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EFFECT OF SUPERDISINTEGRATING AGENT ON ORAL DISINTEGRATING TABLET OF MEFENAMIC ACID AND DICYCLOMINE HYDROCHLORIDE COMBINATION

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ABSTRACT

Objective of this study was to formulate directly compressible oral disintegrating tablet of mefenamic acid and dicyclomine hydrochloride combination with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration and to show the effect of different concentration (1 - 4 %) of superdisintegrants such as crospovidone and croscarmellose sodium on disintegration time. Tablets were evaluated for wetting time, hardness, thickness, friability, weight variation, taste, drug content, in vitro disintegrating time and in vitro drug release. Other parameters such as wetting time, water absorption ratio were also evaluated. The disintegration time of the optimized batch was found to be 24 secs and drug release of mefenamic acid is 95.68% and dicyclomine was found to be 93.42%.

KEYWORDS: oral disintegrating tablet, mefenamic acid, dicyclomine chloride, superdisintegrants.

1. INTRODUCTION

Over the last decade, the demand for the development of oral disintegrating tablets (ODTs) has skyrocketed due to their significant impact on patient compliance. ODT are advantageous for people who have difficulty swallowing. Dysphagia has been reported to be common in all age groups, with a particular focus on the paediatric and geriatric populations, as well as institutionalised patients and patients suffering from nausea, vomiting, and motion sickness complications.[1] ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population. Oral disintegrating tablets are also known as quick dissolving tablets, mouth dissolving tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, the United States Pharmacopoeia (USP) approved these dosage forms as orally disintegrating tablets out of all of the above terms. The Food and Drug Administration (FDA) of the United States recently defined orally disintegrating tablet as "A solid dosage form containing a medicinal substance or active ingredient that dissolves quickly, usually within seconds, when placed on the tongue." Orally disintegrating tablets typically disintegrate in a matter of seconds to about a minute.[2,3] Because of their numerous advantages over other dosage forms, solid orals are the most popular, accounting for approximately 85 percent of the market. These formulations' therapeutic activity is obtained in a typical manner, such as disintegration followed by dissolution. Hence disintegration(superdisintegrants) has major role for facilitating drug activity and thus gain popularity among other dosage forms. One of the main reasons why businesses prefer ODTs over other delivery systems is that they are relatively easy to develop and often less costly. The use of superdisintegrants such as Cross connected carboxymelhylcellulose (Crosscarmellose) and crospovidone was the basic concept behind the development of these tablets. which provide quick disintegration of tablet after administration.[4]

1.1 Superdisintegrants

Superdisintegrants are pharmaceutical excipients that are added to tablets and some encapsulated formulations to promote the disintegration of tablet and capsule "slugs" into smaller fragments in an aqueous environment there by increasing the availability of surface area and promoting a more rapid release of the drug substance.[5]

Selection of superdisintegrants[6]

While superdisintegrants mainly affect the rate of disintegration, they may also affect mouth feel, tablet hardness, and friability when used in large doses. As a result, there are many ideal considerations to consider when choosing suitable superdisintegrants for a specific formulation:

- Produce rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.

- Be compatible enough to produce less friable tablets.
- Produce good mouth feel to the patients.
- Small particle size is preferred to achieve patient compliance.
- Have good flow, since it improves the flow characteristics of total blend.

Mechanism of Action:[7,8]

The following mechanisms are in charge of breaking tablets and capsule bulk contents into small pieces. They are classified into four types, which are as follows:

1. Swelling action: - When superdisintegrants come into contact with water, they swell (e.g. starch).

2. Capillary (wicking) action: - Disintegrants that do not swell facilitate disintegration in this mechanism due to their physical properties of low cohesiveness and compressibility. As a result, they provide porosity and capillary action for liquid penetration into the bulk, rupture intraparticulate bonds, and cause disintegration.

3. Combination action: -The combination of wicking and swelling action facilitates disintegration in this mechanism. E.g. Crosspovidone

4. Deformation: Starch (such as potato starch and corn starch) is thought to be elastic in nature, but due to high compaction force during tableting, the elasticity deformed to plasticity with energy rich potential. When these tablets are exposed to water, the energy potential of the deformed starch grain is activated, causing disintegration.

2. MATERIAL AND METHODS

2.1. Materials

Dicyclomine HCl and Mefenamic acid were received as gift sample from blue cross industries, Goa, India. Ball pharma, Bangalore, India. and Karnataka antibiotics, Bangalore, India. resp., Croscarmellose sodium, Crosspovidone, Micro Crystalline Cellulose, Magnesium Stearate, Starch were received from Modern Science Apparatus Pvt. Ltd., Nashik.

2.2. Methods

2.2.1. Drug and excipients compatibility studies

2.2.2. UV spectroscopy

The Mefenamic acid and Dicyclomine HCl drugs were scanned in UV Spectrophotometer to detect the λmax and to draw the calibration curve of the drug in 0.1N NaOH, 0.1 N HCl as a solvent resp., The drugs were used in concentration ranges of 2-10 ppm for Mefenamic acid and 100-500 ppm for Dicyclomine HCl. The spectra and calibration curve of both the drugs are as shown in Figure 1, 2, 3, 4 respectively.

2.2.3. FTIR spectral studies

The infrared spectra of Mefenamic acid and Dicyclomine HCl were recorded by SHIMADZU 84005 FTIR spectrometer, equipped with an Inferometer detector. The samples were made using the KBr disc method (2 mg sample in 100 mg KBr) and analysed in transmission mode. Over a frequency range of 4000–400 cm1, each spectrum was measured. The spectra shown in Figure 5, 6 respectively.[9]

2.3. Method of preparation of powder blend

Two excipients (Croscarmellose sodium and Crosspovidone) were used as superdisintegrants at four concentration levels. MCC is applied to maintain superdisintegrant concentration while also serving as a binder, and Mg stearate and starch are added at a constant stage. Formulations coded as F1 to F8 respectively. The formula's composition is shown in Table 1. All of the ingredients were blended for 15 minutes after being passed through a sieve mesh 60#. Finally, the blend was passed through mesh #40 for flow characteristic evaluation.

