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FORMULATION AND EVALUATION OF CYCLODEXTRIN COMPLEX ORALLY DISINTEGRATING TABLETS OF MEFENAMIC ACID

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ABSTRACT

The aim of present study is to formulate and evaluate oral disintegrating tablets (ODTs) of Mefenamic acid and β-cyclodextrin complex based tablet prepared by freeze drying to attainment of improved solubility of Mefenamic acid and overcome the patient complaints. The inclusion complex (1:1 ratio) was formed by freeze drying. Direct compression method was used to prepare oral disintegrating tablets. Thirteen formulations were developed using Face centred composite design to optimize the concentration of crosscarmellose sodium (0/6/12) and microcrystalline cellulose (0/60/120) at different ratios. Prepared formulations were subjected to FTIR and DSC for the drug and for the Mefenamic acid + β-Cyclodextrin and they showed no change or interactions between the drug (Mefenamic acid) and excipients. XRD and ^{1}HNMR were performed for compatibility with the drug and β-cyclodextrin. Then formulated tablets were subjected to post compression evaluation. Due to the freeze drying process, the rate of dissolution and efficiency of dissolution were increased by the complexation with β-cyclodextrin. Diluent and superdisintegrant concentrations played a major role, which affects the development of ODTs formulation. The solubility of the drug was increased due to inclusion with β-cyclodextrin. Higher the concentrations of MCC enhanced the disintegration and improved dissolution. Formulations with a higher concentration of mannitol increased the tablet hardness, compatibility and decreased the rates of dissolution the drug. Stability studies indicated no change in drug property.

KEYWORDS: Mefenamic acid; β-cyclodextrin; Freeze drying; Face centred CCD; ODTs; Patient compliance.

INTRODUCTION

Patient compliance is a very important aspect in the pharmacy companies for the formulation of the newer drugs which ensure the drug delivery to the patients efficiently and fewer side effects.

Solid dosage forms are available in different forms, such as tablets and capsules, one of the most important drawbacks of this dosage form for some patients, is difficult to swallow. Where geriatrics and paediatric due to under developed muscular system and nervous system they have a problem in swallowing the solid dosage form.[1]

Due to this, it led to the emergence of the oral disintegrating tablets formulation which was developed in the consideration of patient compliance.[2]

“Oral disintegrating tablets "(ODTs) is a promising approach which has improved the rate of in-soluble and poorly soluble drugs. The oral disintegrating tablet quickly dissolves or disintegrates after contact with saliva to eliminate some common problems with oral dosage forms such as difficulty swallowing, the need of chewing tablet, and need for water intake. Ideally, Oral disintegrating tablet disintegrates easily within seconds, when placed on the tongue without water intake.[3][4]

Recently several numbers of pharmaceutical active ingredients have been increased for formulation of the oral disintegrating dosage form. Where there are currently more than 145 products launched (both branded and generic) on the market.

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) an anthranilic acid derivative. It is used for the treatment of mild pain to moderate pain even used to postoperative pain, postpartum pain, headache, dental pain, dysmenorrhea and osteoarthritis. The daily oral dosage is 500 mg three times a day. Where, the drug is absorbed in the gastrointestinal tract. After ingestion, peak plasma concentrations occur for about 2 to 4 hrs.

Most NSAIDs comes under Biopharmaceutical Classification System (BCS), Class -II, i.e. they are extremely permeable across biological membranes but exhibit poor aqueous solubility.[5][6]

Poor solubility and poor absorption are the major problems with the production of the formulation of new chemical substances as well as the development of generic drugs. Approximately 35-40% of new drug entities show poor solubility.

Various methods have been developed to increase the solubility of drugs including physical and chemical modifications of drug, and others include solid dispersion, application of surfactant, complexation, salt formation, reduction of particle size, crystal engineering and so on. When choosing the method to improve solubility, it depends on the drug's properties, site of absorption and the necessary dosage form characteristics.[7]

Several researches have reported that usage of β-cyclodextrin (β-CD) and its derivatives in pharmaceutical formulations showed improved drug bioavailability and decreased the toxicity. β-Cyclodextrin, despite its minimal aqueous solubility it has been extensively studied. Several alkylated derivatives, such as 2-hydroxypropyl-β-cyclodextrin (HP-β –CD), have attracted growing interest due to their enhanced complexing ability, higher water solubility and lower toxicity than β-cyclodextrin. It modifies chemical, physical and biological properties, and complexation provides increase drug solubility, stability, bioavailability and improves the dissolution rate of poorly and insoluble soluble drugs.[8][9]

MATERIALS AND METHODS

Materials

Mefenamic acid was a gift sample from Blue Cross Laboratories, Goa, India and β-Cyclodextrin from Rolex chemicals, Mumbai, India. Crosscarmellose sodium from Shreeji chemicals Mumbai, India. Microcrystalline cellulose and Mannitol from SD-Fine chemical ltd, Mumbai, India. All other chemicals used were laboratory grade.

