reference batch at time t

T_j = Dissolution value of the test batch at time t

Table: 3 Composition of Optimized Formulation

FORMULATION INGREDIENTS	F10
Piroxicam-β-CD complex	191.45
MCC PH 112	45
Crospovidone XL	**20.22**
Croscarmallose sodium	**12.69**
Aspartame	1.5
Mango powder	1
Aerosil	1.5
SSF	6
Mannitol up to….	300

Stability studies[18]

Stability studies on the optimized formulation was carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH for time period of 4 weeks (nearly a month). Samples were withdrawn at the end of every week and evaluated for Disintegration time, % Drug content, %Drug release.

RESULT AND DISCUSSION

Drug excipient Compatibility study

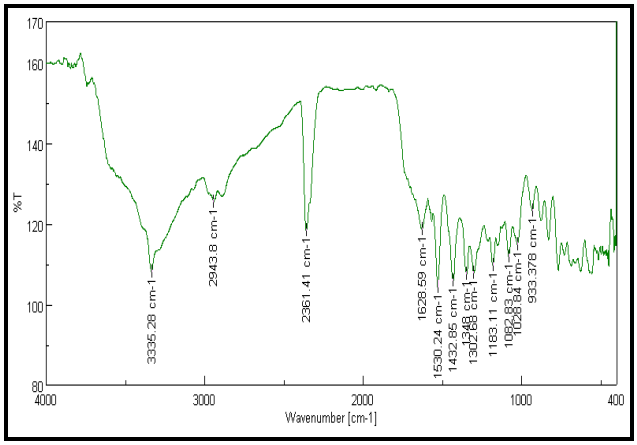

Figure: 1 FTIR Spectra of Mixture

To study the compatibility of drug with excipients IR spectra of drug in combination with excipients in 1:1 ratio was studied prior to preparation of Piroxicam orally disintegrating tablets. FTIR spectrum of Piroxicam was described in FTIR of Piroxicam- β-cyclodextrin Complex. The IR spectrums of piroxicam and its combination with crospovidone, croscarmellose, etc. were shown in Figures 3 and 1 indicate that there was no physicochemical interaction in between drug and studied excipients because all characteristics bands due to main function groups of Piroxicam were presented in physical mixture.

Dissolution Studies of Piroxicam-β-CD complex

Based on % drug release from different molar ratios of complex piroxicam: β- cyclodextrin, 1:2.5 molar ratio was selected as optimized ratio as it was shown 99.87 % drug release in 50 min as compared to 1:2 molar ratio that was shown 91.24% release at the end of 60 min. 1:3 molar ratio was not shown significant increase in %drug release when shift from ratio 1:2.5M to 1:3M. So, 1:2.5 molar ratio was optimized.

The increase in the dissolution of piroxicam with β-CD could be explained by the principal of hydrophilicity, inclusion complex formation and the amorphous form generation of piroxicam. The high solubility of β-CD in water resulted in better wettability of drug particles and local enhancement of its solubility at the diffusion layer surrounding the drug particles.

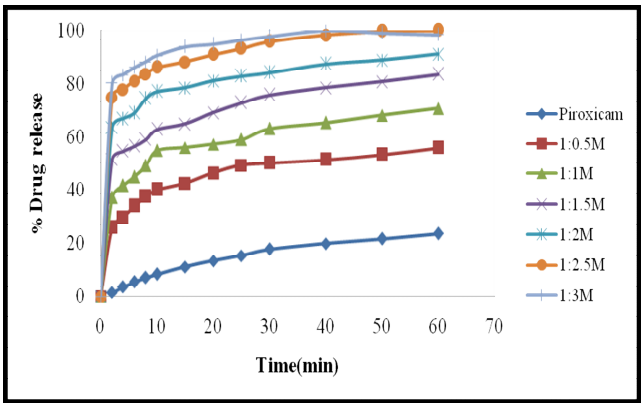

Figure: 2 Comparative Dissolution Profiles of Various Molar Ratios of Piroxicam-β-CD complex

Gustatory evaluation of Piroxicam-β-CD complex:

Here in this study complexation of Piroxicam with β-CD was carried out in order to mask the bitter and after taste of Piroxicam. So, gustatory evaluation was carried out to determine that whether it masked taste or not.

