

Development and Evaluation of RDT containing NSAIDS by using Natural superdisintegrants

Azharuddin*, Abhay Gupta, Mukesh Kumar Gupta

Faculty of Pharmacy, Lords University, Chikani, Alwar, Rajasthan, India

*Correspondence

Azharuddin

Faculty of Pharmacy, Lords University, Chikani, Alwar, Rajasthan, India

Email: drazharalwar@gmail.com

Abstract

The objective of the present study was to develop a pharmaceutically active, stable, safe, cost effective and quality improved formulation of NSAIDS. Rapid Dispersible Tablets are an alternative to swallowing tablets, since they are made with a unique composition that dissolves rapidly in water to create a drinkable solution. As soon as a pill makes contact with the fluid, it begins to disintegrate. Next, the granules begin to de-aggregate, or break down into smaller, fundamental particles than they were originally. Less than three minutes is ideal for the RDT's rate of dispersal or disintegration. Now days natural and synthetic Super disintegrants such as Chitosan, Starch, Guar gum, Xanthan gum, Gum-karaya, Fenugreek seed, carboxymethyl cellulose, polyvinyl pyrrolidine, and sodium starch glycolate are crucial to the RDT development process. Solubility of drug is the basic factor which controls the release profile of the finished product. Particle size reduction or Co-Micronization (e.g. by high pressure homogenization) might also increase the saturation solubility of a drug, further enhancing the dissolution rate. The purpose of this study was to create a fixed-dose combination formulation for the efficient management of migraines. Co-micronization was used to enhance the release profile of tolfenamic acid.

Keywords: NSAIDS, RDT, Co-micronization, Drug.

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Introduction

Most medication formulations are taken orally, either as capsules, tablets, or fluids. One kind of tablet, with a particular formulation, rapidly dissolves in water to generate a drinkable solution, providing both improved bioavailability and an easier time taking the medicine. A dispersible pill is often administered to a patient after being dissolved in water. In place of a standard formulation that requires approximate dosage; dispersible tablets may be used instead. There is some evidence that dispersible tablets may provide stability for pharmaceutical active chemicals that are unstable in aqueous solution. Oral administration of the formulation has recently emerged as the preferred route of administration owing to its convenience, lack of discomfort, adaptability, and, most importantly, patient compliance. Rapid disintegration tablets are intended for patients who cannot swallow, such as the bed-ridden patients, elderly, stroke victims, patients with renal

impairment, and patients who decline to swallow, such as geriatric, paediatric, and psychiatric patients.[1-4]

Studies aimed at increasing Tolfenamic Acid's solubility will use a co-micronization technique to create a formulation with a rapid release profile. Particle size, surfactants, and co-micronization of the active with the surfactant all played roles in the studies conducted.

It was investigated how granule size and the kind of intra-granular disintegrant (Natural and synthetic superdisintegrants) affect tablet characteristics, particularly dispersion and wetting aspects of the formulation.

In an attempt to provide the most effective treatment for paediatric migraines. The organoleptic properties of the formulation were also assessed for the purpose of increasing patient compliance. It was also being determined whether or not the enhanced formulation met ICH stability standards.[5]

Material and Methods

API of Tolfenamic acid was obtained as a gift sample from Elder Pharmaceuticals Limited, India. Microcrystalline cellulose, Lactose Monohydrate, Croscarmellose sodium, Sodium Starch Glycolate, Magnesium Stearate and many other additives was procured from Elder Pharmaceuticals Limited, India. Chitosan, Starch, Guar gum, and Xanthan gum was taken as natural super disintegrants. All the other chemicals used were of analytical grades.[6-7]

Methodology:**Co-Micronization as a Formulation Principle for Rapidly Absorbing Tablets**

Modifying drug release using methods such as solid dispersion, particle size reduction, micronization, the direct compaction approach, melt granulation techniques, and solvent deposition inclusion has received considerable study in recent years. Complexation tactics were a part of the formulation process. Accelerating the release of drugs that aren't highly water-soluble is the driving force behind all of these developments.

Tolfenamic acid's solid dispersions (SDs) of Tolfenamic acid (TA) and poly vinyl pyrrolidone K-30 were used to increase the release rate of poorly soluble Tolfenamic acid. A solid dispersion of Tolfenamic acid was developed by him using the spray drying method. Tolfenamic acid's release profile was shown to improve in all solid dispersion formulations, as evidenced by dissolution experiments.