Methods

Preparation of inclusion complex (Mefenamic acid and β-cyclodextrin)

1:1 ratio of Mefenamic acid and β-cyclodextrin was dispersed in ethanol and stirred using magnetic stirrer for 48hrs at room temperature (25℃) to form complex and avoid volatile loss to the atmosphere. Then the solution was frozen at -20℃ and inclusion complex lyophilized at -50℃ and stored in desiccator until further use.

Preparation of oral disintegrating tablet

Then inclusion complex (1:1) and excipients were mixed thoroughly in a geometric ratio and the blend obtained was finally compressed into tablet of 200mg by direct compression. Before the use of ingredients it were measured correctly and passed separately through # 60 sieve. The formulation compositions of ODTs are shown in Table-1.[10]

Table 1: Composition of Oral Disintegrating Tablet (200mg).

Ingredients	Weights (mg)
Mefenamic acid: β-cyclodextrin (inclusion complex) (1:1 ratio)	10
Crosscarmellose Sodium (CCS)	0/6/12
Microcrystalline Cellulose (MCC)	0/60/120
Magnesium stearate	2
Flavor	2
Mannitol	Quantity sufficient (200)

Design of Experiments (DOEs)

The central composite design consists of an imbedded factorial fractional design with center points that are augmented with the axial point group that enables curvature estimation. Face centered central composite design (CCD), the star points are at the center of the factorial design points or of each face of the factorial space. Two factor, three level central composite design was used to optimize the factors i.e. diluent microcrystalline cellulose, MCC (X_1) and superdisintegrant crosscarmellose sodium, CCS (X_2) concentrations. The factors were assessed at the three high, medium and low levels (+1, 0, and -1) (Table 2).[11]

EVALUATIONS

Preformulation studies

Melting point determination

Melting point of pure mefenamic acid was determined using the capillary method. The capillary tube was closed at one end by fusion and was filled with drug sample by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100°C min rise of temperature per minute. The temperature at which the drug started melting was recorded. This was performed thrice and the average value was calculated.

Fourier Transform Infrared Spectrophotometer

FTIR spectral analysis of the obtained drug sample was carried out individually, using Shimadzu FTIR-8400s, Japan spectrophotometer, observation was made. Potassium bromide was mixed with drug and the spectra were taken from wavelength range of 400cm^{-1} - 4000 cm^{-1} at 4 cm^{-1} spectrum was scanned. The absorption maxima in the spectra were compared with the reference spectrum.[12]

Evaluation of inclusion complex

Drug content

An accurately weighed 100 mg of complex was taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1 N HCl and assayed for drug content using the UV spectrophotometric method at 241 nm.

X-ray diffractometery (XRD)

X-ray diffraction pattern of drug and Mefenamic acid + β-Cyclodextrin complex were recorded using (Proto AXRD, Benchtop system, Canada) X-ray diffractometer where voltage 30.00Kv, current 20.00mA, at a scanning speed of 0.30°C/min was applied.[13]

Proton nuclear magnetic resonance (^{1}HNMR)

^{1}HNMR was done for pure Mefenamic acid and inclusion complex were recorded using VNMRS-400 (Agilent-NMR, Santa Clara, CA, USA) and they were recorded.[14]

Evaluation of formulated oral disintegrating tablet formulations

Differential Scanning Calorimetery (DSC)

The DSC analysis of drug and Mefenamic acid + β-Cyclodextrin complex combination was carried out by using a Shimadzu DSC-60, Japan calorimeter to check any possible drug polymer interactions. It was performed at a rate 5 ºC min^{-1} from 10 to 300 º C temperature ranges under nitrogen flow of 25 ml min^{-1}.

Hardness

Hardness is indication of tablet strength. 3 tablets were selected from each batch of formulations and were evaluated for durability using Monsanto hardness apparatus.