Table: 4 Bitterness Evaluation of Different Molar Ratio of Piroxicam-ß-CD Complex by Panelist of 9 Volunteers

Volu-nteer	Observation of taste					
	1:0.5	1:1	1:1.5	1:2 M	1:2.5 M	1:3 M
1	****	****	***	**	*	*
2	****	****	****	***	**	*
3	****	****	***	**	*	*
4	****	***	**	*	*	*
5	****	****	***	***	*	**
6	****	****	***	***	*	*
7	***	***	***	**	*	*
8	****	****	**	*	*	*
9	****	****	***	**	*	*

Bitter[****], **Moderately bitter**[***], **Slightly bitter**[**], **Tasteless/Good**[*]

Eight of nine volunteers sense bitter taste in 1:0.5 ratio of Piroxicam ß-CD complex. In case of 1:1 molar ratio, seven volunteers sense bitter taste while two sense moderately bitter taste. Further evaluation of bitterness in case of 1:1.5, six volunteers sence the moderately bitter taste while two sense slightly bitter. With 1:2 molar ratio four volunteers feel slightly bitter taste while two volunteers sense good taste. In case of 1:2.5 molar ratio eight of nine volunteers sense good taste or they told the sweet taste of betacyclodextrin was gave good mouth feel. Similar observations were found in case of 1:3 molar ratio. So, 1:2.5 ratio was optimized based on result of bitterness evaluation. The result shows that there was decreased in bitterness of drug as molar ratio increase from 1:0.5 to 1:3. This was due to decrease in free drug content and increase in amount of inclusion complex with drug.

Fourier transform infrared (FTIR) spectroscopic analysis

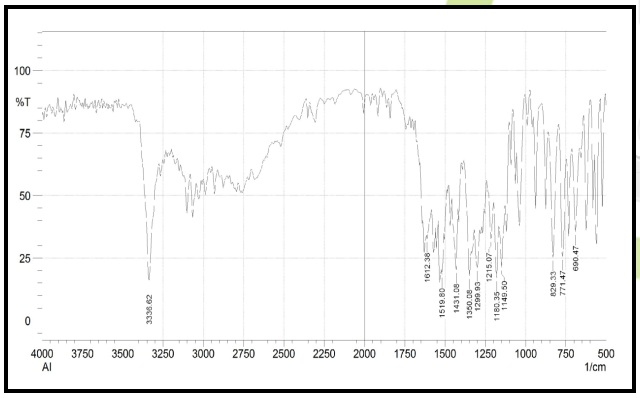

Figure: 3 FTIR Spectra of Piroxicam

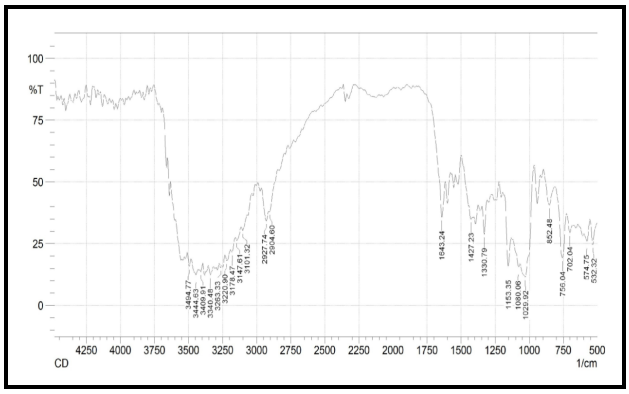

Figure: 4 FTIR Spectra of Piroxicam-β-Cyclodextrin Complex

FTIR spectrum of Piroxicam was showing strong band at 3336.62 cm^{-1}, which indicates that the drug is in the cubic polymorphic form.

Other characteristic bands are attributed to the stretching of different group vibrations are 1612.38 cm^{-1} stretching of amide carbonyl, 1519.80cm^{-1} stretching of the second amide band, 1431.80 cm^{-1} stretching of asymmetric methyl group, 1350.08 cm^{-1} stretching of symmetric methyl group, 1149.50 cm^{-1} stretching of –SO2-N- group and 771.47 cm^{-1} as stretching of ortho-disubstitued phenyl.

In the FTIR spectra of prepared complexes, Piroxicam band at 3336.62 cm^{-1} are almost completely obscured by very intense and broad β-CD bands. Absorption bands of Piroxicam at 1612.38 and 1519.80 cm^{-1} experience a dramatic broadening in the spectra of the prepared complexes, and the peaks are shifted toward lower frequencies. This change is probably related to the formation of intramolecular hydrogen bonds between the guest and host molecules. It seems that when the carbonyl group is joined to a hydroxylic group by hydrogen bonds, the stretching band is shifted to lower frequency due to the weakening of the carbonyl double bond.