% of drug content

$$= \frac{\text{Test Absorbance} \times \text{Standard Concentration}}{\text{Standard Absorbance} \times \text{Weight of SD taken}} \times \text{dilution factor} \times 100$$

Drug – Excipient compatibility studies**Table 1: Scheme for Drugs - Excipients Compatibility Studies**

Sr. No.	Condition	Time -point	Type of packing
1	Initial	Zero day	Glass vial
2	Stress Condition 50 ⁰ C	Up to 15 days	Glass vial
3	40 ⁰ C/ 75% RH	Up to 30 days	Glass vial

Fourier Transform Infrared (FTIR) spectroscopy

Infrared spectroscopy of the medication samples further validated the identification of the active ingredients. A Fourier transform infrared (FTIR) spectrometer was used to collect the spectra. Before making KBr discs, the powders were triturated and mixed well with potassium bromide in a 1:5 (Sample: KBr) ratio, and then they were compressed at a pressure of 5 tonnes for 5 minutes in a hydraulic press. Between 4500 and 400 cm, we were able to produce scans with a resolution of 2 cm¹. The purpose of the study was to identify potential pharmacological functional groupings. The spectrum was then matched to the active ingredient standard spectrum

Tolfenamic acid's solubility improved linearly with the addition of Brij 58 (Non-ionic surfactant or Detergent) and polysorbate 80 to an aqueous solution. A higher hydrophobic fraction in the surfactant molecules was linked to improved solubility. Using Brij 58 as a surfactant led to the optimum release profile for the formulated product.

Analytical method development for drug.**Assay of Drug Content in Tablets****Standard Preparation**

Tolfenamic acid, around 150 mg, weighed precisely, transferred to a 100 ml volumetric flask, dissolved in 50 ml of 0.1 M NaOH, and diluted to the mark with 0.1 M NaOH. Use 0.1 M NaOH to dilute 1 ml of the solution to 100 ml.

Sample Preparation

Twenty pills from each formulation were crushed and analysed in a Petri dish as an assay. The volumetric flask containing 100 ml was filled with powdered Tolfenamic acid with an equal weight of 240 mg. The 0.1 M NaOH should be added, along with 80 ml. Keep shaking for 30 minutes, and then add 0.1 M NaOH until you get 100 ml. To create 100 mL of working solution, discard the first few millilitres after filtering and dilute 1 mL of the remaining solution with 0.1 M NaOH. Get the absorbance at 289 nm of the sample and the standard preparation using 0.1 M NaOH as the blank in a UV spectrophotometer (Shimadzu). Use the following formula to determine the amount of Tolfenamic acid in each pill[8-9].

published in the British Pharmacopoeia.

UV Spectrophotometer

The identification of actives was characterized by using UV spectrophotometry. The method is adopted from British Pharmacopoeia.

Tolfenamic Acid:

20 mg of Tolfenamic acid was dissolved in a mixture of 1 volume of 1 M hydrochloric acid and 99 volumes of methanol R and dilute to 100 ml with the same mixture of solvents. 5.0 ml of above solution was again diluted to 50 ml with a mixture of 1 volume of 1 M hydrochloric acid and 99 volumes of methanol R. When the diluted solution is studied between 250 and 380 nm

in wavelength, it reveals two absorption maxima, at 286 and 345 nm, respectively. Absorbance peaked at 286 nm and 345 nm, respectively, and the ratio between the two values is 1.2% to 1.4%.

Formulation development of Rapid Dispersible Tablets

Manufacturing of Co-micronization Blend

Air-jet mill was used to micronize the Tolfenamic acid and diluents. The formulation was co-micronized as shown in the table below. The right amount of particle size reduction of mixture was ensured by completing a total of three cycles of micronization. Formulation TAF-

1 was not micronized; rather, it served as a control against which the effects of micronization and co-micronization could be measured. However, the non-micronized Tolfenamic acid used in Formulation TAF-1 was sifted through #60 meshes to ensure a consistent mix. When it came time to granulate the resulting formulations, the same co-micronized mixes were utilised. The steps involved in co-preparation micronizations were laid out in Table below[10-13].

Table 2: Quantity Available in each tablet

Ingredients	Quantity Available In Each Tablets			
	(mg/tabs)			
	TAF-1	TAF-2	TAF-3	TAF-4
Intra-Granular				
Tolfenamic Acid	100.00	100.00	100.00	100.00
Microcrystalline Cellulose	80.000	80.000	81.250	80.000
Sodium Lauryl Sulfate	1.250	1.250	--	1.250
Starch	2.500	2.500	2.500	2.500
Purified Water	QS	QS	QS	QS
Extra-Granular				
Sorbitol	45.000	45.000	45.000	45.000
Sodium Starch Glycolate	2.500	2.500	2.500	2.500
Magnesium Stearate	1.250	1.250	1.250	1.250
Aspartame	5.000	5.000	5.000	5.000
Flavor Vanilla	2.500	2.500	2.500	2.500
Tablet Weight in mg	240.00	240.00	240.00	240.00

Table 3: Formulation of Rapid Dispersible Tablets of Tolfenamic Acid

Co-micronization Blend Preparation for Better Solubility:

Formulation	TAF-1	TAF-2	TAF-3	TAF-4
Processing	Simple mixing of un-micronized TA with MCC and SLS for reference	Micronization of TA and mixing with MCC and SLS	Co-micronization of TA and MCC.	Co-micronization of TA, with MCC & SLS.