Friability

Friability was measured by using Roche friabilator. From each formulation 10 tablets was weighed and transferred to a friability chamber, rotated for 4 min at 25 rpm and weighed again. Percent friability was calculated using below formula.

%Friability= $[(W_1-W_2)/W_1]$ *100

Where, W1 is the weight of tablets before test

W2 is weight of tablets after test

Weight variation

From each formulation 10 tablets was taken and the individual weight and the average weight was determined. The percent deviations of each tablet were determined by using average weight.[15]

***In-vitro* disintegration time**

Randomly 6 tablets was selected and taken and disintegration was done using disintegration tester apparatus containing 6 glass tubes, using pH 7.4 buffer solution as medium and maintaining temperature at 37±2℃.

***In-vitro* dissolution test**

The drug release pattern was determined by using USP dissolution apparatus (paddle-type) maintaining temperature at 37±0.5℃ at 50 rpm. 900ml of phosphate buffer, pH 7.4 was used as medium and was placed in dissolution flask. The prepared formulation was placed in the flask and apparatus was started. Samples were taken at interval of 0 upto 30 min and sink condition was maintained. And then collected samples were observed at 285 nm using spectrophotometer.[16]

Stability studies: Accelerated stability study was conducted for optimized formulation as per ICH guidelines at 40℃ ± 2℃/75% RH±5% for 3 months period and then tablets were examined for any changes in the formulation characteristics.[17]

RESULTS AND DISCUSSION

In the present work Oral disintegrating tablet containing Mefenamic acid and β-Cyclodextrin were prepared and evaluated.

Factorial Design

In the present research work Central composite design (CCD) was applied to study the effect of independent variables, i.e. concentration of diluent microcrystalline cellulose MCC (X_1) and superdisintegrant crosscarmellose sodium CCS (X_2) on dependent variables like Hardness, Cumulative % Drug release and Disintegration time by using design expert software.

Table 2: Value code for face centred-CCD.

Independent variables (factors)		Design level		Code level
Crosscarmellose sodium-CCS, X_1 (mg)	**A**	0	Low	-1
		6	Medium	0
		12	High	+1
Microcrystalline cellulose-MCC, X_2 (mg)	**B**	0	Low	-1
		60	Medium	0
		120	High	+1

Table 3: Design matrix of face centered CCD for ODT formulations.

Formulation No.	Coded Levels of Independent Variables	
	Factor X_1: CSS	Factor X_2: MCC
F1	-1	+1
F2	-1	0
F3	0	+1
F4	0	0
F5	0	0
F6	0	-1
F7	+1	-1
F8	+1	+1
F9	0	0
F10	+1	0
F11	0	0
F12	-1	-1
F13	0	0

- **Melting point**

The melting point of the drug (Mefenamic acid) was found to be 230-231℃, which complied with IP standards, thus indicating the purity of drug.

- **Fourier Transform Infrared spectroscopy**

The IR spectral analysis of Mefenamic acid and inclusion complex presented in Figure 1. Pure Mefenamic acid spectra showed principal peaks at different wave numbers

corresponding to its functional groups, confirming the purity of the drug as per established standards.

The IR Spectra of Mefenamic acid exhibited peak at 3346.53 cm-1, 1650.85 cm-1, 3314.86 cm-1, 2924 cm-1, 1453 cm-1, 2858 cm-1, 1568.65 cm-1 (NH group, C=O Stretching, O-H Stretching, C-H Stretching C-H bending, CH group, C=C). The IR spectra of β-CD showed prominent absorption bands at 3421 cm-1 (0-H stretching). This result suggested that there was no chemical interaction between drug and β-CD in their combination. The characteristic peaks appear in the spectra of physical mixture of inclusion complex of Mefenamic acid and other excipient indicates no modification or chemical interaction between the drug and excipients.