Differential scanning calorimetry (DSC) analysis

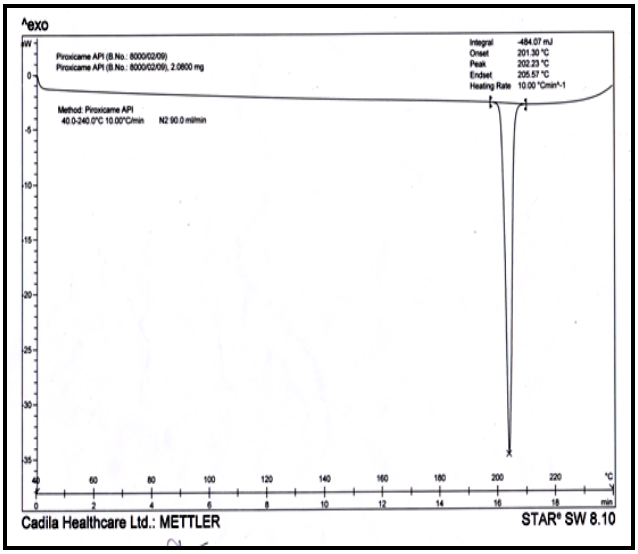

Figure: 5 DSC Thermogram of Piroxicam

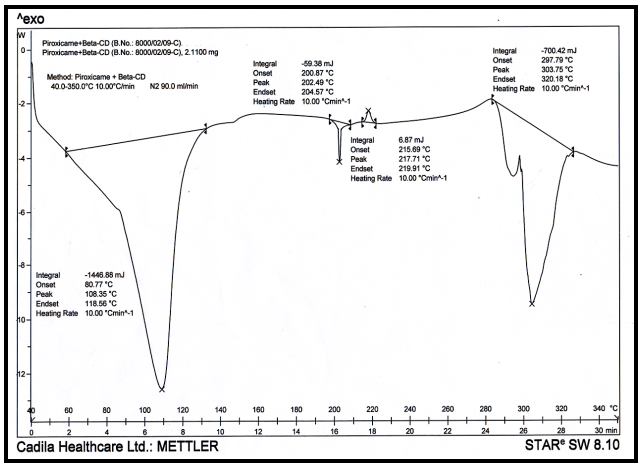

Figure: 6 DSC Thermogram of Piroxicam- β-cyclodextrin Complex

Piroxicam exhibits a characteristic endothermic fusion peak at 201.30 °C, corresponding to the Piroxicam melting point and indicating that the drug is in a cubic crystal polymorphic form. Furthermore, ß-CD show broad endothermic events in the range from 60 to 130 °C, which are related to evaporation of water from the cyclodextrin, and small endo or exo effects at 297–320 °C due to thermal degradation.

DSC curve of Piroxicam- β-CD complex shows three peaks: a broad endotherm between 60 and 130 °C, corresponding to evaporation of water from the cyclodextrin, followed by endothermal melting peak at 202.49 °C typical of crystalline piroxicam. The integration of this peak gives the melting the crystalline piroxicam present in the sample, and by comparison with the melting enthalpy of the pure drug, the free piroxicam content was found out. There was decrease in intensity of peak of piroxicam and also broadening of β-CD peak gave conformation of complex formation between piroxicam and β-CD.

Evaluation parameters of powder blends

The powder blend for all nine formulations were evaluated for bulk density which ranged from 0.491 to 0.526, tapped density which ranged from 0.472 to 0.624, Carr's index ranged from 10.03 to 16.94, Hausner's ratio ranged from 1.11 to 1.21 and angle of repose ranged from 26.88 to 29.18 °. All these results indicate that, the power blend possess good flowability and compressibility properties. Hence, tablets were prepared using direct compression method.

Table: 5 Pre-Compression Evaluation Parameters of Powder Blend of Factorial Batches

Batch Code	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Angle of repose(°)	Hausner's ratio
F1	0.51±0.01	0.59±0.03	27.81±0.01	13.55±0.03	1.15±0.02
F2	0.52±0.04	0.61±0.01	28.33±0.04	14.75±0.01	1.17±0.01
F3	0.41±0.02	0.47±0.02	27.74±0.02	12.39±0.03	1.14±0.02
F4	0.52±0.01	0.58±0.01	26.88±0.03	10.03±0.03	1.11±0.02
F5	0.49±0.03	0.59±0.02	29.05±0.04	16.94±0.02	1.20±0.01
F6	0.52±0.01	0.61±0.01	28.38±0.01	14.75±0.01	1.17±0.02
F7	0.51±0.01	0.62±0.04	29.10±0.02	14.54±0.01	1.21±0.02
F8	0.50±0.02	0.59±0.02	29.18±0.03	15.24±0.02	1.18±0.03
F9	0.51±0.03	0.60±0.03	28.85±0.04	15.24±0.03	1.17±0.02

