APPROACH OF CO-MICRONIZATION IN SOLUBILITY ENHANCEMENT AND RELEASE PROFILE OF RAPID DISPERSIBLE TABLETS OF TOLFENAMIC ACID

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ABSTRACT

Tolfenamic Acid is an orally and parenterally administered Non – steroidal anti-inflammatory drug belonging to the fenamate group. Dissolution is the rate limiting step for the absorption of Tolfenamic acid due to its poor solubility. In order to improve the solubility of drug and its dissolution rate concept of co-micronization of Tolfenamic acid with diluents and surfactants was studied in present study. Tolfenamic acid was co-micronized with microcrystalline cellulose and surfactants as sodium Lauryl sulfate. One reference formulation was also manufactured with conventional method using non-micronized Tolfenamic acid with surfactants. The formulation was then evaluated for various physical and analytical properties of rapid dispersible tablets. Results obtained showed that there was a significant increase in dissolution rate of drug in first 5 minutes of time interval as compare to reference formulation. The wetting and dispersion properties of formulation also found superior as compare to reference formulation.

Keywords: Tolfenamic Acid, Particle Size Reduction, Co-micronization, Sodium Lauryl Sulfate, Dissolution Profile, Rapid Dispersible Tablets

Abbreviations: TA shows Tolfenamic Acid, IP: Indian Pharmacopoeia, BP: British Pharmacopoeia, RMG: Rapid Mixer Granulator, FFBE: Flat Face Beveled Edge, mm: millimeter, mg: milligram, RPM: Round per minute, RH: Relative Humidity, QS: Quantity as sufficient, w/w: weight by weight.

1.0 INTRODUCTION

The concept of rapid dispersible, fast dissolving, quick dissolving, and orodispersible tablets dosage forms have acquired great importance in recent years due to their unique properties and advantages over other available dosage forms.¹, ² In the recent years, great interests in the modification of drug release by using various methods such as solid dispersion, particle size reduction, micronization, direct compaction method, melt granulation techniques, solvent deposition inclusion complexation methods were adopted in formulation.³ The basic goal behind all of such innovations include developing a suitable formulation with rapid release of poorly water-soluble drugs.⁴ Nearly one-third of drugs in development are water insoluble and one-half fail in trials because of underprivileged pharmacokinetics.⁵ Tolfenamic Acid also falls in the same category, the basic challenge in formulation of Tolfenamic acid is its poor solubility.⁶ Tolfenamic Acid is an orally and parenterally administered Non – steroidal anti-inflammatory drug belonging to the fenamate group.⁷ Since the Tolfenamic acid is poorly water soluble drug so the dissolution is the rate limiting step for the absorption of drug. The Tolfenamic acid was originally formulated as hard gelatin capsules probably because of difficulties in preparing tablet being a reasonable size and rapid disintegration of active in compressed dosage form, with suitable size that can be easily swallowed by patients.⁸ There are various approaches for improvement of release profile by application of various techniques such as solid dispersion,⁹ by using surfactants,¹⁰ and size reduction⁸ of Tolfenamic acid is reported in the various literature and patents.

Nowadays Co-micronization of active with specific excipients becomes interesting approach to enhance the release profile of poor water soluble compounds.¹¹, ¹², ¹³ Tolfenamic acid is insoluble in nature, therefore in present study efforts were made to improve the release profile of active and to formulate rapid dispersible tablets of Tolfenamic acid by using novel concept of co-micronization.

2.0 MATERIALS

Tolfenamic Acid was a gift sample from Elder Pharmaceuticals Ltd, Navi Mumbai, India. Aspartame and Flavor Vanilla was a gift sample from Cadila Pharmaceuticals Limited, Ahmadabad, India. Microncrystalline cellulose, Sodium Lauryl sulfate, Povidone, Mannitol, and sodium starch glycolate were obtained from commercial sources.

3.0 METHODS

The basic aim of the study was to enhance the release profile of Tolfenamic acid by using co-micronization concept. Approximately 1% of disintegrants was added to make dispersion and wetting of tablets but it did not had a greater impact on dissolution enhancement. The details of formulations were summarized in the table-1.
3.1 Solubility Enhancement of Tolfenamic Acid and its evaluation

Total four formulations were designed to evaluate the effect of the co-micronization on the dissolution and dispersion properties of finished product. Formulation A-1 was manufactured with non micronized Tolfenamic acid as reference to check the impact of co-micronization on the various physico-chemical properties of formulation.