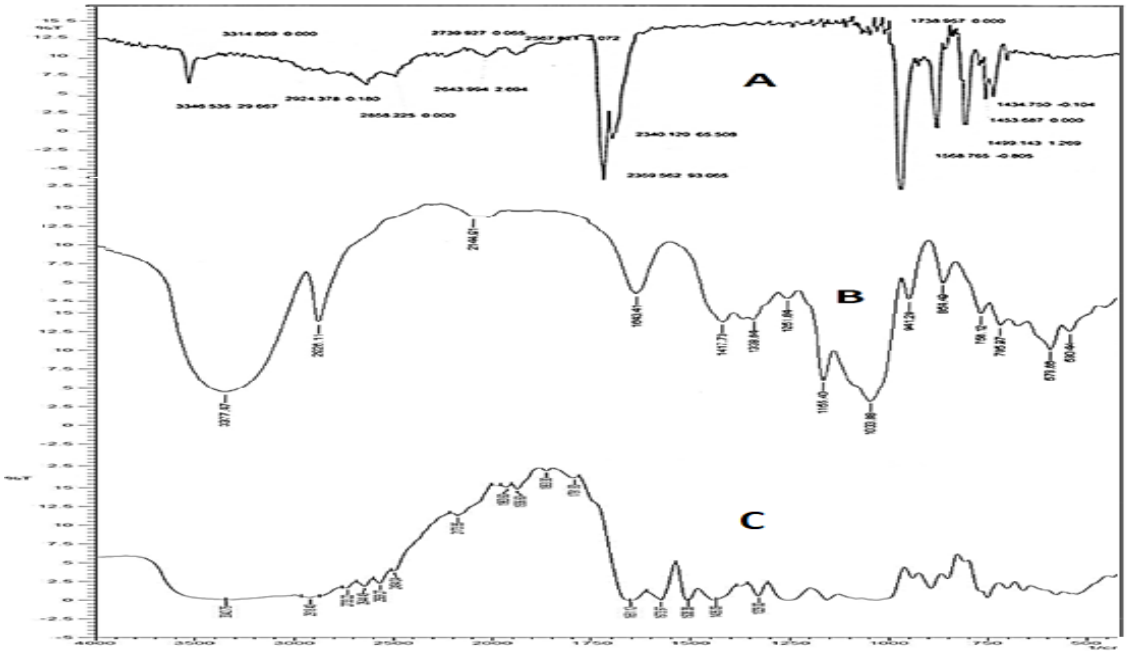


Figure 1: FTIR spectra of Mefenamic acid (A), β-Cyclodextrin (B) and inclusion complex (C)

- **Differential scanning Calorimetery**

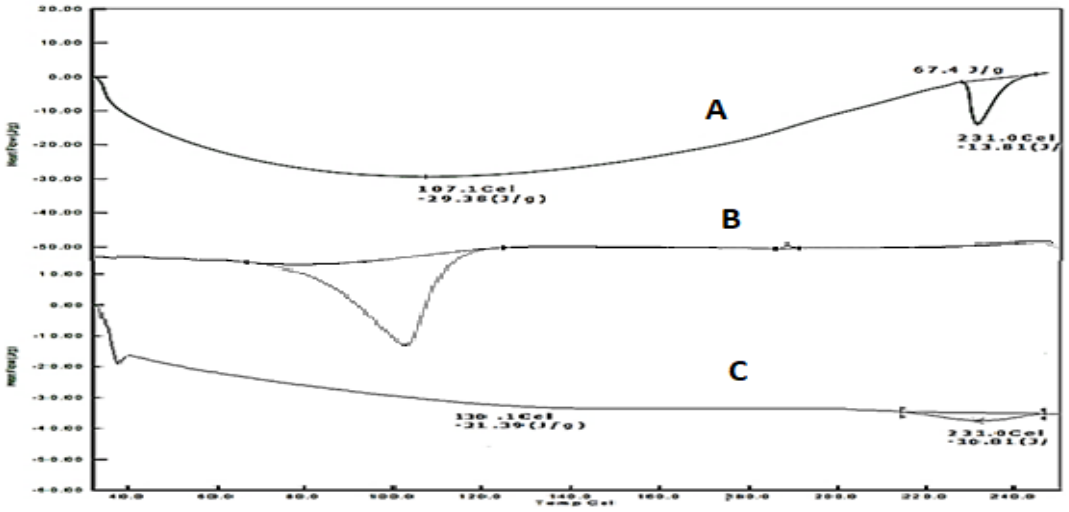


Figure 2: DSC thermogram of Mefenamic acid (A), β-Cyclodextrin (B) and inclusion complex (C)

DSC studies were carried out for the drug (Mefenamic acid) and inclusion complex using DSC in the temperature range 10ºC -300 ºC. The DSC of the drug showed a sharp endothermic peak 231 °C corresponding to melting point, indicating the crystallinity. The Inclusion complex of Mefenamic and β-Cyclodextrin (C) showed an endothermic peak corresponding to melting point of Mefenamic acid and a broad endothermic peak at around 100°C representing the dehydration where due this result obtained showed there was no interaction between drug and β- cyclodextrin and concluded that it is compatible with all the excipients.