All values are expressed as mean ± standard deviation, n=3

Evaluation parameters of ODT

Table: 6 Evaluation Parameters of Tablets of Factorial Batches

Batch Code	Weight Variation (mg) ±SD, n=20	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec)	Wetting time (sec)	Drug content (%)± SD	Q10 (%Drug release in 10 min)
F1	302.52±2.16	4.2 ± 0.23	4.95± 0.02	0.48±0.02	46± 1	51± 2	99.48±1.23	66.18±0.76
F2	301.21±1.54	4.5 ± 0.52	4.93 ±0.03	0.42±0.01	41± 1	46± 1	99.21±1.12	70.65±1.24
F3	300.45±1.64	4.4 ± 0.29	4.95± 0.02	0.37±0.04	34± 1	39± 1	99.67±1.49	76.82±0.81
F4	301.26±1.47	3.9 ± 0.52	4.93± 0.04	0.56±0.03	29± 2	34± 3	98.32±1.56	82.71±1.46
F5	299.82±2.64	3.8 ± 0.59	4.97± 0.01	0.49±0.01	24± 1	30± 1	98.53±1.39	86.65±1.37
F6	301.65±1.86	4.3 ± 0.26	4.95± 0.03	0.41±0.03	21± 1	26± 2	98.56±1.43	90.03±1.76
F7	302.23±1.48	3.5 ± 0.52	4.93± 0.02	0.61±0.02	17± 1	22± 3	99.14±0.87	93.12±1.05
F8	301.62±1.68	3.7 ± 0.53	4.95± 0.01	0.54±0.01	15± 2	19± 2	99.78±1.32	96.65±1.12
F9	300.72±1.72	4.2 ± 0.28	4.93± 0.02	0.46±0.02	12± 2	17± 2	98.23±1.67	99.76±0.72

All values are expressed as mean ± standard deviation, n=3

Tablet weights in all the 9 batches varied between 299.82 to 302.52 mg. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5%. Thickness of all tablets was in the range between 4.93 mm to 4.97 mm. Hardness of tablets was in range between 3.5 to 4.5 kg/cm^2. Friability was in range between 0.37 to 0.61 %. Thus, all the physical parameters of the manually compressed tablets were quite within control. Friability values were less than 1 % in all cases shows good mechanical strength at the time of handling and transports.

The results shown in Table 6 indicate that concentration-dependent disintegration was observed in batches prepared using combination of crospovidone and croscarmellose. As crospovidone combined with croscarmellose, by keeping concentration of crospovidone constant and increase concentration of croscarmellose from 1 to 5%, disintegration time was decreased as shown in result. This might be due to combination of two superdisintegrants can provide both the swelling and capillary action for disintegration of tablets and thereby improve the efficacy. A blend of swelling and wicking types of excipient may prove to be efficient because the medium (usually water) required for swelling will be brought into the tablet more easily if a wicking (hydrophilic) type of superdisintegrant is also present. Also the combination will reduce the amount of individual superdisintegrant required in a single tablet. Thus, the two best superdisintegrants (Crospovidone and Croscarmellose) from the preliminary studies were selected for factorial design. The goal was to develop a formulation

that meets criteria set forth earlier under objectives.

The wetting time of tablets as shown in Table 6.14 of all nine formulations was in the range of 17 to 51 seconds. The wetting time is closely related to the disintegration time.

The % drug content for tablets of all formulation was found to be in the range of 98.23 to 99.67%. Thus the assay of Piroxicam was found to be quite within the range.

Dissolution Study

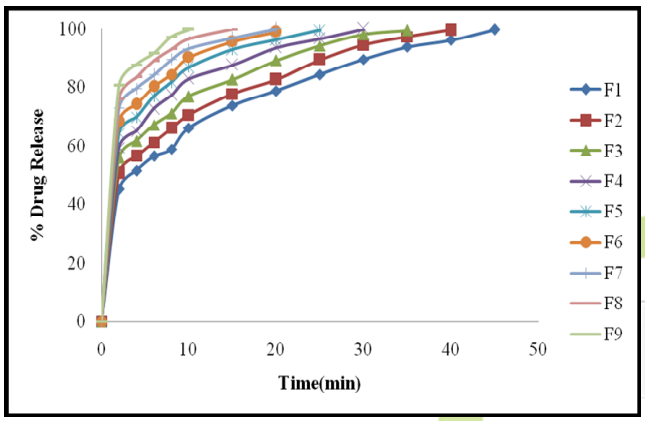

Figure: 7 Effect of Superdisintegrants on Dissolution Profiles of (F1-F9)

The dissolution profiles of all the nine formulations are shown in Figure 6. From graph it was concluded that as the concentration of superdisintegrant increases, % drug release was also increased. % drug release from F4 and F7 formulations prepared with Crospovidone 4% and crospovidone 8% and both contained 1% croscarmellose was shown 82.71 and 93.12 % in 10 minutes. % drug release from F4 and F6 formulations prepared with Crospovidone 4% and croscarmellose 1, 3 1nd 5 % respectively were shown 82.71, 86.65 and 90.03 % in 10 minutes. Combination of two disintegrates also improves dissolution rate as compared to individual superdisintegrant because wicking action of crospovidone improve water penetration in tablet matrix and thus facilitate swelling of croscarmellose and provides rapid disintegration of tablet. The release of drug was largely depended on the disintegration time. That is faster the disintegration of tablets, better and faster is the release.

