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FORMULATION AND EVALUATION OF TOLFENAMIC ACID MOUTH DISSOLVING TABLETS USING DIFFERENT SUPERDISINTEGRANTS

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Abstract:

The current study aimed to create and assess mouth-dissolving tablets containing Tolfenamic acid using different superdisintegrants such as Sodium starch glycolate (SSG), Crospovidone (CP), and Microcrystalline Cellulose (MCC). Variations in the concentrations of these superdisintegrants were employed to enhance the release rates. Tablets were prepared using direct compression technique, incorporating varied concentrations of different superdisintegrants. Pre-compression and post-compression assessments including Bulk density, Tapped density, Angle of repose, Cars index, Hauser's ratio, etc., were conducted. Post-compression evaluations encompassed thickness, weight variation, hardness, friability, uniformity of drug content, and dissolution studies. The in-vitro drug release study in 0.1N NaOH for 5 minutes and in phosphate buffer pH 6.8 for 30 minutes indicated that formulations F4 and F8 exhibited the maximum drug release within 1 minute, attributed to the presence of Crospovidone, demonstrating cumulative drug releases of 99.86% and 99.97%, respectively. Consequently, these formulations were deemed optimal and subjected to stability studies over three months, during which their pre-compression and post-compression properties were re-evaluated, revealing no significant changes.

Keywords: *Mouth dissolving tablets, Tolfenamic acid, Sodium starch glycolate, Direct compression method.*

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INTRODUCTION:

The present study was aimed to develop the generic formulation of mouth dissolving tablets of Tolfenamic acid using different superdisintegrants. The selection of excipients a plays a vital in role in drug release.The selected excipients are necessary to instantly release its contents in the oral cavity. The mouth dissolving tablets compose and drug and the instant drug releasing excipients which offer undemanding approach in designing an mouth dissolving system[1]. A number of superdisintegrants have been investigated to develop in situ release of medicament, due to the ability of these superdisintegrants to release the drug in aqueous medium and to release of such drug by rapid disintegration. Mouth dissolving dosage form that mitigate the delibitating throbbing headache instantly as compared to that drug present in an conventional dosage form. Ex:Fast dissolving mouth disintegration tablets so tolfenamic acid is used for the treatment of migraine. Long-term therapy of Tolfenamic acid found to have some drawbacks, accumulation of drug in multi-dose long-term therapy, poor patient compliance and high cost. For the treatment of migraine, the dosage of conventional oral formulations of Tolfenamic acid is 400 mg per day (i.e. 200 mg twice daily) with an absolute bioavailability of 87 % ± 17 %, peak serum concentration of Tolfenamic acid (C*max*) of 1.6 ± 0.6 mcg/ml and mean elimination half-life (t½) of 3 to 6 hours, thus necessitating frequent dosing.[4,5] Tolfenamic acid is a nonsteroidal anti-inflammatory drug (NSAID) known for its analgesic and anti-inflammatory properties[2]. Mouth dissolving tablets (MDTs) offer a convenient dosage form that quickly dissolves in the mouth without the need for water, providing rapid onset of action and ease of administration.[8] These tablets are designed to disintegrate within seconds upon contact with saliva, allowing for swift absorption of the medication through the oral mucosa. Tolfenamic acid mouth dissolving tablets are particularly beneficial for individuals who have difficulty swallowing conventional tablets or require fast pain relief. The formulation of these tablets involves specialized techniques to ensure stability, effectiveness, and a pleasant taste for improved patient compliance.The formulation involving tolfenamic acid and metoclopramide, incorporating various synthetic superdisintegrants.Formulations like these are typically designed in pharmaceutical development to enhance drug dissolution and absorption rates. Superdisintegrants are excipients added to formulations to facilitate the breakup of tablets or capsules into smaller particles, aiding in faster dissolution and absorption in the body.[15-18]

When formulating a combination of tolfenamic acid and metoclopramide with different synthetic superdisintegrants, the choice of superdisintegrant can significantly impact the characteristics of the final dosage form. Superdisintegrants such as croscarmellose sodium, crospovidone, sodium starch glycolate, and others are commonly used in pharmaceutical formulations to promote rapid disintegration.[2-3]

The specific combination and ratio of these active pharmaceutical ingredients (APIs) with superdisintegrants would depend on various factors.[7-9]

Compatibility: Ensuring that the selected superdisintegrants are compatible with both tolfenamic acid and metoclopramide without affecting their stability or efficacy.