3.1.1 Manufacturing of Co-micronization blend

Table 2: Preparation of Co-micronization blend for solubility enhancement

<table>
<thead>
<tr>
<th>Formulation</th>
<th>A-1</th>
<th>A-2</th>
<th>A-3</th>
<th>A-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing</td>
<td>Simple mixing of un-micronized TA with MCC and SLS for reference</td>
<td>Micronization of TA and mixing with MCC and SLS</td>
<td>Co-micronization of TA and MCC.</td>
<td>Co-micronization of TA, with MCC &amp; SLS.</td>
</tr>
</tbody>
</table>

3.1.2 Physical evaluation of Co-micronization blend

The evaluation of micronized mixtures of Formulation A-1 to A-4 was confirmed for particle size of TA mixture. The particle size was evaluated by using Malvern Mastersizer 2000. The average particle size which was the mean particle size of 90% (d-0.9) of particle in sample was recorded for evaluation.14

3.2 Manufacturing of Granules

Co-micronized blend of Tolfenamic acid was mixed in rapid mixer granulator (HSMG-10, Kevin Machinery) with slow impeller speed (75 RPM) for 10 minutes, PVP K-30 was dissolved in distilled water to give a binder concentration of 6.0% w/v. To granulate, the binder was added slowly over five minutes through a glass funnel to control the flow rate. The resultant material was wet massed through the required sieve. Granules were vacuum dried using vacuum dryer (Shree Engineering) at 55°C for 150 – 180 minutes. In addition to the temperature and the duration of the drying process, the moisture content and flow rate of the circulating air could affect granule strength and therefore to standardize, the amount of granules in each tray-dried was kept within an approximate range of 600-900g. The residual granule moisture content was determined by loss on drying. Granules were stored in double polythene bags until use to prevent moisture loss / gain. The dried granules than blended with extra granular excipients as per the given details of formulation in table – 1 using bin blender (Solace Engineering) at 12 RPM for 10 minutes. The blends were lubricated with Magnesium Stearate using bin blender at 12 RPM for 3 minutes.

3.3 Manufacturing of Tablet

The compression of granules was completed by using Cadmach single rotary compression machine. 9.00 mm FFBE chrome plated punching tools was used to avoid any sticking problem during compression. The average turret speed during compression was also kept in range of 10 – 12 RPM. In preliminary work, problems with uncontrolled moisture sorption occurred in granules during tabletting. Highly variable moisture contents made direct effect on physical properties of tablets. The relative humidity of the tabletting area monitored during compression of tablets. The higher humidity had significant effect on tablets properties, so a limit of 50% RH was set as the maximum relative humidity at which tabletting was carried out.

3.4 Physical Evaluation of Granules

3.4.1 Loss on drying

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that could be driven off under specified conditions. The loss on drying was calculated by using equation,

\[
\% \text{ LOD} = \frac{\text{Weight of solvent in sample}}{\text{Total weight of initial sample}} \times 100
\]
Approximately 2.0 gms of dried granules were placed on aluminum disk of IR moisture balance. The loss on drying was recorded at 105°C for 10 minutes of time interval.

3.4.2 Tapped and Untapped Density\textsuperscript{15,16}

Un-tapped and tapped density was determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus which was operated for fixed number of taps (~100) until a powder bed volume had reached the minimum. The ratio of mass (weight) to volume is known as the untapped bulk density of material. The bulk density of a powder depends on particle size distribution. The equation for determining the bulk density and tapped density is,

\[
\rho_b = \frac{M}{V_p} \\
\rho_t = \frac{M}{V_t}
\]

Where, \(\rho_b\) is untapped bulk density, \(\rho_t\) is tapped density, \(M\) is weight of sample in grams, \(V_p\) is final volumes of powder in \(\text{cm}^3\), and \(V_t\) is tapped volume of powder in \(\text{cm}^3\).