Data Analysis

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The disintegration time and wetting time were selected as dependent variables. The polynomial equations (full and reduced) relating the responses, disintegration time and wetting time to the transformed factor are described below. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table 8 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Since the values of r^2 are quite high for all the two responses, i.e., 0.9986 to 0.9992, the polynomial equations form excellent fits to the experimental data and are highly statistically valid.

Table: 7 Summary Output of Regression Analysis for Effect of X1 and X2 on Dependent variables*[19]

For Disintegration Time							
Response (disintegration time)	**b0**	**b1**	**b2**	**b11**	**b22**	**b12**	**R^2**
FM	24.78	-12.83	-4.167	1.75	2.83	-0.167	0.9986
RM	24.66	-12.83	-4.167	1.75	2.83	-	0.9986
For Wetting Time							
Response (wetting time)	**b0**	**b1**	**b2**	**b11**	**b22**	**b12**	**R^2**
FM	30.11	-13	-4.167	1.75	2.33	-0.167	0.9992
RM	30	-13	-4.167	1.75	2.33	-	0.9992

**FM, full model; and RM, reduced model.*

Polynomial Equation for Dependent Variables

Polynomial Equation for Disintegration Time

$Y= 24.78-12.83X_1-4.16X_2+1.75X_1X_2+2.83X_{11}-0.167X_{22}$

The Disintegration time is an important parameter for orally disintegrating tablets. Disintegration time of orally disintegrating tablets varied from 12 to 46 sec and showed good correlation coefficient as R^2 is 0.9986.The negative coefficients for all two independent variables indicated a favorable effect on DT, while positive effect for interaction between two variables(X1X2) indicated unfavorable effect on DT.

Polynomial Equation for Wetting Time

$Y= 30.11-13X_1-4.167X_2+1.75X_1X_2+2.33X_{11}-0.167X_{22}$

The Wetting time is an important parameter for orally disintegrating tablets. Wetting time of orally disintegrating tablets varied from 17 to 51 sec and showed good correlation coefficient as R^2 is 0.9992. The negative coefficients for all two independent variables indicated a favorable effect on WT, while positive effect for interaction between two variables(X1X2) indicated unfavorable effect on WT.

Calculations for testing the model in portions:

The reduced model was tested in portions to determine whether the coefficient b_{22} contributes significant information for the prediction of disintegration time or not. The results for testing the model in portions are shown in Table 6.17. The critical value of *F* for $\alpha = 0.05$ is equal to(DF =5,3). Since the calculated value (*F* = 0.108) is less than the critical value (F_{cal} = 9.01), it may be concluded that the interaction term b_{22} does not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model.

Table: 8 Calculations for Testing the Model in Portions*

DT						
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	
FM	5	1120.694	224.14	440.13	0.998639	
RM	4	1120.639	280.16	707.77	0.998589	**Fcal= 0.108 Ftable=9.01** DF(5,3)
Error						
FM	3	1.528	0.509			
RM	4	1.583	0.396			
WT						
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	
FM	5	1141.361	228.27	795.27	0.999246	
RM	4	1141.306	285.33	1245.06	0.999197	**Fcal=0.195 Ftable=9.01** DF (5,3)
Error						
FM	3	0.861	0.287			
RM	4	0.917	0.229			

**DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient; FM, full model; and RM, reduced model.*

Contour Plot

Contour plots were drawn using design expert software 8.0.7.1.

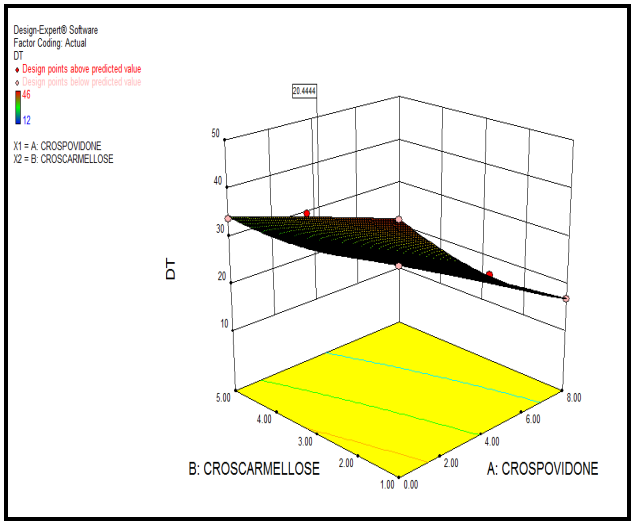

Figure: 8 3-D graph showing effect of CP and CCS on Disintegration Time (R1)