Dosage form: Whether it's intended for tablets, capsules, or another form. Different dosage forms might require different superdisintegrants or combinations thereof.

Dissolution profile: The desired rate of dissolution and absorption of the drugs will influence the choice of superdisintegrants.

Manufacturability: Considerations for manufacturing processes and the feasibility of producing the formulation.

Regulatory standards: Compliance with regulatory requirements and guidelines for pharmaceutical formulations.

Developing such a formulation involves a series of experiments and formulation studies to determine the most suitable combination, ratios, and manufacturing processes to achieve the desired characteristics, such as fast disintegration and efficient drug release.[7]

If you're working on a specific formulation or looking for more detailed information, consulting scientific literature, pharmaceutical formulation textbooks, or speaking with experts in pharmaceutical formulation and development would be advisable. Each formulation can be unique, and detailed research and experimentation are usually necessary to create an optimized formulation.[5-8]

MATERIAL AND METHODS:

Tolfenamic acid was obtained from Centaur Labs, Mumbai., Microcrystalline cellulose, Sodium starch glycolate,Crospovidone, Magnesium stearate, Talc was obtained from Merck chemicals and S.D fine

chemicals,Mumbai. Tablets were formulated using direct compression method using different superdisintegrants.

Pre-Compression Parameters:

Bulk density (Db):

Bulk density is elucidated that the ratio of mass of powder(w) to the bulk volume (Vb).Generally, the bulk volume is measured by weighing 25 g of blended mixture and transferred it into a 50 ml of measuring cylinder.[9] The volumes of blended mixture that are occupied in the measuring cylinder are taken as bulk volume and then calculate the bulk density by using formula.Bulk density (weight of granules (w)/ bulk volume (Vb)

Tapped density (Dt):

Tapped density is elucidated that the ratio of mass of powder (w) to the tapped volume (Vt). Approximately 50 g of granules are introduced into a 100 ml measuring cylinder. The volume occupied by the granules is noted initially.[10-13] Tapped volume is measured by tapping the cylinder (containing granules) on to hard wooden surface 3 times from a height of 1 inch at 2 second intervals. Tapped volume is the volume occupied by the same mass of powder after a standard tapping of measure.It is expressed in g/cc and is given by

Tapped density = weight of granules / tapped volume

Angle of repose:

Angle of repose is elucidated that the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose is calculated.

Procedure to determine angle of repose:

A glass funnel is fixed to the stand by using a clamp. Approximately 50 g of granules is passed through a 20 number mesh sieve and the obtained granules are transferred into the glass funnel, the orifice of the funnel blocked by the thumb. The thumb is removed from the orifice and the powder is emptied from the funnel.[12-17] The distance between the bottom of the funnel stem and the top of the powder pile must be 6.4mm. The height and radius of pile is measured with the ruler. The angle of repose is thus estimated by using above formula. A value for angle of repose ≥ 40o suggests a poorly flowing material.

Carr's Consolidation Index (Compressibility index)

Compressibility index can be measure of the potential strength that the granules could build up in its arch in a hopper and also ease with which such an arch could be broken.[4-7]

Hausner's ratio:

Hausner's ratio is elucidated that ratio of tapped density to the bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.[5-9]

Hausner's Ratio (HR) =Tapped density/Bulk density.

