Original Research Article

Formulation and Evaluation of Rapid Dispersible Tablets of NSAIDS using Co-Micronisation Method

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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. Superdisintegrants such as 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, Tolfenamic Acid.

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 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].

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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. All the other chemicals used were of analytical grades[6-10].

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[11-12].

Tolfenamic acid's solid dispersions (SDs) of Tolfenamic acid (TA) and polyvinylpyrrolidone K-30 were used to increase the release rate of poorly soluble Tolfenamic acid, (PVP). 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.

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[9].

$$\%\ of\ drug\ content = \frac{\text{Test Absorbance X Standard Concentration}}{\text{Standard Absorbance X Weight of SD taken}} \text{X dilution factor X } 100$$

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 °C	Up to 15 days	Glass vial
3	40 °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 cm 1. The purpose of the study was to identify potential pharmacological functional groupings. The spectrum was then matched to the active ingredient standard spectrum published in the British Pharmacopoeia.

U V 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 2 below.

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
Povidone (PVP K-30)	2.500	2.500	2.500	2.500
Purified Water	QS	QS	QS	QS
Extra-Granular				
Mannitol	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-microniozation of TA and MCC.	Co-microniozation 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 super disintegrants such Sodium starch glycolate (Explotab), Croscarmellose Sodium (Ac Di-Sol), Crospovidone (Kollidon-CL), and Polacrillin Potassium (Kyron T-314) 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[8,13].

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 Explotab, Ac-Di-Sol, Kollidon-CL, and Kyron T-314 as intra granular disintegrants. The granulation and drying processes followed the same protocols as the earlier research [10].

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content[12].

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 TAFF-4 tablets are shown in Table 4 & 5.

Table 4: Evaluation parameters

Evaluation Parameters	TAF-1	TAF-2	TAF-3	TAF-4
Drug Content (%) n=3 (Tolfenamic Acid)	98.62±1.30	100.61±1.97	102.15±1.15	100.01.24

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	70	76	68	78
10	79	82	84	86
15	87	90	89	92
30	95	97	94	96
45	100	99	98	99
60	100	99	102	100

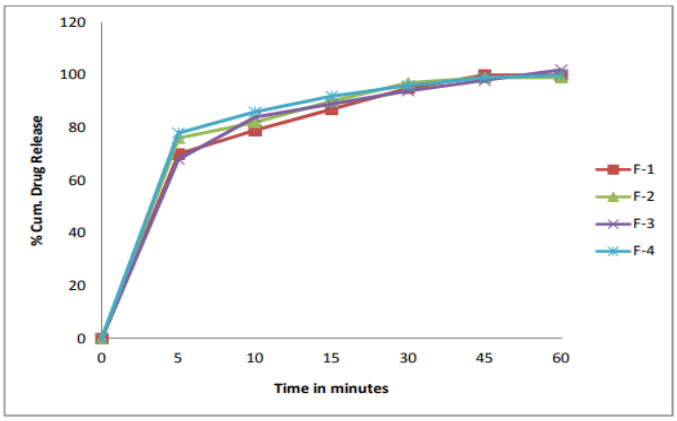

Figure 1 : Comparative Release Profile of Formulations Tolfenamic Acid

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). Table 5.8 is a summary of the results of the evaluations of various physical and analytical parameters performed according to the stability procedure specified[11].

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 , 400C ± 2°C I 75%RH ± 5%Rh for 1 month. Therefore, the proposed formulation of Rapid dispersible formulation of Tolfenamic acid and 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 Explotab / Kyron T-314 has poor tablet dispersion quality. Intra-granular disintegrants' efficacy is measured by the following standards: While Explotab is superior than Kyron T-314 and Kollidon-CL, Ac-Di-Sol is superior to both.

References

1. Kuchekar BS, Bhise SB, Arumugam V. Design of fast dissolving tablets. Ind J Pharm Edu2001;35(4):150-152.
2. Srikonda VS, Janaki RMN, Joseph A. Recent technological advances in oral drug delivery-A review. Res Focus 2000;4:138-145.
3. Chein YW. Oral drug delivery and delivery systems, 2nd Marcel Dekker, New York,1992:139.
4. PilgaonkarPS, Rustomjee MT, Gandhi AS, Bagde P, Barve V. Novel dispersible tablet composition, U. S. Patent 052289. 2007.
5. Gaud RS, Yeole PG, Yadav AV, Gokhale SB. A Textbook of Pharmaceutics, 3rd ed. Published by Nirali Prakashan, Pune, India. 1987:295-345.
6. Pade V, Stavchansky S. Link between drug absorption solubility and permeability measurements in CaCo-2cells. J Pharm Sci 1998;87:1604-1607.

7. Shyamala B, Narmada GY. Rapid dissolving tablets: A Novel Dosage Forms. The Indian Pharmacist (2002); 13(8): 09-12.
8. Bi YX, Sunada H, Yonezawa Y, Danjo Evaluation of Rapidly Disintegrating Tablets Prepared by a Direct Compression Method .Drug Dev Ind Pharm (1999) ; 25:571-581.
9. Ansel HC, Popovich NG. Pharmaceutical Dosage Forms and Drug Delivery System, 5th ed. Lea and Febiger, Philadelphia, 1990:158.
10. Fonner DE, Anderson NR and Banker GS. Granulation and Tablet Characteristics in Pharmaceutical Dosage Forms, 1982;2:202.
11. Bhaskaran S, Narmada GV, Rapid Dissolving tablet A Novel dosage form, Indian Pharmacist, 1, 2002, 9- 12.
12. Bi Y, Akinobu O, "Evaluation of a compressed tablet rapidly disintegrating in the oral cavity", Chem.Pharm. Bull, 44, 1995,2011-17.
13. Patidar A, Mishra P, Main P, Harsoliya MS, Agarwal S., A Review On- Recent Advancement in the Development of Rapid Disintegrating Tablet. International Journal of Life science & Pharma Research. 2011; 1(1): 7-16.

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