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MOUTH DISSOLVING TABLETS OF TOLFENAMIC ACID: DESIGN FORMULATION AND INVITRO EVALUATION

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Abstract:

The study aimed to create easily dissolving tablets for an anti-nausea drug using synthetic substances that speed up disintegration. The Cross carmellose sodium (2-8%) from a synthetic source using direct compression. Testing involved extracting the drug from the prepared tablets with solutions of 0.1 N HCL and pH 7.2 phosphate buffer, measuring absorbance at 262.7nm. Post-compression tests were also conducted.

These tests included examining how the drug was released in different solutions, stability over six months at 40ºC/75% RH, and any interactions between the drug and other substances using IR spectroscopy. The formulations with 8% cros carmellose sodium , stood out as the most promising (FM8) formulation.

Short-term stability assessments of these successful formulations showed no significant changes in drug content or in how quickly they dispersed in solution ($p<0.05$). IR spectroscopy revealed no interactions between the drug and other components. Overall, this study indicates that natural disintegrants, particularly CCS outperformed other ones, resulting in improved dissolution of the drug.

Keywords: *Tolfenamic acid, Sodium starch glycolate, Cross carmellose sodium,Direct compression method,FTIR.*

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INTRODUCTION:

Oral drug administration remains highly favored, accounting for around 50-60% of all dosage forms. Solid forms are particularly popular due to their ease of use, precise dosing, convenience for self-medication, and patient compliance. However, a significant challenge arises for some individuals who experience difficulty swallowing (known as dysphagia). This difficulty becomes pronounced in situations where water is not readily available, like during motion sickness, sudden coughing fits from common colds, allergic reactions, or bronchitis, making conventional tablets hard to ingest. Consequently, there's been a growing interest in tablets that dissolve or disintegrate rapidly in the mouth, offering a solution to such challenges.[1-3]

Mouth dissolving tablets (MDTs) cater not only to those with swallowing problems but are also suitable for active individuals. These tablets go by various names such as "fast-melting," "fast-dissolving," "oral disintegrating," or "orodispersible" tablets. As per the European Pharmacopoeia, a "mouth dissolving" tablet refers to one that swiftly disperses in the mouth before being swallowed. Fast dissolving tablets are those that, when placed on the tongue, instantly disintegrate, releasing the drug to dissolve or disperse in saliva.[4-6]

The rapid dissolution of these tablets in saliva leads to faster drug absorption, thereby hastening the onset of the drug's clinical effects.[7] This aspect highlights the crucial link between the speed of drug dissolution, absorption, and the onset of therapeutic action.

MATERIALS AND METHODS:

Tolfenamic acid was acquired from Karnataka Antibiotics Pvt. Ltd., located in Bangalore. Sodium Starch Glycolate was obtained from Vijlak Pharma Ltd. in Mumbai. All other necessary ingredients were sourced from SD Fine Chemicals Pvt Ltd, based in Mumbai.

Calibration Curve Preparation for Tolfenamic acid:

The procedure involved dissolving 100 mg of Tolfenamic acid in 100 ml of distilled water by agitation in a volumetric flask (yielding a concentration of 1000 µg/ml). From this solution, 1 ml was withdrawn and diluted to 50 ml with distilled water, resulting in a concentration of 20 µg/ml (considered as the stock solution).

Subsequently, various concentrations (2, 4, 6, 8, and 10 µg/ml) were prepared by further dilution from the stock solution using distilled water. The absorbance of these diluted solutions was measured at a wavelength of 272.6nm, and a graphical representation was created using the collected data (refer to figure no.1, illustrating the spectrum of Tolfenamic acid drug). The absorbance values corresponding to different concentrations are presented in table no.4.

The method involved dissolving 100 mg of Tolfenamic acid in 100 ml of pH 7.2 phosphate buffer by agitation in a volumetric flask (yielding a concentration of 1000 µg/ml). From this solution, 1 ml was withdrawn and diluted to 50 ml with pH 7.2 phosphate buffer, resulting in a concentration of 20 µg/ml (considered the stock solution) Subsequently, various concentrations (2, 4, 6, 8, and 10 µg/ml) were prepared by further dilution from the stock solution using pH 7.2 phosphate buffer. The absorbance of these diluted solutions was measured at 272.6nm, and a graphical representation was constructed using the obtained data (refer to figure no.2, illustrating the spectrum of Tolfenamic acid drug). The absorbance values corresponding to these concentrations are detailed in table no.5.

The formulation of mouth dissolving tablets (MDTs) involved selecting the most effective synthetic and synthetic superdisintegrants—namely, Cross carmellose sodium and Plantago ovate. Before incorporating these superdisintegrants into the tablet formulation, they underwent a screening process to ensure their compatibility with other excipients for compression using the direct compression method. These superdisintegrants exhibited favorable properties: upon contact with liquid, they facilitated the breakdown of the tablet into smaller particles by swelling, hydrating, altering volume, and inducing a disruptive change within the tablet structure.

This study aimed to utilize the direct compression method with the assistance of synthetic superdisintegrants in developing mouth dissolving tablets of Metoclopramide hydrochloride. In the market, Metoclopramide hydrochloride tablets are available in 5mg and 10mg doses, with the 10mg dose selected for this particular investigation.