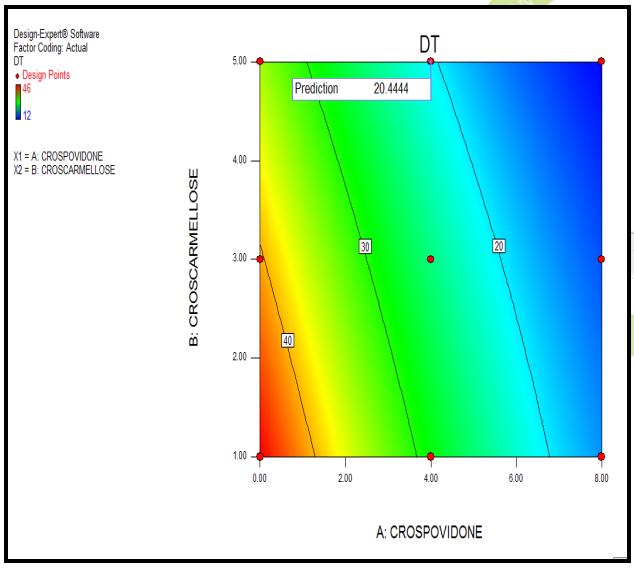

Figure: 9 Two-Dimensional Contour Curve for Disintegration Time

This contour plot shows the effect of concentration of crospovidone (X1) and concentration of croscarmellose on disintegration time (Y1). As concentration of X1 and X2 increases, the value of response Y1 decreases.

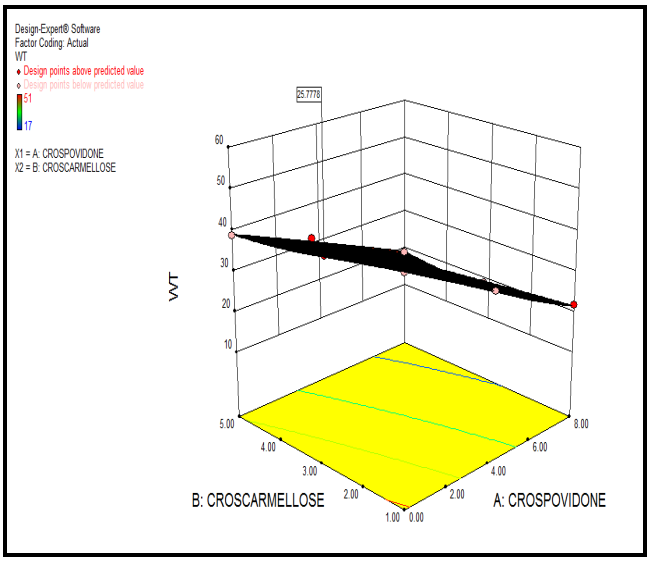

Figure: 10 3-D Graph Showing Effect of CP And CCS on Wetting Time (R2)

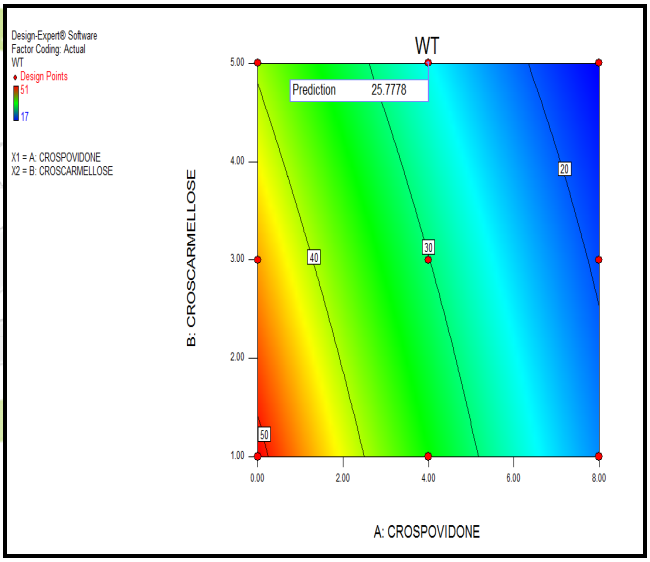

Figure: 11 Two-Dimensional Contour Curve of the Wetting time

This contour plot shows the effect of concentration of crospovidone (X1) and concentration of croscarmellose on wetting time (Y2). As concentration of X1 and X2 increases, the value of response Y2 decreases.

Optimization of formulation ingredients:

Validation of 3^2 Full Factorial Design is necessary for confirmation of applied model. Check point batch F10 contains 6.74 % of crospovidone and 4.23% of croscarmellose was

formulated and evaluated for different physico-chemical parameter to validate the design.