Table 1: Formula for oral disintegrating tablet of Mefenamic Acid and Dicyclomine HCl.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Mefenamic acid	250	250	250	250	250	250	250	250
Dicyclomine HCl	10	10	10	10	10	10	10	10
MCC	24	21	18	15	24	21	18	15
CCS	3	6	9	12	-	-	-	-
Crospovidone	-	-	-	-	3	6	9	12
Starch	9	9	9	9	9	9	9	9
Mg stearate	4	4	4	4	4	4	4	4
Flavouring agent	q,s	q,s	q,s	q,s	q,s	q,s	q,s	q,s

2.4. Pre-formulation studies of pure drug and excipients

2.4.1. Bulk Density [10]

It is known as the untapped volume and which is expressed as gm / cm^3. divides the weight of the sample. The apparent bulk density (Bv) was calculated by placing a weighed quantity of powder (W) in a measuring cylinder and using the formula below to calculate volume (Bv).

BD =W/ Bv

Where,

BD =Bulk Density

W = Sample weight

Bv = untapped or bulk volume

2.4.2. Tapped Density

The volume was measured after a weighed amount of the sample powder was discharged into the measuring cylinder. It is tapped 100 times on a hard surface at a height of 10cm until the volume of difference is reduced, at which point the final reading is measured and denoted by Tv. It is expressed in g/ml.

D = W/ Tv
Where,
W- Powder weight
Tv- Tapped volume

2.4.3. Angle of repose[11]
It is the measurement of the friction between the particles. The powder consists of individual particles of different sizes and shapes. It is taken into account in the flow of powder during powder mixing, the flow of powder in the hopper, and the flow between the dying cavity and punches. It is the angle formed by the horizontal plane and the powder's free-standing surface. A low angle of repose indicates that the particles are flowing or that the friction between them is high.
$\theta = \tan^{-1} (h/r)$
Where,
θ = the angle of repose,
h = height of the cone
r = Radius of the cone base

2.4.4. Carr's Compressibility Index
It indicates the flow properties of the powder. It is expressed in %.
Carr's index = $\frac{TD-BD}{TD} \times 100$
Where,
TD is tapped density
BD is bulk density

2.4.5. Hausner's Ratio[12]
It defines the flow property of powder that is measured by the ratio of tapped and bulk density. It shows good flow if the value is less than 1.25.
Hausner Ratio = $\frac{TD}{BD}$
Where, TD- Tapped Density
BD -Bulk Density

2.5. Evaluation of tablets
2.5.1. Hardness
The Pfizer Tablet Hardness Tester was used to measure hardness or tablet crushing strength, which is the force required to break a tablet in a diametric compression.

2.5.2. Thickness
Twenty tablets were chosen at random from the formulations and their thickness was measured individually with a Vernier calliper.

2.5.3. Friability test[13]
Friability of tablets was determined using Roche Friabilator. This device subjected the tablets to abrasion and shock in a plastic chamber that rotated at 25 rpm and dropped the tablets at a height of 6 inches with each revolution. A pre-weighed sample of tablets was placed in a friabilator and rotated for 100 revolutions. The tablets were then reweighed after being dusted with a soft muslin cloth.
Friability (F) = (1- Wo / W) x 10
Where,
Wo = weight of the tablets before the test.
W = weight of the tablet after the test.

2.5.4. Weight variation[14]
The weight variation test of tablet was conducted by weighing 10 tablets randomly. Calculating the average weight and individual weight. By comparing each tablet to the average tablet. The percentage difference in weight should be within acceptable limits. The percent deviation was calculated using the formula below.

Individual weight – Average weight / Average weight x 100 = percent Deviation

2.5.5. Water absorption capacity[15]
A piece of tissue paper folded twice was placed in small Petri dish (6.5cm) containing 5 ml water. A tablet was placed on the tissue paper to allow complete wetting. After that, the wetted tablet was weighed. The following equation was used to calculate the water absorption ratio R.
$R = \frac{Wa - Wb}{Wa} \times 100$
Where,
Wb = Weight of tablet before water absorption
Wa =Weight of tablet after water absorption

2.5.6. Wetting time
A folded piece of tissue paper was placed in a small Petri dish containing 6 ml of water. The time required for complete wetting was measured using a tablet placed on the paper.

2.5.7. Mouth feel[16]
Mouth-feel is critical, and patients should receive a product that feels pleasant. By placing the tablet on the tongue, one tablet from each batch was tested for the sensation. The mouth feel was evaluated using healthy human volunteers. A panel of five members used the time intensity method to evaluate taste. A sample equivalent to 40mg, i.e. a drug dose, was held in the mouth for 10 seconds. Tastes were recorded immediately, then after 10 seconds, 1, 2, 4, and 6 minutes. Volunteers' opinions on taste were rated by assigning different score values, such as 0 for good, 1 for tasteless, 2 for slightly bitter, 3 for bitter, and 4 for awful.

2.5.8. *In-vitro* disintegration test[17]
The test was conducted for six tablets of each formulation at 37℃ ± 0.5℃ using disintegration apparatus. Distilled water was used as disintegration medium. A tablet was placed in each of six tubes of the apparatus which consist of 10-mesh sieve at the bottom end of the basket rack assembly and one disc was added to each tube, complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds, by using the conventional disintegration apparatus.