The formulation development for mouth dissolving tablets in this study primarily revolved around the selection and concentration of synthetic superdisintegrants. Different concentrations (ranging from 2% to 8%) of these superdisintegrants were utilized to achieve tablets with desirable physical properties. The formulation included various ingredients such as Microcrystalline cellulose and

mannitol as directly compressible diluents, magnesium stearate and talc as lubricants, aerosil as a flow promoter, aspartame as a sweetening agent, and pineapple flavor to enhance palatability.

The preparation of powder blends for these mouth dissolving tablets involved a systematic process. The ingredients listed in Table no. 1 were individually sifted through a 60-mesh sieve and collected. Subsequently, they were accurately weighed and combined following a specific sequence. Initially, Microcrystalline cellulose, Mannitol, and Super disintegrants were weighed and homogeneously mixed in a glass mortar using a pestle. Then, the Drug and Aspartame were incorporated into this first mixture. Following this, Magnesium stearate, Talc, and Aerosil were added and thoroughly mixed. Finally, the flavoring agent (Pineapple flavor) was introduced and mixed for 10-20 minutes.

Before the tablet preparation phase, the blended mixtures of all formulations underwent compatibility studies using IR spectroscopy. Additionally, various pre-compression parameters like Angle of repose, Bulk density, Tapped density, Percentage compressibility, and Hausner ratio were assessed.

Tolfenamic acid mouth dissolving tablets were created using a direct compression method, generating nine formulations labeled FM0 to FM8, utilizing the ingredients listed in Table no.1. Throughout all formulations, the total tablet weight was maintained at 150mg. The process involved sieving all ingredients separately through a 60-mesh sieve and then accurately weighing and sequentially mixing them.

Initially, microcrystalline cellulose, mannitol, and super disintegrants were weighed and blended in a glass mortar using a pestle. Subsequently, the drug and aspartame were combined and added to this initial mixture. Following this, lubrication was performed by integrating magnesium stearate, talc, and aerosil into the blend. Finally, the flavoring agent was included in the mixture. The resulting powder blend was then compressed using 8 mm round flat-faced punches within a 16-station rotary tablet compression machine from Cadmach Machineries Ltd., maintaining a consistent compression force across all formulations.[8-10]

The manufactured mouth dissolving tablets underwent a series of post-compression assessments, including hardness, friability, thickness, weight variation, in-vitro dispersion time, wetting time, water absorption ratio, drug content, in-vitro disintegration time, and in-vitro dissolution testing.

Table no. 1: Formulation of Tolfenamic acid Mouth Dissolving Tablets

S.N0	Ingredients (mg/tab)	FM0	FM1	FM2	FM3	FM4	FM5	FM6	FM7	FM8
1	Tolfenamic acid	200	200	200	200	200	200	200	200	200
2	Metoclopramide Hcl	10	10	10	10	1	10	10	10	10
3	Cross carmellose sodium	--	3	6	9	12	--	--	--	--
4	Sodium starch glycolate	---	---	---	---	---	3	6	9	12
5	Microcrystalline cellulose	50	50	50	50	50	50	50	50	50
6	Aspartame	5	5	5	5	5	5	5	5	5
7	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
8	Talc	1.5	1.5	1.5	1.5	1.5	1	1	1	1
9	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
10	Pineapple flavour	0.5	0.5	0.5	0.5	0.5	1	1	1	1
11	Mannitol	30	27	24	21	19	27	24	21	19
	TOTAL	300	350	300	300	300	300	300	300	300

The prepared powder blend underwent assessment through various parameters using specific methods:[11-14]

Angle of Repose:
The angle of repose represents the maximum angle achievable between the surface of a pile of powder and the horizontal plane. This angle is indicative of the flow properties of the powder. The angle of repose was determined using the fixed funnel method. A funnel was fixed to a stand at a specific height (h), with graph paper laid on a flat horizontal surface below it. The powder blend was allowed to freely fall onto the paper through the funnel until the apex of the conical pile just touched the funnel's tip. Measurements of the pile's height and radius were taken to calculate the angle of repose using the formula provided.

Bulk Density:
Bulk density refers to the ratio of the total mass of powder to the bulk volume of powder. For measurement, precisely weighed 2g of powder blend (passed through a 20 mesh sieve) was placed into a 10ml graduated measuring cylinder. The initial volume observed after adding the powder is known as the bulk volume. Bulk density was then calculated using the formula: Mass of the powder / Bulk volume.

Tapped Density:
Tapped density indicates the ratio of the total mass of powder to the tapped volume of powder. The procedure involved placing an accurately weighed amount of powder blend into a measuring cylinder. The volume was measured by tapping the powder 500 times, and the resulting volume (tapped volume) was noted. Tapped density was calculated using the formula: Mass of the powder / Tapped volume.

Compressibility Index:
The compressibility index signifies the flow properties of the powder and is expressed as a percentage. It relies on the bulk density and tapped density measurements. The percentage compressibility of the powder blend was determined using a formula derived from these densities.

Hausner's Ratio:
Hausner's ratio serves as an indirect indicator of powder flow ease. It was calculated using a specific formula derived from the bulk density and tapped density measurements.