Table 2 Pre-compression properties of Tolfenamic acid powder blend

Formulatiton code	Loose bulk density (gm/cm3)	Tapped density (gm/cm3)	Angle of Repose (θ)	Carr's Compressibility index	Hausner' ratio
F1	0.61±0.03	0.75±0.01	27.94±0.02	13.10±0.024	1.121±0.03
F2	0.62±0.01	0.79±0.01	26.69±0.03	15.20±0.022	1.119±0.02
F3	0.63±0.02	0.78±0.02	26.42±0.05	13.89±0.009	1.122±0.05
F4	0.62±0.01	0.76±0.01	27.85±0.02	15.87±0.017	1.124±0.04
F5	0.61±0.03	0.76±0.3	28.01±0.03	14.68±0.014	1.129±0.02
F6	0.68±0.04	0.79±0.02	26.76±0.05	13.37±0.024	1.128±0.01
F7	0.65±0.01	0.78±0.01	27.40±0.07	15.24±0.019	1.121±0.04
F8	0.61±0.02	0.79±0.01	28.32±0.09	12.20±0.027	1.128±0.05

Formulation of tolfenamic acid mouth dissolving tablets:

Tolfenamic acid mouth dissolving tablets were crafted via the direct compression method utilizing the Elite 10-station mini press. The employed direct compression process proved to be optimal and easily reproducible.[12-17] Precise collection and measurement of all ingredients were conducted. Tolfenamic acid, Metoclopramide Hcl along with superdisintegrants like sodium starch glycolate, crospovidone, and microcrystalline cellulose were formulated into the tablet form, promoting swift tablet disintegration. These superdisintegrants demonstrated effectiveness in the creation of tablets designed for rapid release.Formulations of orally disintegrating tablets containing tolfenamic acid and metoclopramide were developed with varying the types and concentrations of superdisintegrants.[14-18]

Table 1 Composition of Tolfenamic acid Formulations by using various superdisintegrants

Name of Ingredients (mg)	Composition of ingredients							
	F1	F2	F3	F4	F5	F6	F7	F8
Tolfenamic acid	200	200	200	200	200	200	200	200
Metoclopramide Hcl	10	10	10	10	10	10	10	10
Crospovidone	8	8	8	8	8	8	8	8
Sodium starch glycolate	7	9	11	13	7	9	11	13
Microcrystalline cellulose	20	20	20	20	20	20	20	20
Mannitol	47	45	43	47	45	45	43	41
Magnesium stearate	3	3	3	3		3	3	3
Talc	1	1	1	1	1	1	1	1
Aspartame	2	2	2	2	2	2	2	2
Pineapple flavour	2	2	2	2	2	2	2	2
Total tablet weight (mg)	300	300	300	300	300	300	300	300

Post Compression Parameters Tablets:

Thickness:

The thickness of mouth dissolving tablets was measured by placing the randomly selected 5 tablet between the arms of the Vernier Calliper's.

Weight variation:

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weightand percentage weight variation.

Weight variation = (Individual weight –Avg weight/Individual weight) x 100

Hardness:

Tablet hardness was determined for 10 tablets using a Monsanto hardness tester. Hardness are used to measure the degree of force (in kilograms, pounds, or in arbitrary units) required to break a tablet. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet.

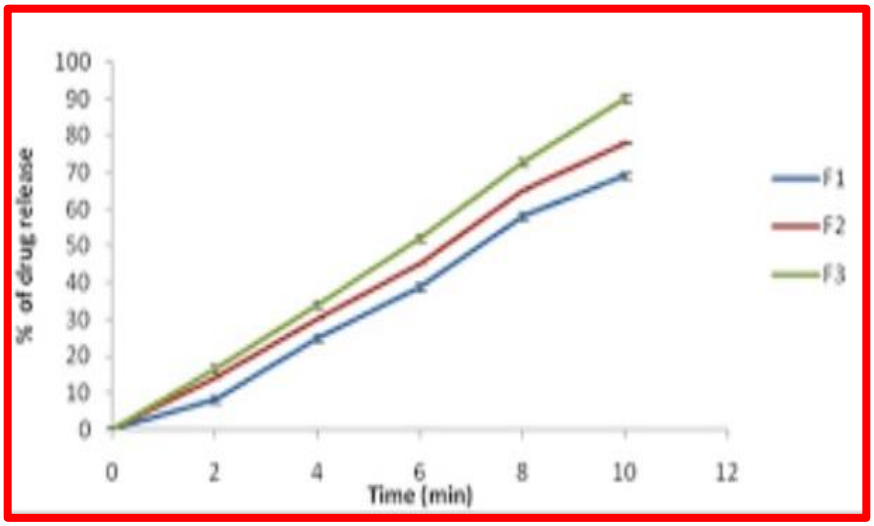
Table 3 Evaluation of mouth dissolving tolfenamic acid tablets