- **XRD**

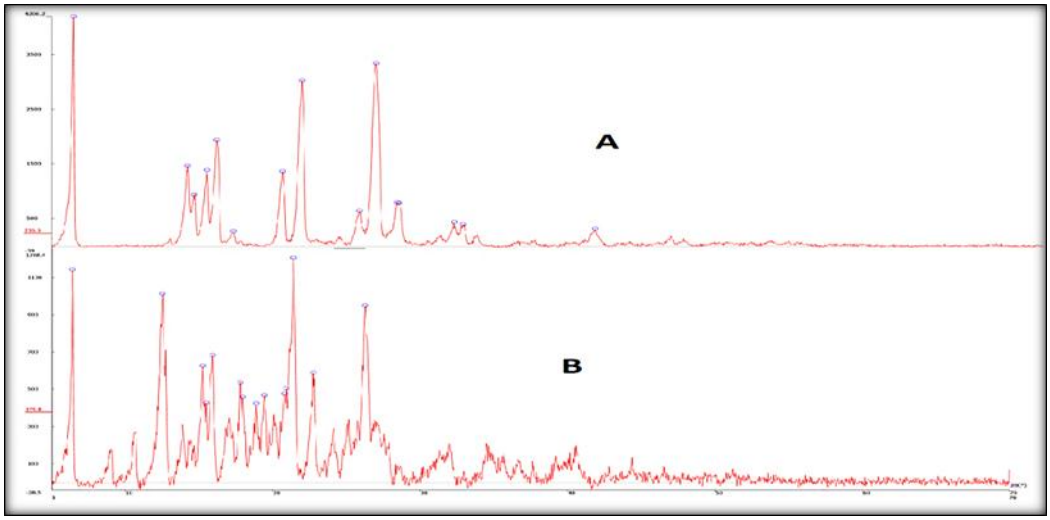


Figure 3: XRD of pure Mefenamic acid (A) and (1:1) inclusion complex (B)

The XRD pattern of Mefenamic acid and inclusion complex is exhibited in Figure 3. X-ray diffraction of Mefenamic acid shows a sharp peak at 2θ values of 6.4°, 15.8°, 21.4° and 26.3°. The diffraction pattern of Mefenamic acid and inclusion complex (Mefenamic acid + β-Cyclodextrin) showed more intense peaks, but the prominent crystalline peak of Mefenamic acid situated at 6.4° was observed. These results confirmed that the drug and excipient does not have interaction between them.

^{1}HNMR

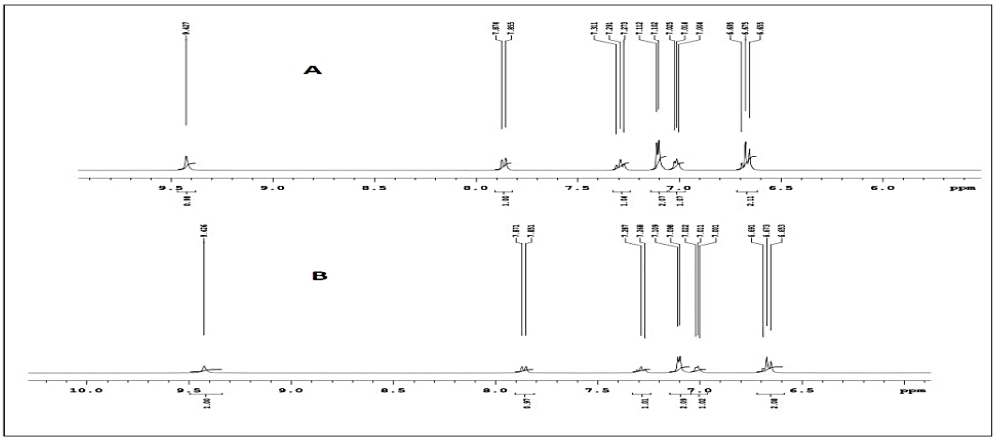


Figure 4: ^{1}HNMR of pure Mefenamic acid (A) and inclusion complex (B)