Post-Compression Assessment of Powder Blend (6-9):

Thickness:
The thickness of the tablets was measured using Digital Vernier Calipers. It primarily depends on die filling and the physical characteristics of the material when subjected to compression force. Mean and standard deviation values were calculated from measurements taken from three randomly selected tablets of each formulation. The thickness is expressed in millimeters (mm).

Hardness:
The Monsanto hardness tester was employed to determine tablet hardness. A tablet was held between fixed and moving jaws, and the scale was adjusted to zero before gradually increasing the load until the tablet fractured. The load value at fracture provides a measure of tablet hardness. Mean and standard deviation values were calculated from measurements taken from three randomly selected tablets of each formulation. Hardness is expressed in kilograms per square centimeter (kg/cm^2).

Friability:
The friability test assesses tablet resistance to abrasion and shock. A Roche friabilator was utilized to measure the percentage friability of the tablets. This device subjects the tablets to combined abrasion and shock within a plastic chamber revolving at 25 revolutions per minute (rpm), dropping the tablets from a height of 6 inches in each revolution. Pre-weighed tablet samples underwent 100 revolutions, were then removed, de-dusted using a soft muslin cloth, and reweighed. The weight loss should not exceed 1.0%. Percentage friability was calculated using a specific formula based on the initial and final weights of the tablets.

The weight variation test involves randomly selecting twenty tablets from each batch, weighing them individually, calculating the average weight, and comparing each tablet's weight to this average. For the tablets to pass this test, no more than two tablets can exceed a certain percentage limit, and none should differ by more than two times the specified limit.

The in-vitro dispersion time is determined by placing a tablet into a Petri dish with 10ml of pH 7.2 phosphate buffer solution at 37± 0.50°C. Three tablets are randomly chosen from each batch to measure the time required for complete dispersion, expressed in seconds.

To measure wetting time, a folded tissue paper in a Petri dish containing 6ml of water is used. The tablet is placed on the paper, and the time it takes for complete wetting is measured in seconds. The water temperature is maintained at 37°C, and the wetting time represents the tablet's disintegration when stationary on the dish.

The water absorption ratio is determined by placing a tablet on folded tissue paper in a Petri dish with 6ml

of water. After measuring the time for complete wetting, the tablet is weighed before and after absorption. The absorption ratio, R, is calculated using the formula R = 100 (Wa - Wb) / Wb, where Wa is the weight after absorption and Wb is the weight before absorption.

Disintegration time refers to the breakdown of a tablet into smaller particles. The in-vitro disintegration time is determined using an apparatus following specifications from the Indian Pharmacopoeia (I.P.). One tablet is placed in each of six tubes with a disc, immersed in pH 1.2 solution at 37°± 2°C, and the apparatus is operated at a specific cycle rate for testing maintained at a temperature range of 37° ± 2°C, the duration in seconds required for complete tablet disintegration, leaving no detectable mass in the apparatus, was measured and recorded.

For drug content assessment, three tablets were crushed, yielding a powder equivalent to 10mg of the drug. This powder was then dissolved in 100ml of pH 1.2 phosphate buffer in a volumetric flask. After filtration, suitable dilutions were prepared, and the final solution was analyzed using a Shimadzu UV-2450 UV-visible spectrophotometer at a wavelength of 272.6nm.

In vitro dissolution studies of mouth-dissolving tablets were conducted in a USP type-II dissolution apparatus (Electrolab) with a paddle stirrer. The dissolution medium used was 900ml of pH 7.2 phosphate buffer, maintained at a constant temperature of 37±0.5ºC, and stirred at 50 rpm. Single tablets were utilized in each test. Samples of the dissolution medium (5ml) were periodically withdrawn using a syringe fitted with a pre-filter, and their drug release was analyzed at 272.6nm. The withdrawn volume was replaced with fresh dissolution medium. The cumulative percentage of drug released was computed and graphed over time, with detailed results presented in tables and figures.

The obtained in vitro release profiles for all formulations underwent data treatment in different modes for kinetic study analysis:

Zero-order kinetic model: Plotting cumulative % drug released against time.

First-order kinetic model: Graphing log cumulative percent drug remaining versus time.

Higuchi model: Analyzing cumulative percent drug released versus the square root of time.

Korsmeyer equation/Peppas model: Representing log cumulative percent drug released versus log time.

Zero-order kinetics can be anticipated using the equation:

$At = A0 - k0t$

Where,

At stands for the drug release at time 't'

A0 represents the initial drug concentration.

k0 signifies the zero-order rate constant (hr-1).

When the data is graphed as cumulative percent drug release against time, a linear plot indicates compliance with Zero-order kinetics. The slope of this line equals the Zero-order release constant k0.

First-order kinetics are anticipated based on the equation:

$Log\ C = log\ Co – Kt / 2.303$

Where,

C denotes the amount of drug remaining at time 't'

Co represents the initial amount of drug.

K stands for the first-order rate constant (hr-1).

When the data is plotted as log cumulative percent drug remaining against time, a linear relationship signifies adherence to first-order kinetics. The constant 'K1' can be derived by multiplying 2.303 with the slope value.

Higuchi's model explains drug release from matrix devices via diffusion using the equation:

$Q = [DЄ / ι (2A – ЄCs) Cst]\ ½$

Where,

Q represents the amount of drug released at time 't'

D signifies the diffusion coefficient of the drug in the matrix.