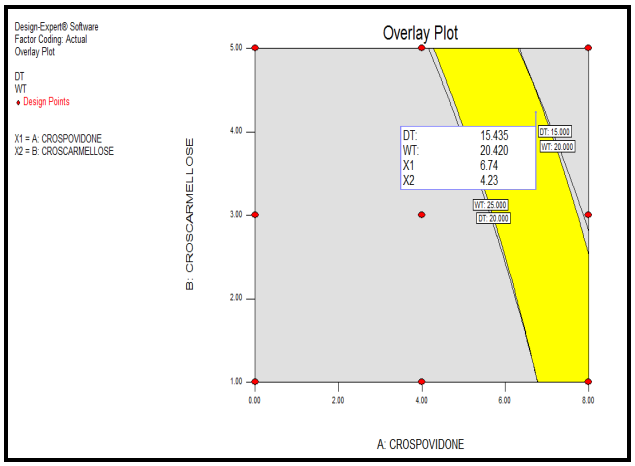

Figure: 12 Overlay Plot of Response Variables

Table: 9 Evaluation Parameters of Optimized Formulation

PRECOMPRESSION EVALUATION PARAMETERS	
Bulk density(gm/ml)	0.49±0.01
Tapped density(gm/ml)	0.57±0.01
Carr's compressibility index(%)	14.03±0.02
Hausner ratio	1.16±0.01
Angle of repose(°)	27.42±0.03
EVALUATION PARAMETERS OF TABLETS	
Weight variation	301±1.21
Hardness (kg/cm^2)	4.2 ± 0.19
Thickness (mm)	4.95±0.02
Friability (%)	0.46±0.03
Disintegration time (sec)	16±1
Wetting time (sec)	21±1
% Drug content	99.12±1.15
Drug release (%) in 10 min	94.23±0.87

From the full factorial model, it is expected that the Disintegration time and Wetting time of the check point batch should be 15.43 and 20.42 sec respectively. Table 9 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid.

Comparison of Optimized formulation with market product using similarity factor (f_2)

Table: 10 Comparison of Marketed Formulation with Optimized Formulation Prepared by Direct Compression Method

Parameters	Marketed Preparation	Optimized formulation
Hardness(kg/cm^2)	4.5±0.23	4.2±0.35
Disintegration time (sec)	18±1	16±1
Wetting time (sec)	22±1	21±2
Q10(% Drug release in 10 min)	95.63±1.16	94.23±1.52

From the result, it was concluded that optimized formulation had similar disintegration time, wetting time and % drug release with marketed product.

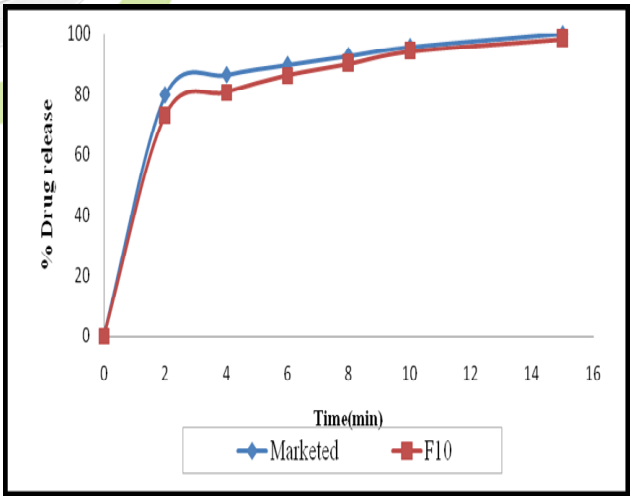

Figure: 13 Comparative Release Profile between Marketed Formulation and Optimized Batch (F10)

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between

the two curves. The dissolution profiles are considered to be similar when f_2 is between 50 and 100.The f2 value calculated using equation of similarity was found to be 69.045. So, f2 value ensures sameness or equivalence of two curves.

Stability Study

Table: 11 Stability study of optimized formulation (F10) carried out at 40 ± 2°C/ 75 ± 5 % RH

No. of week	Disintegration time (sec)	%Drug Content	Q10 (% Drug release in 10 min)
0	16±1	99.12±1.15	94.23±0.87
1	17±2	99.04±1.52	93.87±1.21
2	17±1	98.95±1.32	93.56±1.18
3	18±2	98.65±1.21	93.12±1.15
4	18±2	98.44±1.29	92.97±1.26

Stability study of ODT of piroxicam was carried out for 4 weeks at specified condition. All data are mentioned in Table 11.The stability studies of the optimized formulation (F10) of ODT revealed that no significant changes in the physical parameters, disintegration time, %drug content and % drug release in 10 min when stored at temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH. So, we can say that formulation having good stability.