2.5.9. Drug content uniformity[18]

Twenty tablets were weighed accurately and crushed into a fine powder. Mefenamic acid tablet powder weighing 25 mg equivalent weight was accurately weighed and transferred to a 100 ml volumetric flask. After shaking for 10 minutes, 50 ml of phosphate buffer (pH 7.4) was added. The volume was then increased to 100 by adding phosphate buffer. The solution in volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 285 nm. The amount of drug was estimated by using standard calibration. The percentage drug content was calculated. Same procedure was followed for dicyclomine hydrochloride.

2.5.10. *In-vitro* dissolution studies[19]

An in-vitro drug release studies of the prepared eight formulations of oral disintegrating tablets were conducted for a period of 18 minutes using an eight station USP type 2 apparatus (paddle type) (LABINDIA-DISOTEST, 6 F 622). The agitation speed was 50 rpm. Prepared tablets were added to 900 ml of phosphate buffer 7.4 at 37 ± 0.5° C and stirred at 50 rpm .5 ml samples were withdrawn at time intervals of 2,4,6,8,10,12,14,14,16,18 min. and filtered through Whatman's No. 41 filter paper. To maintain the volume of dissolution medium, an equal volume of fresh dissolution medium was replaced. The filtered samples were tested at the zero-crossing point of the respective drugs. The cumulative percentage of the labelled amount of drug released was determined.

2.5.11. Stability Studies[20]

The best formulation was charged for one month of stability studies at temperatures and relative humidity of 400°C / 75 percent RH. The parameters used to assess the effect of stress on tablets are as follows: Disintegration time, wetting time, drug content, and drug release percentage.

3. RESULTS AND DISCUSSION

- In this study, the presence of disintegrants may cause the matrix to be distorted, resulting in a larger surface area, allowing the super disintegrant to easily pick up water and thus a faster rate of dissolution. The dissolution rate is also affected by the concentration of superdisintegrants in the formulation.
- The drug mefenamic acid and dicyclomine hydrochloride was exposed to a superdisintegrants such as crospovidone and croscarmellose. They were used in different range of concentration like 1%, 2%, 3% and 4% respectively.
- The compositions of different formulations are presented in table 1.
- Standard calibration curve of Mefenamic acid and dicyclomine hydrochloride obeys the Beer's law. Both showed linear relationship between concentration and absorbance was shown in Figure 1 and 3. UV spectra of Mefenamic acid at 0 – 80 µg/ml was shown in Figure 2 and UV spectra of dicyclomine hydrochloride at 0 – 80 µg/ml was shown in Figure 4.
- The compatibility studies are conducted The IR spectral analysis of Mefenamic acid, dicyclomine hydrochloride and the physical mixture of Mefenamic acid, dicyclomine hydrochloride and polymers are presented in Figure 5,6 and 7 respectively. 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}, (NH group, C=O Stretching, O-H Stretching, C-H Stretching C-H bending, CH group,).
- The IR spectra of dicyclomine hydrochloride showed prominent absorption bands at 1134.07 cm^{-1}, 1193.85 cm^{-1}, 2929.67 cm^{-1}, 1719.45 cm^{-1}, 1712.85 cm^{-1}, (C-N stretching, C-O stretching, C-H stretching, C=O (ester) group, C=C stretching, C-H bending).
- The IR spectra of combination showed prominent absorption band at 3350.48 cm^{-1}, 3311.89 cm^{-1}, 2928.04 cm^{-1}, 1712.95 cm^{-1}, 1615.12 cm^{-1}, 2858.60 cm^{-1} (NH stretching, OH stretching, C-H stretching, C=C stretching, C=O stretching, C-H group).
- This result suggested that there was no chemical interaction between drugs and in their combination. The characteristic peaks appear in the spectra of physical mixture of combination of drugs and other excipient indicates no modification or interaction between the drug and excipients.
- The preformulation studies and evaluation parameters such as weight variation, friability, hardness, thickness, disintegration time, wetting time, dissolution rate, and assay for drug content were found to be satisfactory, as shown in tables 2, 3 and 4.
- It was found that there is extremely significant difference between two superdisintegrants and their concentration ranges.
- The disintegration time of formulations containing crosscarmellose is less (24 sec) in F4 compared to crospovidone and other concentrations of the formulations.
- The drug release of mefenamic acid in F4 was found to be 95.68% which is greater from other formulations and also drug release of dicyclomine hydrochloride in F4 was found to be 93.42% which is also greater from other formulations which is shown in table 5 and 6. Which is depicted in Figure 8,9,10 and 11 respectively.
- From the results we came to know that CCS is best disintegrant than crospovidone and higher the concentration of disintegrant decreases the disintegration time hence we will get rapid onset of action.

- Stability studies were carried out with selected formulation i.e. F4 and the results of studies indicated the formulation was stable at 400C / 75%RH as presented in table 7.

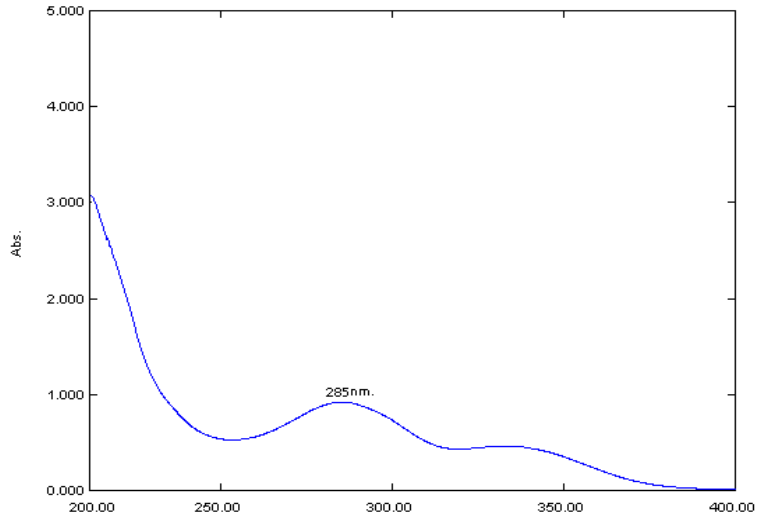

Figure 1: λmax of pure mefenamic acid.