A denotes the total amount of drug in a unit volume of the matrix.

Cs stands for the solubility of the drug in the matrix.

Є represents the porosity of the matrix.

ι denotes tortuosity.

T signifies time (in hours) at which the amount 'q' of drug is released.

This equation can be simplified under certain assumptions Assuming 'D', 'Cs', and 'A' remain constant, the equation simplifies to:

When the data is plotted according to this equation, wherein cumulative drug release is plotted against the square root of time, a linear relationship indicates drug release occurring through a diffusion mechanism. The slope of this line equates to 'K'.

The Korsmeyer Equation, also known as the Peppas Model, was employed to investigate the drug release mechanism from the liposomal solution. This well-known exponential equation is commonly used to describe drug release behavior from polymeric systems.

$Mt / Mα = Ktn$

Where,

Mt / Mα represents the fraction of drug released at time 't'.

K is a constant that encompasses the structural and geometrical characteristics of the drug polymer system.

'n' denotes the diffusion exponent linked to the release mechanism.
By applying the logarithm to both sides, the equation simplifies to:
Log Mt / Mα = Log K + n Log t
Stability studies aim to assess the drug product's ability to maintain the specifications ensuring its identity, strength, quality, and purity (FDA, 1987).

These studies, conducted following ICH guidelines, are designed to accelerate the chemical or physical degradation of the drug substance or product using exaggerated storage conditions. [14]
Generally, stability studies are categorized into two types:
Short-term stability studies
Long-term stability studies

Table no: 2: Stability conditions according to ICH guidelines

Types	Conditions		Minimum time period at submission (month)
	Temperature (^{0}C)	Relative humidity(%)	
Short-term testing	40 ± 2	75± 5	6
Long-term testing	25± 2	60± 5	12

Method:
Various formulations were kept under different storage conditions at elevated temperatures: 25°C ± 20°C / 60% ± 5% RH and 40°C ± 20°C / 75% ± 5% RH for a duration of 90 days. Samples were withdrawn at 30-day intervals to assess physical changes, hardness, friability, drug content, and the percentage of drug release.[15]

PHYSICOCHEMICAL EVALUATION OF DRIED POWDERED MUCILAGE[12-14]
The following physicochemical tests were conducted on mucilage:
Organoleptic properties: Assessment included the physical appearance, color, odor, and taste of the dried powdered mucilage.

Solubility test: The solubility of the dried powdered mucilage was determined by adding a small amount to a solvent such as water.

Total ash: The total ash content was determined using 1 gram of dried powdered mucilage.

Loss on drying: This test involved determining the moisture content of an appropriate quantity of dried powdered mucilage at 105°C for 5 hours.
LOD (%) = (Weight of water in the sample / Weight of dry sample) × 100

Swelling factor: Measured by placing 1 gram of the drug in a 25 ml measuring cylinder with 20 ml of water, occasionally shaking. The volume occupied by the substance after 24 hours of wetting was recorded.
Flow properties of dried mucilage powder: Several characteristics including Angle of repose, Bulk density, Tapped density, Carr's index, and Hausner's ratio were determined to evaluate the flow properties of the dried mucilage powder.

TABLE NO. 3: PHYSICOCHEMICAL TESTS FOR SODIUM STARCH GLYCOLATE

S.No	Physico chemical parameters	Sodium starch glycolate
1	**Solubility**	**Slightly soluble in water**
2	**Loss on drying (%)**	**10±0.011**
3	**Swelling ratio**	**9±0.145**
4	**Total ash (%)**	**4±0.021**
5	**Angle of repose**	**26.56^0±0.251**
6	**Bulk density g/cm^3**	**0.42±0.055**
7	**Tapped density g/cm^3**	**0.46±0.085**
8	**Carr's index (%)**	**10.03±0.012**
9	**Hausners ratio**	**1.08±0.056**

All parameters (±SD) n=3

Determination of λ max and standard Calibration Curve of Tolfenamic acid in pH 7.2 phosphate buffer: 100 mg of Tolfenamic acid was dissolved in 100 ml of pH 7.2 phosphate buffer by shaking in volumetric flask (1000 µg/ml). 1 ml of this solution was taken and made up to 50 ml with pH 7.2 phosphate buffer, which gives 20 µg/ ml concentration (stock solution).
From the stock solution, concentrations of 2, 4, 6, 8 and 10 µg/ml in pH 7.2 phosphate buffer were prepared. The absorbance of diluted solutions was measured at 272.6nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated. The absorbance data of the concentrations are shown in table-5.