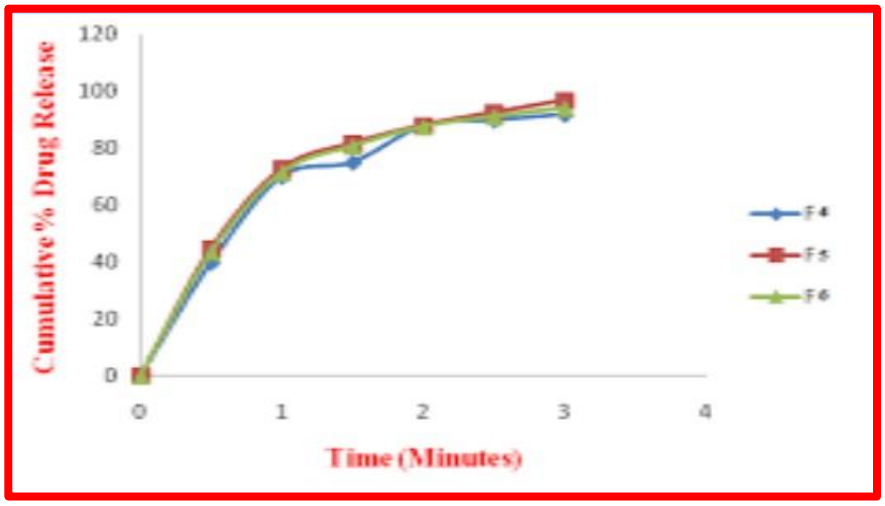
Formulation code	Parameters				
	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm2)	Friability	% drug content
F1	3.8±0.02	601±2.0	5.4±0.4	0.18	299.5±0.5
F2	4.2±0.01	599±3.0	5.6±0.3	0.13	297.3±0.5
F3	4.3±0.03	602±3.0	5.6±0.3	0.19	299.6±0.5
F4	4.1±0.01	598±2.0	5.7±0.2	0.18	298.9±0.2
F5	4.2±0.01	598±4.0	5.6±0.3	0.16	299.2±0.3
F6	4.2±0.02	604±2.0	5.7±0.2	0.17	298.8±0.5
F7	3.9±0.02	606±3.0	5.8±0.3	0.18	299.6±0.5
F8	4.1±0.02	598±3.0	5.6±0.4	0.17	298.8±0.3

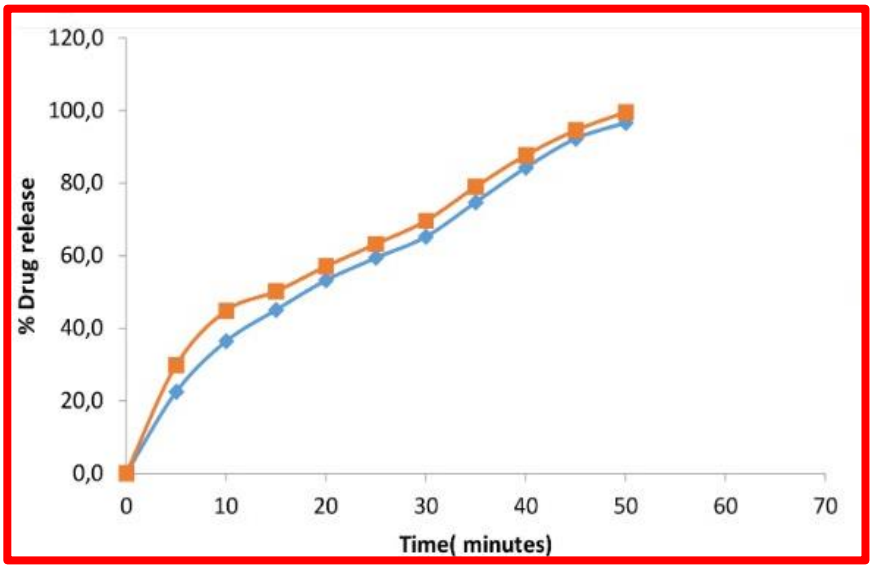
Table 4 In-vitro drug release of tolfenamic acid mouth dissolving tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	16.34	13.21	16.65	12.56	15.23	21.24	18.36	19.24
20	37.95	27.37	26.12	24.24	26.68	34.26	39.21	34.84
30	55.72	49.74	51.68	48.35	53.31	51.54	54.47	51.31