Experimental Design

Rapid dispersible tablets' breakdown and distribution are greatly influenced by the size of the granules used to make them. It has been found that relatively little effort has been put on optimising the granule size by utilising different kinds of disintegrants. The system's specifics are what determine the impact of granule size, and super disintegrants have seen very little research. This research looks at the impact of granules of different sizes to identify the impact of disintegrant type and optimise dispersion. The effectiveness of natural and synthetic

superdisintegrants such Chitosan, Croscarmellose Sodium (Ac Di-Sol), Guar Gum, and Xanthan Gum was evaluated by measuring the disintegration and dispersion of tablets down to 710 m. The formulation with superior disintegration and dispersion capabilities was also assessed in terms of its release profile[8].

Manufacturing of Bulk Granules

Based on the findings that the co-micronization method improved Tolfenamic acid solubility, formulation TAF-4 served as the starting point for the further optimization research. According to the formula provided in the

research, granules were prepared utilising Chitosan, Ac-Di-Sol, Guar gum, and Xanthan gum as intra granular natural and synthetic super disintegrants. The granulation and drying processes followed the same protocols as the earlier research[10,11].

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation,

Evaluation Parameters	TAF-1	TAF-2	TAF-3	TAF-4
Drug Content (%) n=3 (Tolfenamic Acid)	98.62±1.30	100.66±1.97	102.22±1.30	100.02±1.24

hardness, thickness, friability and drug content[12].

Table 4: Evaluation Parameters

Results and Discussion

Determination of drug content for Tolfenamic acid

The findings of the drug content test and the in vitro drug release profile for formulations TAF-1 through TAF-4 tablets are shown in Table 4 and 5

Table 5: In-vitro Drug Release Profile of Tolfenamic Acid

Sample withdrawal Time Intervals (Min.)	TAF-1	TAF-2	TAF-3	TAF-4
% Drug Release				
5	71	77	69	79
10	80	83	85	87
15	88	91	90	93
30	96	98	95	97
45	100	99	98	99
60	100	99	102	100

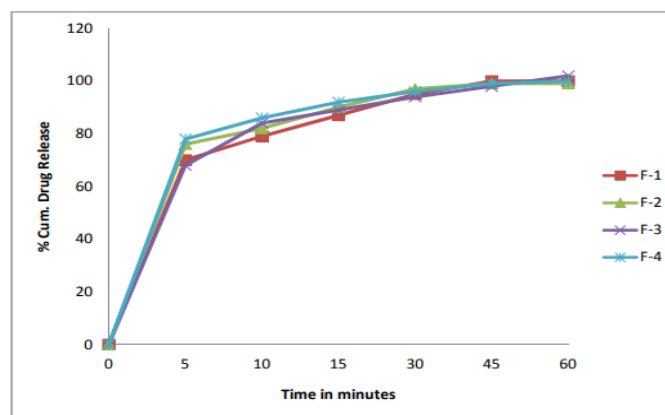


Fig. 1 : Comparative Release Profile of Formulations Tolfenamic Acid

Stability Studies

The physical, analytical, and organoleptic stability of the optimised formulation (F-2) was maintained at both the rapid (40±20 C & 75±5% RH) and intermediate storage conditions (30±20 C & 65±5% RH)[13-15].

Conclusion

Dispersible tablet excipients were chosen after extensive research was conducted using the available literature and a database of innovative goods. To recheck the drug's compatibility with the excipients, a preformulation study was conducted. Physical testing, including a stress study and expedited testing, showed no appreciable change in the blend's visual appearance. According to the results of the Drug: excipients compatibility study, the chosen

excipients were found to be compatible with the Active Pharmaceutical Ingredient at both the short- and long-term stability conditions of 50°C ± 2°C (Stress Condition) for 15 days, 40°C ± 2°C I 75%RH ± 5%Rh for 1 month. Therefore, the proposed formulation of Rapid dispersible formulation of Tolfenamic acid is suitable for the excipients selected for it. Spectrophotometric analysis of the drug in conjunction with its excipients was also performed as part of the preformulation studies to confirm the impact of environmental factors on the degradation of active ingredients. The disintegration times of Ac-Di-Sol tablets were the most consistent and had the quickest average rates. It has been reported that intra-granular

Chitosan / Xanthan gum has poor tablet dispersion quality. Intra-granular disintegrants' efficacy is measured by the following standards: While Chitosan is superior than Xanthan gum and Guar gum and Ac-Di-Sol is superior than Chitosan and Xanthan gum.

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