Table-5: Standard graph of Tolfenamic acid in pH 7.2 phosphate buffer(λmax 272.6nm)

Concentration's µg/ ml	Absorbance			
	I	II	III	Mean±SD
0	0.000	0.000	0.000	0.000±0.000
2	0.084	0.087	0.090	0.087±0.003
4	0.170	0.174	0.176	0.173±0.003
6	0.245	0.257	0.260	0.254±0.007
8	0.342	0.348	0.346	0.334±0.003
10	0.422	0.428	0.431	0.417±0.004

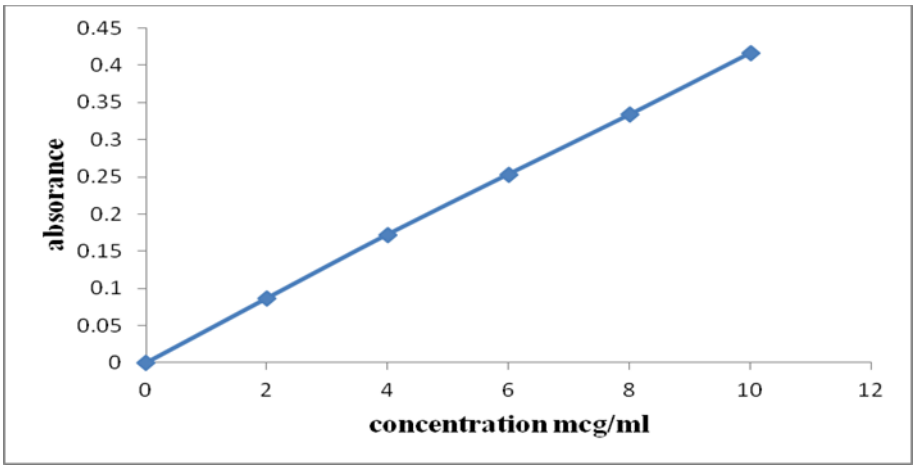

Figure-2: Standard graph of Tolfenamic acid in pH 7.2 phosphate buffer(λmax 272.6 nm

Powder blend for direct compression containing drug and various excipients were subjected for pre compression parameters (micromeritic properties) to study the flow properties of powder blend to achieve uniformity of tablet weight.
The bulk density of powder blend was found to be in the range of 0.27 to 0.37 g/cc, tapped density was found to be in the range of 0.36 to 0.54 g/cc, angle of repose was found to be in the range of 27.16 to 32.11°, Carr's index was found to be in the range of 10.75% to 19.88%, Hausner's ratio was found to be in the range of 1.11 to 1.19. All the formulations show good results and lies within the acceptable range which indicate good flow properties.

The results of all the pre compression parameters are given in table no.6

Table no 6: Pre-compression parameters of Tolfenamic acid powder blend FM0 – FM8

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
FM0	0.33	0.36	30.19	10.75	1.11
FM1	0.34	0.45	27.16	19.88	1.18
FM2	0.29	0.39	28.19	19.76	1.19
FM3	0.27	0.46	27.98	16.18	1.18
FM4	0.29	0.43	28.88	14.28	1.18
FM5	0.29	0.54	31.14	15.38	1.19
FM6	0.37	0.38	32.11	14.93	1.16
FM7	0.29	0.46	30.19	16.29	1.18
FM8	0.27	0.44	29.27	17.44	1.17

All results expressed as mean ± SD, n = 3

Post Compression parameters of Tolfenamic acid Mouth dissolving tablets:[15-18]

All the tablet formulations were subjected for organoleptic, physical and chemical evaluation. Shape and colour, Weight Variation, Thickness, Hardness, Friability, Drug Content, Wetting time, Water absorption ratio, Disintegration time, *In vitro* dispersion time, *and In-vitro* drug release studies were carried out.

Appearance of the tablets: Tablets were selected randomly from each formulation batch and examined under lens for shape and in presence of light for colour. Tablets showed concave, circular shape in white color and all tablets showed very good appearance without any capping or lamination and found satisfactory.

Thickness: Thickness of all the formulations were found in the range between 2.11±0.04 mm to 2.22±0.01 mm and summarized in table no.7.

Weight Variation: The percent Weight Variation of all the formulations were summarized in table. All the tablets were passed weight variation test as the % variation was within the pharmacopoeial limits of 7.5%. It was found to be from 146.4±1.69 to 150.5±0.58, the weight of the all tablets was found to be uniform due to good flow property and compressibility of all the formulations.

Hardness: The hardness of tablets was tested using Pfizer hardness tester to find out whether they could retain their physical shape or not. The hardness of all the tablets was found to be in the range of 2.81±0.1 kg/cm^{2}to 2.99±0.5 kg/cm^2 and the results were summarized in table no.7.

Friability: Tablet strength was tested by Roche Friabilator and the tablets of all formulations showed very good friability with less than **0.53%** which is well and within wide accepted range of Pharmacopoeia limit (1.0%) and results were given in table no.7.

Drug Content uniformity: The drug content uniformity was performed for all the formulations, the mean value and standard deviation of all the formulations were calculated, the low values of standard deviation indicates uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 99.28±1.52 to 101±2.02 percent (which was

within the acceptable limits of ±5%) and results were given in table no. 7.

Table no 7: Post Compression parameters of formulations FM0 – FM8

Formulation code	Weight Variation *	Thickness*	Hardness**	Friability**	Drug Content**
FM0	149.8±1.61	2.11±0.04	2.86±0.5	0.49	99.28±1.52
FM1	148.5±2.54	2.13±0.01	2.18±0.5	0.55	101±1.09
FM2	147.3±2.21	2.22±0.01	2.96±0.5	0.54	99.45±2.11
FM3	150.0±1.49	2.14±0.12	2.91±0.1	0.49	99.45±1.01
FM4	148.4±1.89	2.16±0.06	2.91±0.1	0.51	101.0±1.57
FM5	150.5±0.58	2.22±0.01	2.86±0.5	0.54	99.28±1.52
FM6	147.1±1.14	2.14±0.12	2.81±0.1	0.49	99.70±1.14
FM7	149.5±2.12	2.16±0.06	2.83±1.4	0.51	100±1.57
FM8	146.4±1.69	2.12±0.02	2.99±0.5	0.42	101±2.02

All results expressed as mean ± SD, n = 3 Water

absorption ratio:
The water absorption ratio of all the formulations was found to be 45±1% to 85.11±1.11 %. The results were depicted in Table.no.8.