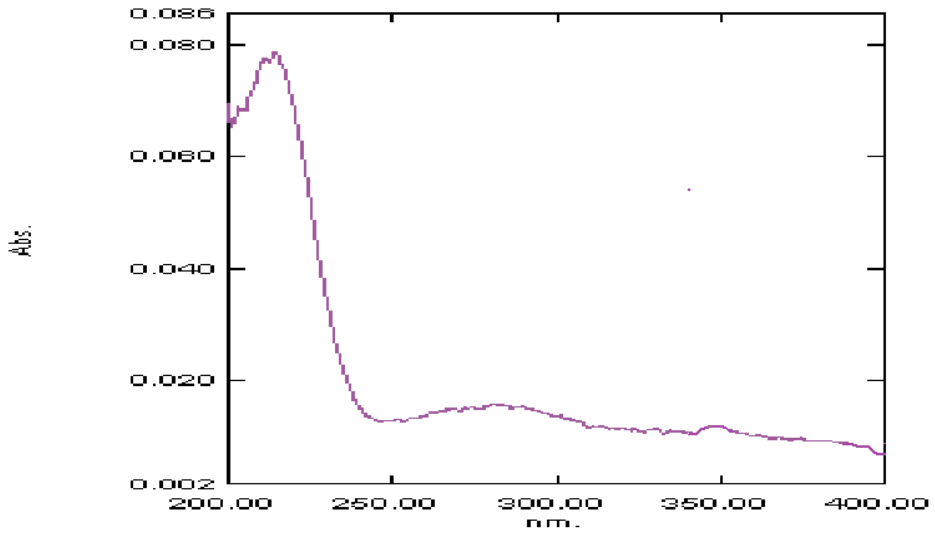

Figure 2: λmax of pure dicyclomine hydrochloride.

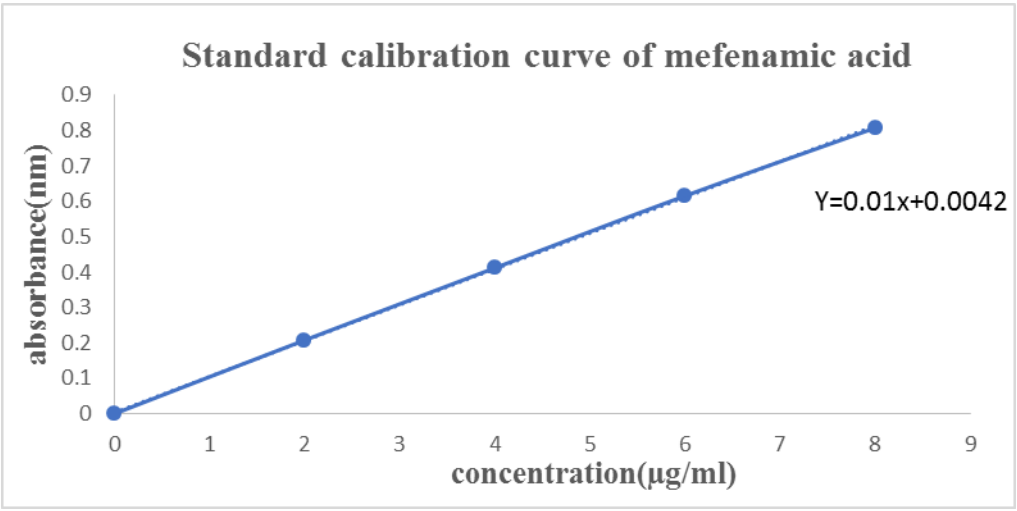

Figure 3: Standard calibration curve of Mefenamic Acid.