FIG 1-3 Drug Release of Tolfenamic Acid Mouth Dissolving Tablet







RESULTS & DISCUSSION:

In this research, eight formulations of Tolfenamic acid mouth dissolving tablets were successfully prepared. These formulations varied in superdisintegrant concentrations and their ratios concerning the drug, aiming to rapidly release the drug via direct compression.

The tablets underwent a range of evaluations including pre-compression properties, thickness, weight variation, hardness, friability, drug content uniformity, in-vitro dissolution studies, and stability assessments.

Results showed that the loose bulk density and tapped density of Tolfenamic acid ranged from 0.62±0.01 gm/cm3 to 0.69±0.01 gm/cm3 and 0.78±0.03 gm/cm3 to 0.81±0.02 gm/cm3 respectively. The angle of repose, Carr's consolidation index (%), and Hausner's ratio for the Tolfenamic acid blended powder were in the range of 26.43±0.06 to 28.33±0.09, 12.21±0.03 to 15.90±0.02, and 1.119±0.03 to 1.128±0.05 respectively. These results, being within certain thresholds (angle of repose < 30, Carr's index < 17%), indicated favorable flow properties for the Tolfenamic acid powder blend.

The mean thickness of the Tolfenamic acid mouth dissolving tablets was consistently uniform across all formulations, ranging between 3.9±0.03mm to 4.5±0.01 mm. The tablets demonstrated good mechanical strength with hardness values in the range of 5.6±0.4 kg/cm2 to 5.9±0.3 kg/cm2. Additionally, their friability values fell between 0.2-0.3%, suggesting good resistance to mechanical stress.

Regarding weight variation, all fourteen formulations of Tolfenamic acid mouth dissolving tablets met the pharmacopoeial limit of ±5% of the tablet, ranging from 550±2.1 to 702±2.0 mg. The percentage drug content of these tablets ranged from 249.3±0.6 to 252.10±0.3 of Tolfenamic acid, well within acceptable limits.

One specific formulation, F4, exhibited an optimal drug release profile over 30 minutes, indicating an efficient release rate. This formulation, containing a certain percentage of crospovidone, potentially promoted tablet disintegration upon contact with the release medium, enhancing drug release by increasing pore size.

Formulations F4 and F8, showing promising results, underwent stability studies under ambient room conditions for three months. After this duration, the mouth dissolving tablets displayed no alterations in physical appearance or drug content.

Composition of Tolfenamic acid Formulations by using various superdisintegrants depicted in table 1 where as Pre-compression properties of Tolfenamic acid powder blend is shown in table 2 and evaluation of mouth dissolving tolfenamic acid tablets is tabled in table 3. In-vitro drug release of tolfenamic acid mouth dissolving tablets is listed in table 4.

Drug Release of Tolfenamic Acid Mouth Dissolving Tablet is shown in figures 1 to 3.The curves indicate the rate of release of drug with respect to time. Instant release of medicament is of prime importance in case of mouth dissolving tablets which was facilitated by the incorporation of different concentrations of superdisintegrants.Rapid relief from throbbing pain associated with migraine is mitigated by the mouth dissolving tablets which exhibits instant action.

CONCLUSION:

Tolfenamic acid mouth dissolving tablets were manufactured via direct compression. Crospovidone and SSG were employed in varying concentrations relative to Tolfenamic acid. It was determined that formulations F4 and F8, specifically those containing crospovidone in relation to Tolfenamic acid, achieved drug release within one minute compared to other formulations (F1 to F8). This study ultimately suggests that augmenting the concentration of superdisintegrants could prompt swift disintegration of mouth dissolving tablets.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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