Disintegration-Time:
The disintegration time of all the formulations was found to be 17±1.12 sec to 299±1.62 sec. The results were depicted in Table.no.8.

Wetting time:
The Wetting time of all the formulations was found to be 13.18±1.5 sec to 294±1.62 sec. The results were depicted in Table.no.8.

In vitro dispersion time:
The *In vitro* dispersion time of all the formulations was found to be 21.11±0.15 sec to 99±2 sec. The results were depicted in Table.no.8.

Table no 8: Post compression parameters of formulations FM0 – FM8

Formulation Code	Wetting time (sec)	Water absorption ratio (%)	Disintegration time (sec)	*In vitro* dispersion time (sec)
FM0	294±1.62	45±1	299±1.62	99±2
FM1	43.11±1.0	60.22±3.8	88 0.34	56.03±2.47
FM2	32.26±0.7	63.21±1.5	71 0.11	47.0± 2.10
FM3	29.33±1.52	70.75±1.01	47 0.29	38.42± 1.90
FM4	25.99±1.5	82.12±1.14	34 0.12	29.34± 0.70
FM5	39.64±2.08	68.12±1.61	69±1.55	42.66±1.52
FM6	26.32±1.01	76.46±2.9	56±1.82	37.66±1.52
FM7	20.19±1.12	80.46±2.9	37±2.05	32.33±2.51
FM8	13.18±1.5	85.11±1.11	17±1.12	21.11±0.15

All results expressed as mean ± SD, n = 3

***In-vitro* drug release studies**

Tablets containing Tolfenamic acid were studied for *In-vitro* drug release studies as per the procedure described in methodology. All formulations were subjected for dissolution studies. The samples were withdrawn at specified time intervals and analyzed by UV-Visible Spectrophotometer at 272.6 nm.

Drug release profile was studied using percentage drug release versus time (hr) plot. The results were depicted in Table No.9 to 11 and figure no 3 to 5. Formulations FM0, FM1, FM2, FM3 and FM4 showed 37.84±0.6 %, 63.08±2.78%, 69.69±2.78, 80.37±1.52% and 92.69±1.54%. Release of drug respectively at 30min.

Formulations FM5, FM6, FM7 and FM8 showed 75.08±2.78%, 80.69±2.78, 90.37±1.52% 98.25±1.65%
respectively at 30 minutes.

Among all formulations FM8 containing 8% cros carmellose sodium as a super disintigrant was found to be promising and has shown faster release of drug.

Table no 9: *In –Vitro* drug release characteristics of Tolfenamic acid without Superdisintegrants (FMO)

Time (min)	Cumulative % of drug release without Superdisintegrant (FMO)
0	**0**
05	**10.97±1.4**
10	**15.27±0.5**
15	**26.67±1.2**
20	**29.29±1.4**
25	**32.71±1.9**
30	**37.84±0.6**

All results expressed as mean ± SD, n = 3

Figure. No.3. %Cumulative amount of drug release Vs Time of FM0.

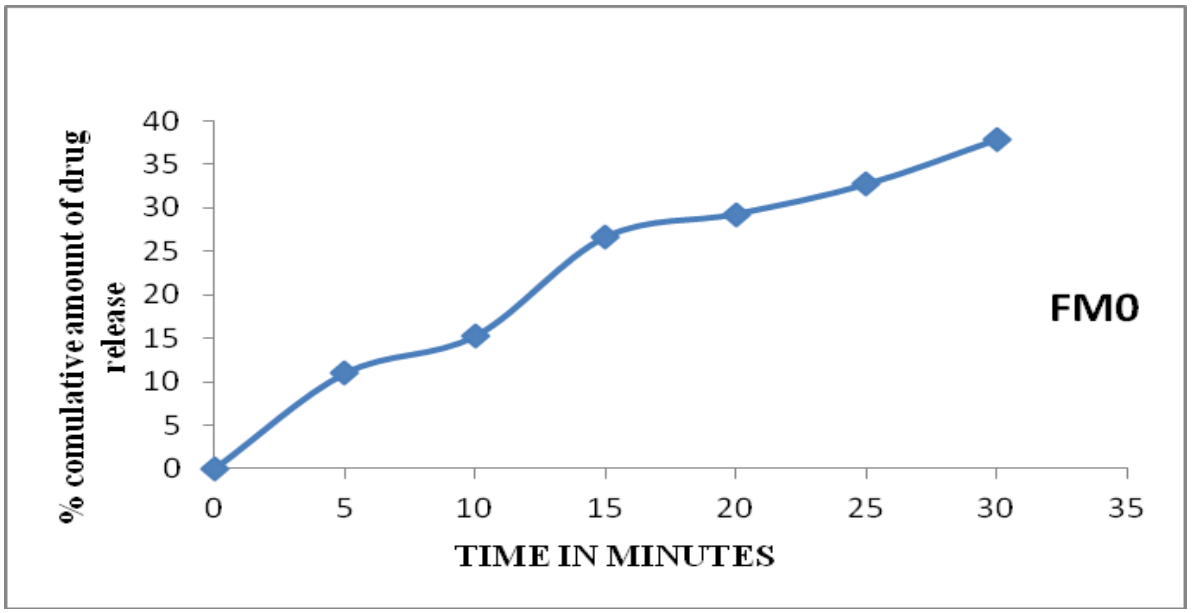

Table no 10: *In –Vitro* drug release characteristics of Tolfenamic acid with Croscarmellose sodium (FM1–FM4)