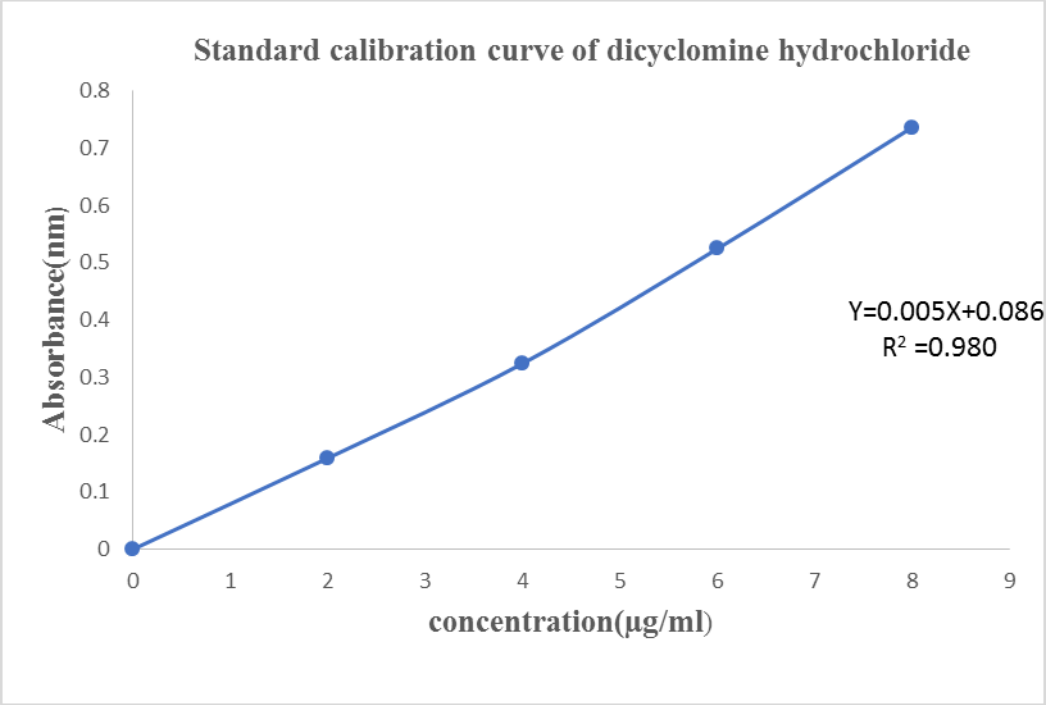

Figure 4: Standard calibration curve of dicyclomine hydrochloride.

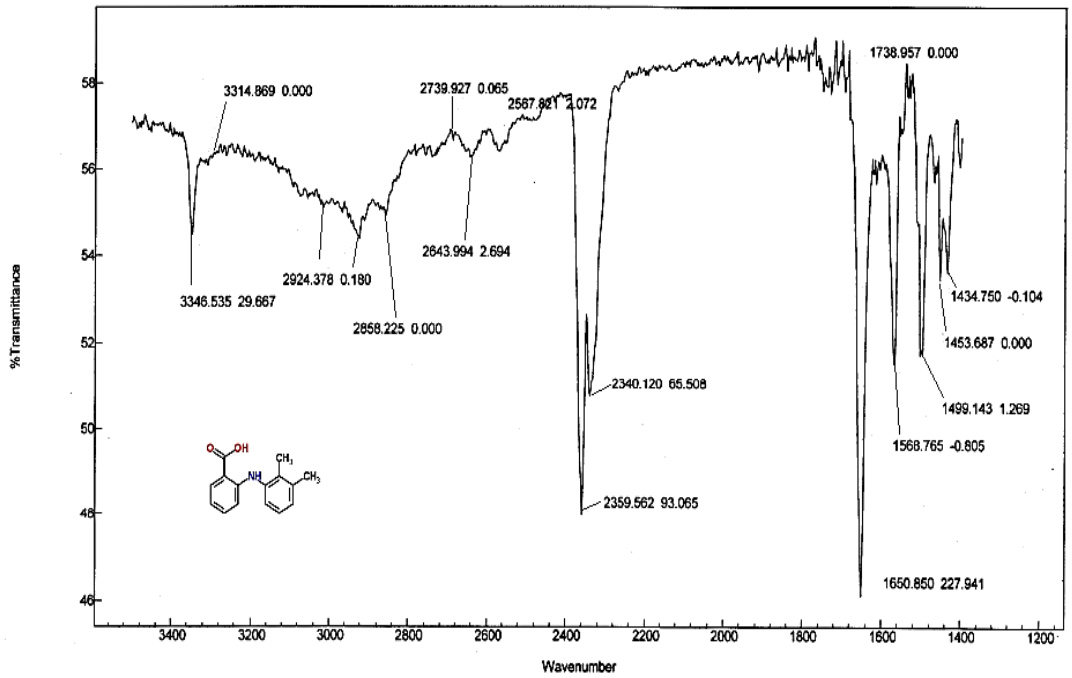

Figure 5: FTIR spectra of Mefenamic acid.

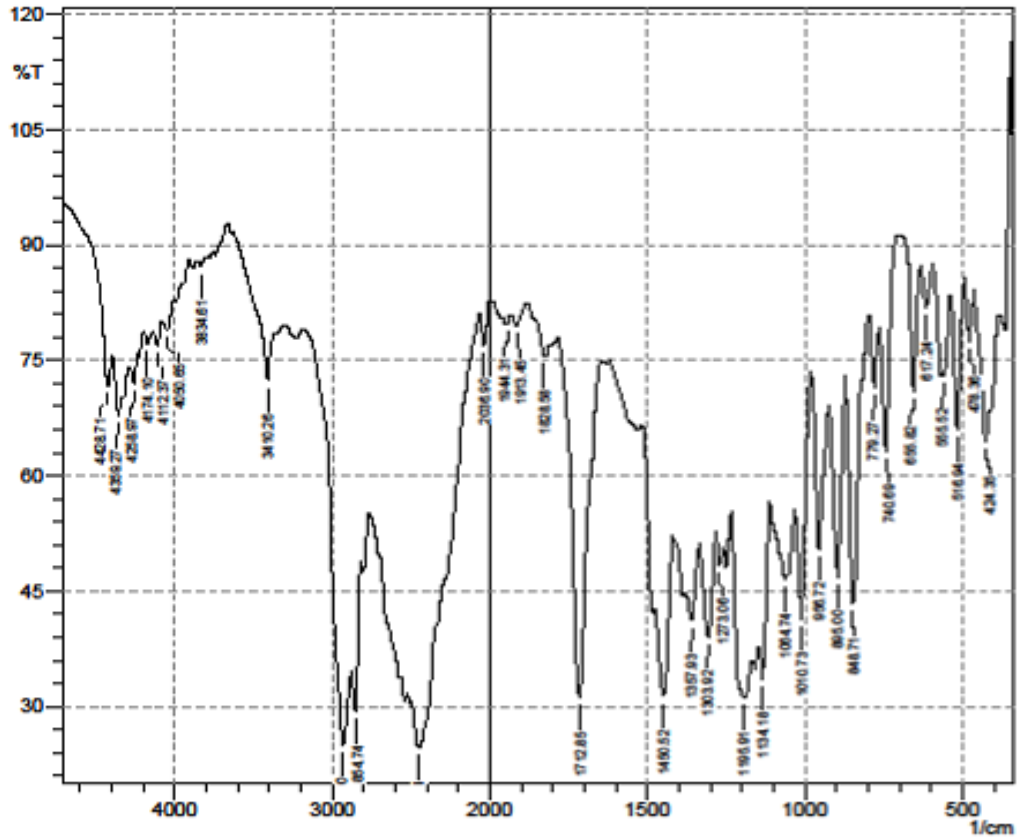

Figure 6: FTIR spectra of dicyclomine hydrochloride.