^{1}HNMR studies relate to the functional groups involved in the complexation, and the chemical shift values in ^{1}HNMR depict the mechanism of complexation. The proton chemical shift between the pure drug and β-CD inclusion complex was observed, and the interaction between the drug and the inclusion complex was compared (Figure 4). The structural interpretation using 1HNMR showed the amino-functional group of mefenamic acid inside the β-CD cavity, which predicted the mechanism of taste-masking of the drug-β-CD complex. The insertion of the Mefenamic acid molecule into the β-CD cavity was demonstrated by changes in the values of the 1HNMR proton chemical shifts. The tertiary amine of mefenamic acid was changed significantly, where there was no change in the chemical shift value of methoxy proton. The results indicated that the mefenamic acid tertiary amine group is enclosed within the β-CD cavity.

Evaluation parameters

Evaluation parameter for prepared formulation tablets (F1-F13) was carried out.

Table 4: Evaluation parameter of ODTs of Mefenamic acid.

Formulation	Hardness (kg/cm^2) ±SD*	Weight variation (mg) ±SD*	Friability (%)±SD*	Disintegration time (Y2) (sec) ±SD*
F1	4.02±0.48	200.35±2.12	0.57±0.12	12.3±0.12
F2	8.12±0.204	199.86±1.68	0.60±0.25	102.2±5.82
F3	3.65±0.258	200.07±1.81	0.54±0.42	198.12±0.51
F4	7.15±0.204	200.03±2.21	0.52±0.85	29.25±0.17
F5	7.11±0.01	200.44±2.05	0.35±0.65	25.80±4.47
F6	6.81±0.204	200.41±1.61	0.42±0.21	132.7±3.41
F7	10.46±0.258	199.93±1.81	0.58±0.08	140.7±0.18
F8	1.51±0.204	200.40±1.97	0.60±0.15	6.25±0.54
F9	2.53±0.35	200.15±1.81	0.39±0.75	11.24±0.63
F10	2.28±0.20	199.92±1.95	0.40±1.85	9.87±0.577
F11	2.62±0.204	199.32±1.76	0.55±1.29	13.45±0.56
F12	10.68±0.01	200.10±1.64	0.60±0.85	230.22±0.48
F13	4.38±0.35	199.77±1.81	0.42±0.94	14.63±0.35

Table 5: Wetting time, Water absorption ratio and % Drug content.

Formulation	Wetting time (min)±SD*	Water absorption time (min)±SD*	Drug content uniformity (%)±SD*
F1	6.30±4.51	62.20±5.42	87.4±0.13
F2	5.66±3.92	52.45±7.70	90.2±0.18
F3	5.20±5.09	63.00±2.32	90.6±0.05
F4	4.90±6.97	54.51±4.22	87.8±0.04
F5	3.22±8.17	42.26±3.04	88.9±0.02
F6	3.65±2.86	30.11±1.38	88.3±1.30
F7	5.25±4.54	34.49±3.54	89.8±0.73
F8	6.66±3.29	45.24±8.14	89.2±0.18
F9	5.42±1.61	80.12±3.36	88.9±0.10
F10	6.51±2.81	96.94±3.20	89.4±0.30
F11	4.87±5.49	84.88±3.00	86.5±0.05
F12	7.41±0.41	20.16±6.01	89.9±0.50
F13	4.14±3.19	69.32±7.54	87.7±0.09

All the tablets (F1-F13) passed the weight variation test and were found in the acceptable limits according to USP (± 10). Hardness of the tablet for every batch was found in the range from 1.51±0.204 to 10.68±0.01. Formulation shows the good mechanical strength and transportation, friability values for all the batches were in range of less than 1% indicating an acceptable limit. The wetting time of all batches was in the range of 4.87±5.49% - 7.41±0.41min (Figure 5). The drug content for all the formulations was calculated by measuring the absorbance at 285 nm was found in the range 86.5±0.05% - 90.6±0.05% with an acceptable limit based on USP.