Time (Min)	Cumulative % of drug release with Croscarmellose sodium			
	FM1	FM2	FM3	FM4
0	0	0	0	0
05	23.34±1.00	26.75±1.54	34.05±0.54	39.55±1.24
10	28.70±1.34	38.20±1.43	45.92±1.37	56.83±2.04
15	39.39±2.01	47.16±2.17	58.23±2.05	66.80±1.51
20	47.50±2.67	58.92±2.53	67.73±0.84	73.77±1.58
25	59.22±1.45	65.70±1.73	76.80±1.54	78.52±1.05
30	63.08±2.78	69.69±2.78	80.37±1.52	92.69±1.54

All results expressed as mean ± SD, n = 3

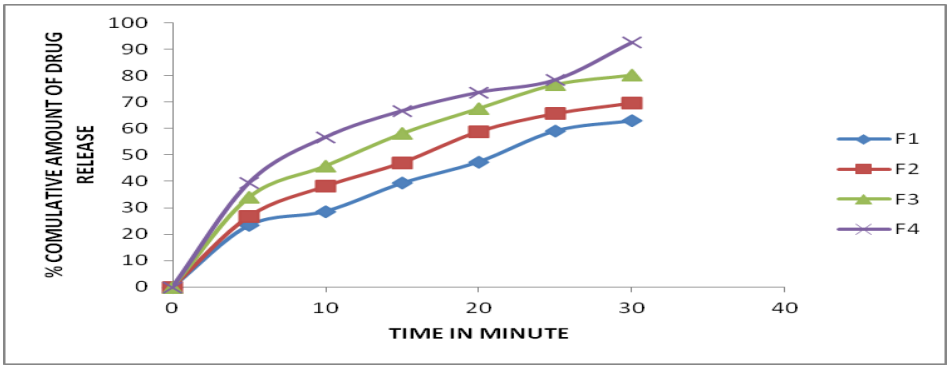

Figure. No.4. %Cumulative amount of drug release Vs Time of FM1 to FM4.

STABILITY STUDIES:

Short-term stability studies conducted on formulation (FM8) at 40^0C/ 75% RH for 3 months have shown no significant changes in physical appearance, drug content and *in vitro* dispersion time and dissolution and results were summarized in table 12.

Table no 12: Stability data for formulation Tolfenamic acid (FM8)

Name of Test	Initial	1st month	2nd month	3rd month	6th month
Physical Changes	No changes	No changes	No changes	No changes	No changes
Dissolution					
05 minutes	39.55±1.24	39.85±1.22	39.89±1.20	39.95±1.21	38.99±1.19
10 minutes	53.83±2.04	53.83±2.14	53.83±2.14	53.83±2.14	53.80±2.14
15 minutes	68.80±1.51	68.80±1.50	68.80±1.50	68.80±1.50	68.80±1.50
20 minutes	79.77±1.58	79.77±1.57	79.77±1.57	79.77±1.57	79.77±1.57
25 minutes	88.52±1.05	88.52±1.05	88.52±1.05	88.52±1.05	88.52±1.05
30 minutes	98.25±1.65	98.15±1.65	98.15±1.65	98.15±1.65	98.15±1.65
Assay (%)	98.25±1.65	98.15±1.11	98.11±1.10	98.11±1.10	98.11±1.10
Friability (%)	0.44	0.44	0.42	0.42	0.42
Disintegration (Sec)	17±1.12	17±1.12	17±0.99	17±0.75	17±0.15
Dispersion time (Sec)	21.11±0.15	21.11±0.19	21.11±0.21	21.11±0.26	20.11±0.29

All results expressed as mean ± SD, n = 3

Table no 11: *In –Vitro* drug release characteristics of Tolfenamic acid with Plantago ovate mucilage. (FM5– FM8)

Time (Min)	Cumulative % of drug release with Plantago ovate mucilage.			
	FM5	FM6	FM7	FM8
0	0	0	0	0
05	29.08±1.73	34.37±1.56	37.42±1.02	39.82±1.65
10	35.54±2.74	44.37±2.34	48.01±1.39	54.78±2.64
15	46.26±2.46	53.91±2.68	59.32±1.75	66.83±2.73
20	57.98±2.39	69.47±2.47	76.89±1.91	79.05±2.78
25	66.32±1.87	75.65±1.47	80.92±2.36	86.17±2.18
30	75.08±2.78	80.69±2.78	90.37±1.52	98.25±1.65