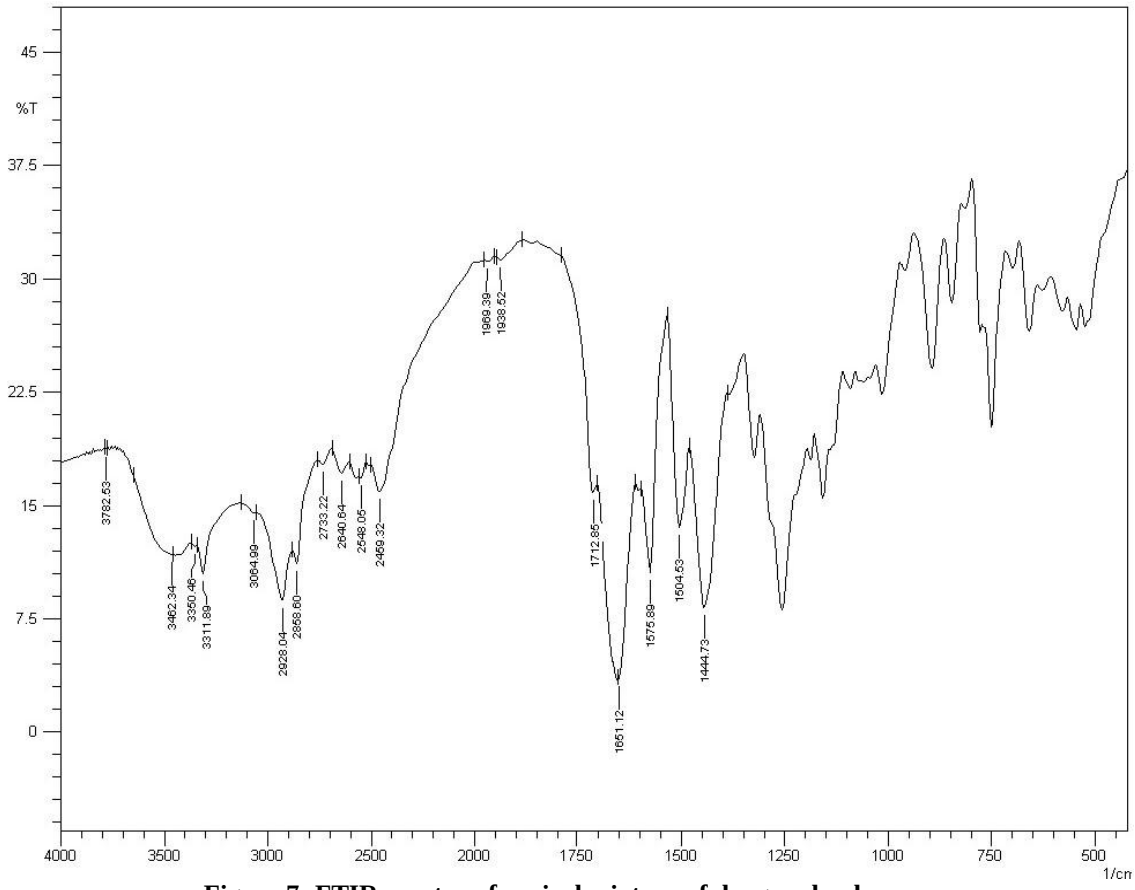

Figure 7: FTIR spectra of pysical mixture of drug and polymer.

Table 2: Evaluation of powder blend containing drug and Excipients.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Bulk density (g/cm3)	0.421±0.024	0.326±0.041	0.302±0.012	0.400±0.25	0.374±0.036	0.384±0.041	0.364±0.013	0.314±0.023
Tapped density (g/cm3)	0.423±0.012	0.483±0.034	0.480±0.021	0.485±0.023	0.458±0.045	0.461±0.032	0.462±0.031	0.492±0.025
Hausers ratio	1.17	1.02	1.05	1.12	1.36	1.23	1.24	1.14
Compressibility index (%)	13.25	14.52	14.12	14.26	13.36	13.28	13.42	13.16
Angle of repose	33.15	28.45	31.21	30.32	26.12	28.42	25.23	29.15

Table 3: Results of thickness, hardness, friability and weight variation of F1- F8.

Formulation batches	Thickness (mm) (±SD) (n=3)	Hardness (Kg/c2) (± SD) (n=3)	Friability (%) (±SD) (n=30)	Weight variation (±SD) (n=20)
F1	4.52±0.012	3.97±0.013	0.61±0.035	0.442±0.085
F2	4.23±0.005	4.25±0.023	0.45±0.015	0.435±0.025
F3	4.29±0.013	4.52±0.017	0.55±0.025	0.441±0.054
F4	4.64±0.031	4.36±0.006	0.37±0.014	0.444±0.013
F5	4.45±0.04	4.18±0.015	0.53±0.016	0.436±0.007
F6	3.98±0.058	4.96±0.016	0.46±0.012	0.437±0.018
F7	4.72±0.014	4.75±0.014	0.48±0.004	0.446±0.045
F8	4.82±0.032	4.85±0.012	0.45±0.017	0.445±0.019

Table 4: Results of wetting time, disintegration time, water absorption ratio and drug content of F1-F8.