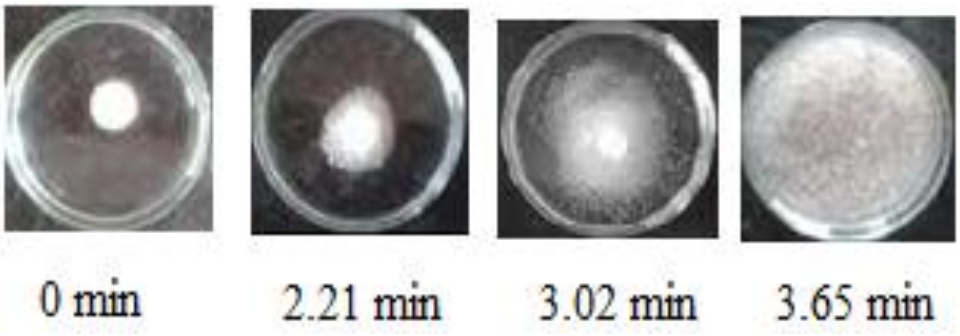


Figure 5: Wetting time of formulation of F6.

- **Comparative drug release profile**

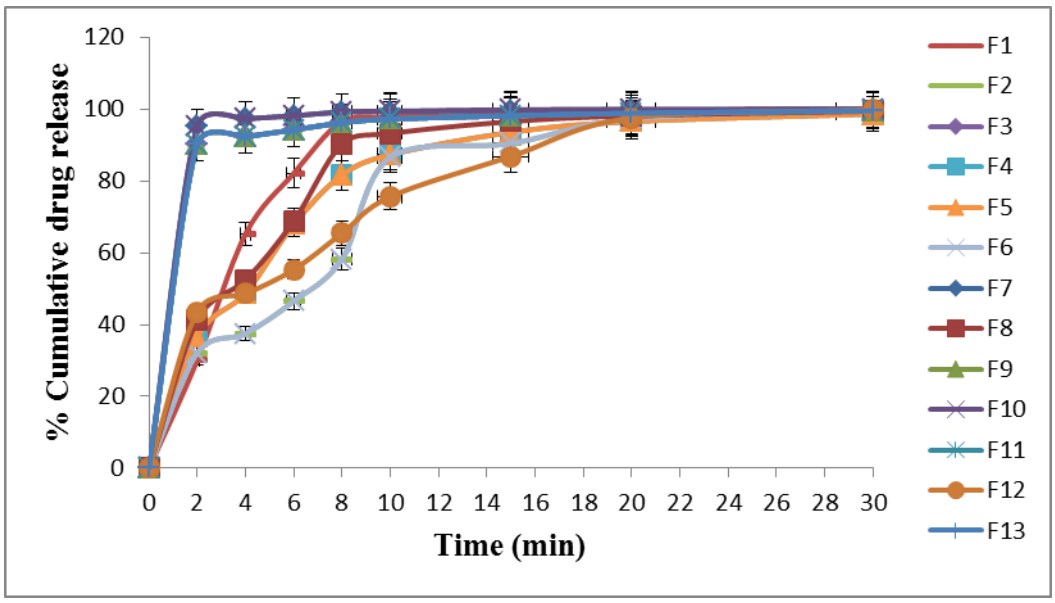


Figure 6: Dissolution of formulations F1-F13 of ODTs.

Figure 6 showed the *in-vitro* dissolution profiles of the ODT formulations. The formulations (F1-F13) Mean dissolution time (MDT) ranged from 1.2 to 5.17 mins. F3, F4, F5, F8, F9, F10, F11, and F13 (with mid to high level concentrations of both CSS and MCC) formulations displayed MDTs in the range from 1.2 to 4.65 mins. F1 and F2, in the absence of CCS, showed MDTs of 4.03 and 5.17 mins, respectively.

The MDTs decreased by F1 and F2 with high MCC concentrations. F6 and F7 showed high MDTs (4.12 and 4.65 min) in the absence of an MCC. MCC is used as a diluent to ease the tablet compaction. However, MCC is a self-disintegrating polymer which have low lubricant requirement due to extremely low friction and as very low residual die wall pressure. Due to higher concentrations of MCC increased the tablet disintegration time and improved the dissolution. Similarly, F12 (in the absence of both CCS and MCC) showed a higher MDT

(5.84 min). Formulations with higher mannitol concentrations (F12) showed decreased tablet dissolution levels.