All results expressed as mean ± SD, n = 3

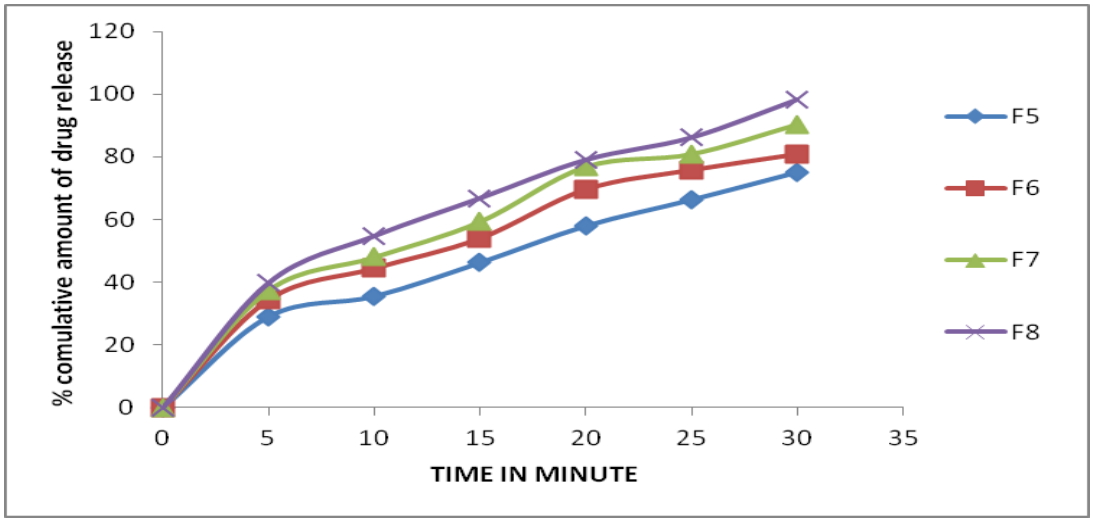

Figure. No.5: %Cumulative amount of drug release Vs Time of FM5 to FM8.

KINETICS STUDIES:

The *in-vitro* drug release data of the fast-dissolving tablets were evaluated kinetically, by Zero order, First order, Higuchhi, Peppas. The data were processed for regression analysis using PCP DISSO V3 Software. The regression coefficient (R) value for Zero order, first order, Higuchhi, Peppas, for all the formulations were shown in Table. No 13. The formulations FM8 follows zero order kinetics. The release of drug may be depending on disintegration time.

TABLE NO 13: KINETIC STUDIES OF TOLFENAMIC ACID MOUTH DISSOLVING TABLET:

Formulation code	Zero order (R^2 value)	First order (R^2 value)	Higuchi (R^2 value)	Korsmeyer-Peppas (R^2 value)
FM0	**0.9554**	**0.9671**	**0.9494**	**0.9589**
FM1	**0.9868**	**0.9790**	**0.9895**	**0.9802**
FM2	**0.9777**	**0.9929**	**0.9862**	**0.9678**
FM3	**0.9761**	**0.9942**	**0.9889**	**0.9842**
FM4	**0.9647**	**0.8887**	**0.9595**	**0.9280**
FM5	**0.9950**	**0.9775**	**0.9984**	**0.9967**
FM6	**0.9768**	**0.9845**	**0.9770**	**0.9460**
FM7	**0.9791**	**0.9598**	**0.9778**	**0.9458**
FM8	**0.9909**	**0.8216**	**0.9942**	**0.9904**

CONCLUSION:

- Mouth dissolving tablets of Tolfenamic acid were successfully formulated by employing direct compression method, using various synthetic super disintegrants.
- Firstly selection of cros carmellose sodium used as a vital super disintegrating agents. .
- The physicochemical parameters like pre-compression and post-compression evaluation were performed as per pharmacopeia standards and compatibility study was done by FTIR method.

Based on the above studies, following conclusions can be drawn:

- The FTIR studies indicated that the drug was compatible with the carriers, polymers and other excipients used in the dosage form.
- Pre-compression parameter results showed good flow properties.
- Mouth dissolving tablets of Tolfenamic acid were prepared by direct compression method.
- Croscarmellose sodium used as synthetic super disintegrants.
- Magnesium stearate is used as a lubricant. Talc is used as a glidant.
- Aspartame is used as sweetening agent.
- Post-Compression parameter results found to be optimum. Thus hardness of the tablets shown sufficient to withstand the shock. All the formulations tablets were found uniformity in weight.
- The drug content was uniform in all the tablet formulations indicating uniform distribution of drug within the matrices.
- Based on the *in-vitro* disintegration time and dissolution studies of Tolfenamic acid formulations FM8 containing superdisintegrant as cros carmellose sodium was found to be promising and showed a disintegration time 17±1.12 sec and drug release profile 98.25±1.65 respectively, when compared to the synthetic and other natural super disintigrant.
- The formulations subjected for kinetic studies and shown zero order kinetics.
- The stability studies carried out as per ICH guidelines for 3 months. Results showed that the formulations were stable and intact without any interaction.
- Finally, it was concluded that the MDTs of Tolfenamic acid formulations containing superdisintegrant as seeds of Sodium starch glycolate showed less disintegration time and *in-vitro* drug release study faster than the synthetic super disintegrant.
- Formulations were found to be complying with all the properties of tablets and the formulations were satisfactory.

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