Formulation batches	Wetting time (sec.) (±SD) (n=3)	Disintegration Time (sec.) (±SD) (n=3)	% Drug content Of MA (±SD) (n=3)	% Drug content Of DIC (±SD) (n=3)	Water absorption ratio (±SD) (n=3)
F1	46±2.3	47±2.51	93.25±0.63	94.21±0.87	75.42±1.45
F2	43±1.2	35±095	95.41±0.12	91.21±0.56	74.11±1.63
F3	42±0.6	25.90±0.51	96.23±0.45	92.25±0.64	72.61±2
F4	30±1.5	24±2.51	97.78±1.25	95.35±1.23	65.12±0.5
F5	41±2.5	52±3.12	96.89±0.63	93.01±1.56	77.2±0.35
F6	41±0.65	29.09±4.12	92.23±0.45	94.98±0.48	67.05±1.25
F7	38±2.1	27±1.56	96.04±0.54	89.08±0.45	69.36±2.45
F8	36±0.89	25±2.59	95.34±0.34	93.19±0.14	75.32±1.05

Table 5: ***In-vitro*** **drug release study of mefenamic acid.**

Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	27.25	29.36	33.25	32.28	27.56	25.19	25.56	28.45
4	35.89	37.67	45.95	38.63	33.42	33.91	32.42	33.12
6	39.18	41.28	49.57	46.33	36.11	37.77	39.11	37.45
8	45.75	48.19	55.26	55.15	40.28	41.92	42.28	41.29
10	51.38	53.29	68.98	62.39	51.48	53.24	51.48	52.64
12	59.49	60.58	74.12	70.85	60.34	61.99	61.34	61.91
14	66.47	72.95	82.69	79.21	74.98	73.28	72.98	75.24
16	74.33	85.52	88.35	88.55	82.33	83.55	81.33	84.94
18	87.53	91.50	93.45	95.68	89.62	92.48	89.02	90.37

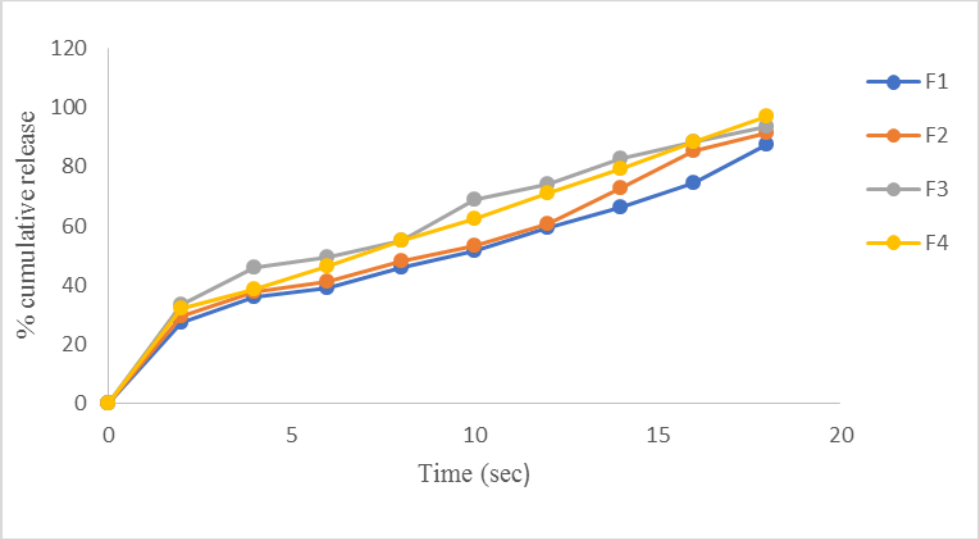

Figure 8: *In vitro* release profile of mefenamic acid of formulations F1-F4.

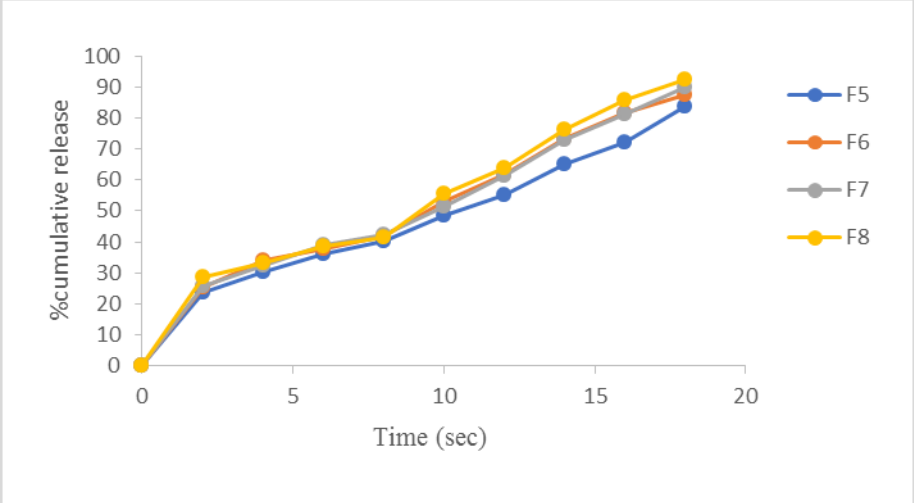

Figure 9: *In vitro* release profile of mefenamic acid of formulations F5-F8.

Table 6: *In-vitro* drug Release Study of Dicyclomine HCl.

Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	19.15	21.6	24.59	24.36	14.52	22.45	25.11	27.0
4	25.68	28.4	29.48	36.4	20.48	31.17	32.05	33.35
6	32.81	36.8	38.05	49.86	29.84	39.28	39.99	40.08
8	39.5	41.91	42	58.45	36.66	47.54	45.28	47.53
10	45.15	49.25	50.69	65.12	48.55	54.27	56.17	57.18
12	51.98	53.67	56.16	77.47	55.28	61.52	63.48	64.28
14	60.35	61.71	65.30	86.91	62.39	70.08	71.95	72.59
16	67.95	68.11	74.08	91.54	69.17	75.22	78.62	80.27
18	73.89	79.43	85.10	93.42	77.25	82.95	88.52	91.78

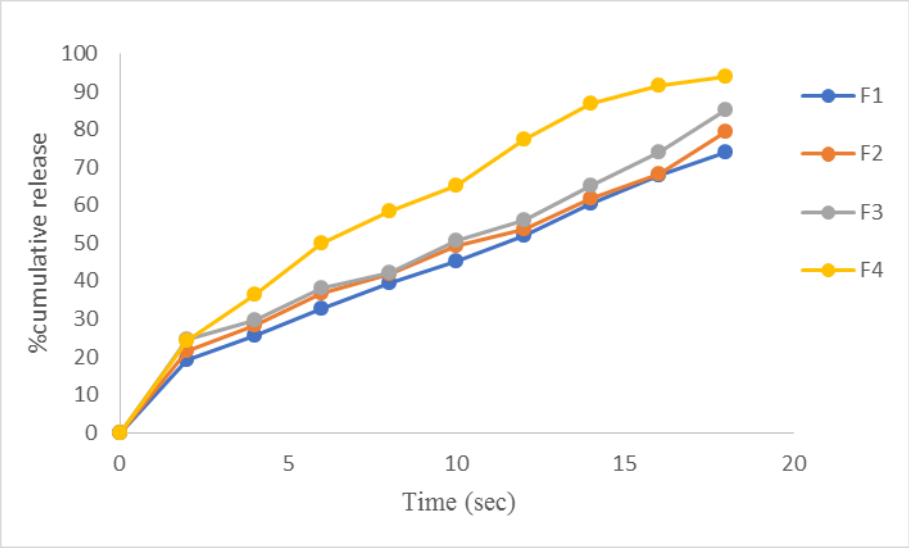

Figure 10: *In vitro* release profile of dicyclomine hydrochloride of formulations F1-F4.

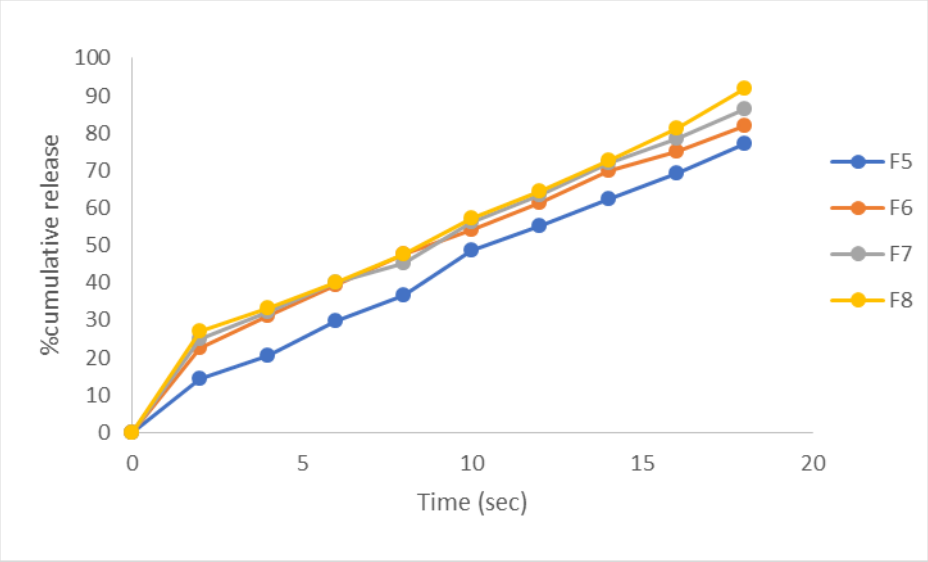

Figure 11: *In vitro* release profile of dicyclomine hydrochloride of formulations F5-F8.

Table 7: Accelerated stability studies for optimized formulation F4.

Temperature and RH	Parameters	Duration in months			
		0	1	2	3
40 ± 2˚C/75%	Wetting time	30.68	30.65	29.60	29.50
	Disintegration time	23.3	23.0	22.9	22.2
	%Drug content of MA	95.35	95.15	95.07	94.98
	%Drug content of DiH	93.45	93.12	92.98	92.74
	%CDR of MA	96.65	96.45	96.27	95.98
	%CDR of DiH	94.25	94.02	93.88	93.64

Where
DiH – dicyclomine hydrochloride.
MA – mefenamic acid.
CDR – controlled drug release.

4. CONCLUSION

From the present study it may be concluded that oral disintegrating tablet of mefenamic acid and dicyclomine hydrochloride can be formulated by direct compression method by using superdisintegrant (Crosspovidone (PPXL) and crosscarmellose) as superdisintegrant. The highest concentration 4% of crosscarmellose was found to be best among the different concentration of superdisintegrants. The formulation F4 was selected to be the best formulation among all the formulations. The proposed oral disintegrating formulations possess ideal

and reproducible characteristics of disintegration time, wetting time, enhanced dissolution and compatibility between drug and polymers, thus give better patient compliance compare to conventional tablet of mefenamic acid and dicyclomine hydrochloride.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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