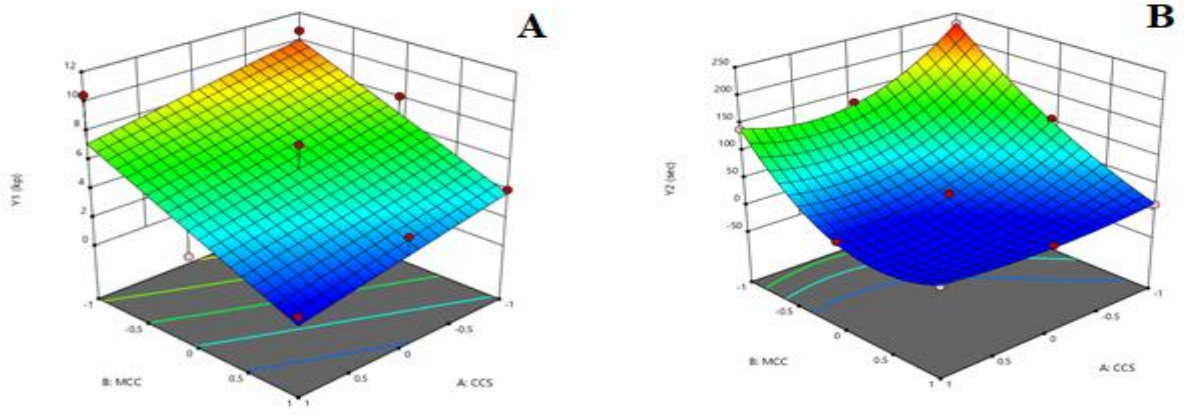
Optimization study outcome

The targeted response parameters were statistically analyzed by applying ANOVA at significant level and the significance of the model was calculated by Design & Expert software 12. The individual parameter was evaluated by using linear and quadratic models. This was generated between the factors dependent variables and independent variables for determining the level of factor which give optimum hardness, disintegration time and mean dissolution time.

The surface response diagram gives knowledge of the contribution of the variables and their interaction. The response curve map is shown for all response in Figure 7. Figure shows variables effect on Hardness (R1), Disintegration time (R2) and Mean dissolution time (R3). The model F-value for Hardness was found to be 7.95, for disintegration time 89.41 and for Mean dissolution time 7.93 which imply model is significant.

Table 6: The result of ANOVA.

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Ade. precision
Hardness	70.96	2	35.48	7.95	0.0086	0.6183	8.979
Disintegration Time	61105.61	7	8729.37	89.41	<0.0001	0.9921	29.293
Mean dissolution time	42.53	5	8.47	7.93	0.0084	0.8499	9.3588



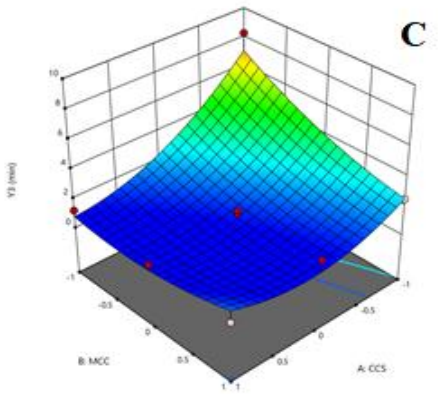


Figure 7: Response surface diagram of Hardness (A), Disintegration (B) and Mean dissolution time (C)

Stability studies

The stability test was accomplished as per the ICH guidelines. In order to assess their stability with respect to their physical appearance and release characteristics, accelerated stability studies were conducted for optimized formulation F5 and F6 at 40 ± 2℃ and 75 ± 5% RH according to ICH guidelines.

Table 5: Accelerated stability studies for optimized formulation F5 and F6.

Specification	Formulation	Parameters	Months		
			0	3	6
40±2˚C and 75±5%	F5	Drug content	88.9	88.61	87.96
		In vitro disintegration	29.25	29.15	28.95
		%CDR	85.4	85.03	84.69
	F6	Drug content	88.3	88.01	87.89
		In vitro disintegration	25.80	25.38	24.93
		%CDR	87.68	87.15	86.89

CONCLUSION

It concluded that, the dissolution rate and efficiency of Mefenamic acid was improved several times by cyclodextrin complexation using freeze drying method. The Face-CCD method was used to optimize the formulation and develop formulation. One of the major factors influencing the ODT properties of lyophilized formulations is the concentration of the diluent and superdisintegrants. F5 and F6 formulation showed increased disintegration time and dissolution time. Due to use of mannitol the hardness was increased (F7) and showed compatibility. Which the formulation formulated was simple to administer and easily disintegrated through the mouth, which addressed the issue of swallowing when taking medicine by paediatrics and geriatrics.

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