CONCLUSION

From the results obtained, it can be concluded that complex of piroxicam with ß-cyclodextrin markedly improved the dissolution behavior of piroxicam. Tablets prepared with crospovidone and croscarmellose showed less disintegration time compared to sodium starch glycolate. Thus concentration of crospovidone and concentration of croscarmellose was selected as independent variable. From the results of 3^2 full factorial design revealed that amount of crospovidone and amount of croscarmellose significantly affect the dependent variables, disintegration time and wetting time. It is thus concluded that by using response surface design, an optimum point can be reached in the shortest time with minimum efforts. The derived polynomial equation and contour plots aid in predicting the values of selected independent variables for the preparation of optimum piroxicam orally disintegrating tablets with desired properties.

REFERENCES

1. Manivannan R, “Oral disintegrating tablets: A future compaction”, Drug Invention Today, 2009, 1(1), 61-65.
2. Wadhwani AR, Prabhu NB, Nandkarni MA, Amin PD, “Consumer friendly mucolytic formulations”, Indian Journal of Pharmaceutical Sciences, 2004, 7(2), 506-507.
3. Mudgal V, Sethi P, Saraogi GK, Singhai AK, “Orally disintegrating tablets: A review”, International Research Journal of Pharmacy, 2011, 2(4), 16-22.
4. Divate S, Kvitha K, Nanjan G, “Fast disintegrating tablets – an emerging trend”, International Journal of Pharmaceutical Sciences Review and Research, 2011, 18-22.
5. Bandari S, Mittapalli R, Gannu R, Rao Y, “Orodispersible tablets: An overview”, Asian Journal of Pharmaceutics, 2008, 2(1), 2-11.
6. Bharawaj S, Jain V, Sharma S, Jat RC, Jain S, “Orally disintegrating tablets: A review”, Drug Invention Today, 2010, 2(1), 81-88.
7. O’Nell, Smith A, The Merck Index-An encyclopedia of chemicals, drugs and biological, 13th Edn, Merck Research Laboratories, New Jersey, 2001, 7588.
8. Sean CS, Martindale - The complete drug reference, Volume A, 37th Edn, Pharmaceutical Press, USA, 2009, 122.
9. Osadebe P, Onugwu L, Attama A, “Energetics of the interaction between piroxicam and beta-cyclodextrin (ß-CD) in inclusion complexes”, Scientific Research and Essay, 2008, 3(3), 86-93.

10. Mady FM, Abou-Taleb AB, Khaled A, Yamasaki K, "Enhancement of the Aqueous Solubility and Masking the Bitter Taste of Famotidine Using Drug/SBE-ß-cyd/Povidone K30 Complexation Approach", Journal of Pharmaceutical Sciences, 2010, 99(10), 4285-4294.
11. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N, "Formulation Design and Optimization of Mouth Dissolve Tablets of Nimesulide Using Vacuum Drying Technique." AAPS PharmSci Tech. 2004, 5 (3), article 2.
12. USP 30, NF-25; Asian Edn., United states Pharmacopoeia convention Inc., Rockville, 2004, 242, 674.
13. Indian Pharmacopoeia; Vol.-I; The Indian Pharmacopoeia Commission, Ghaziabad, 2007, 241-242, A-54.
14. Hasan Basan H, Goger N, Ertas N, "Quantitative determination of piroxicam in a new formulation (piroxicam–ß-cyclodextrin) by derivative UV spectrophotometric method and HPLC", Journal of Pharmaceutical and Biomedical Analysis, 2001, 26, 171-178.
15. Panwar AS, Nagori V, Chauhan J, Jain DK, "Formulation and evaluation of fast dissolving tablet of piroxicam", American Journal of PharmTech Research, 2011, 1(3), 255-273.
16. Bangale GS, Shinde GV, "Piroxicam loaded orodispersible tablet using different superdisintegrants: formulation and *In-Vitro* evaluation", Journal of Pharmacy Research, 2011, 4(8), 2545-2549.
17. Khinchi MP, Gupta MK, Bhandari A, Agrawal D, "Orally disintegrating tablet of Famotidine prepared by direct compression method using 3^2 full factorial design", Asian Journal of Pharmaceutical and Health Sciences, 2011, 1(2), 55-60.
18. Prajapati BG, Patel SN, "Formulation, evaluation and optimization of orally disintegrating tablet of Cinnarizine", e-Journal of Science & Technology, 2010, 5(5), 9-21.
19. Omaima AS, Mohammed AH, Nagia AM, Ahmed SZ, "Formulation and Optimization of Mouth Dissolve Tablets Containing Rofecoxib Solid Dispersion", AAPS PharmSci. Tech. 2006, 7 (2), Article 55.