3.4.3 Compressibility Index\textsuperscript{15,16}

The compressibility index of the granules was determined by Carr’s index. The Carr’s index was determined from the tapped density and poured density (bulk density) as per the formula given below,

\[
\text{Carr’s Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100
\]

3.4.4 Hausner Ratio\textsuperscript{16}

Hausner Ratio was determined from the ratio of tapped density to bulk density using formula given below.

\[
\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}
\]

Flow of granules was evaluated by using interpretation between Hausner Ratio and carr’s index as shown in table 3.

3.5 Physical Evaluation of Tablets

3.5.1 Appearance

Appearance of tablets was evaluated by taking twenty tablets of each formulation and visually checked for any discoloration or surface roughness on the core surface of tablet formulation.

\[
\text{Friability (\%)} = \frac{\text{Initial weight of Tablets} - \text{Final weight of Tablets}}{\text{Initial weight of Tablets}} \times 100
\]
As per the Indian pharmacopoeia the limit for friability tablets should not be more than 1% w/w. The values for both Hardness & Friability can together indicate the mechanical strength of tablet.

### 3.5.6 Disintegration Time
Disintegration is defined as time required by tablet to completely disintegrate and disappear from the basket. Disintegration time of tablets was evaluated as per the specification of disintegration time of dispersible and Orodispersible tablets in British pharmacopoeia. Disintegration was carried out by using 600 ml of disintegration media mentioning the temperature at 15°C – 25°C in disintegration basket. Disintegration discs were not used during disintegration. The use of discs during disintegration reduces discrimination between good and bad formulations since the palpable residue on the mesh would not pass through without applying pressure and thus violating the principle of fluid penetration and particle separation.

### 3.5.7 In vitro dispersion Time and Fineness of Dispersion
Fineness of dispersion is specified in the specification of dispersible tablets. This taste is required to check the fineness and smoothness of dispersion of tablets. The same concepts were applied to correlate the dispersion of tablets in vivo by using pH 6.8 phosphate buffer. The in vitro dispersion time was observed by placing one tablet in a beaker containing 50 ml of pH 6.8 phosphate buffer at 37°C + 1°C, the time required to disperse the tablets was determined. The same dispersion was passed through a sieve screen with a nominal mesh aperture of 710 mm to confirm the fineness of dispersion.

### 3.5.8 Wetting Time and Water Absorption Ratio
Water absorption ratio of tablet was evaluated by using aqueous solution of Methylene Blue. It is also an indicating method to evaluate the disintegrating mechanism of tablets. Absorbent cotton soaked with 0.04 % aqueous solution of methylene blue was placed in a Petri dish, the tablets was placed flat on the surface of cotton, and the time required to change the color of whole tablets to blue was measured as water absorption time. Total six tablets were used for the investigation of water absorption time and mean of water absorption time was calculated.

Water absorption ratio (WAR) was calculated by using the pre weight and post weight of tablet used for wetting time evaluation by using following equation.

\[
WAR (R) = \frac{\text{Weight of wetted tablets} - \text{Weight of dry Tablets}}{\text{Weight of dry Tablets}} \times 100
\]

### 3.6 Analytical Evaluation of Tablets
#### 3.6.1 Assay of drug content in Tablets
The analysis for drug content of formulation was developed based on monograph of Tolfenamic acid in British pharmacopoeia.

**Standard Preparation**

Weigh accurately & transfer about 150 mg of Tolfenamic acid in 100 ml volumetric flask, dissolve it in 50 ml of 0.1 M NaOH & dilute up to mark with 0.1 M NaOH. Dilute 1 ml of the solution to 100 with 0.1 M NaOH.

**Sample Preparation**

Take 250 ml of ethanol 96 % and dilute to 1000 ml with Phosphate Buffer pH 7.2.

**Preparation of Phosphate Buffer pH 7.2**

Dissolve 40.8 g of Potassium dihydrogen phosphate in 1500 ml of distilled water and adjust pH to 7.2 with 40% NaOH and then dilute to 4500 ml with water.

#### 3.6.2 In-vitro drug release kinetics
In-vitro dissolution studies of all formulation were evaluated for the release profile of formulation. The basic objective of formulation was to develop the rapid disintegrating formulations, so release profile at various time intervals such as 5, 10, 15, 30, 45, and 60 minutes were analyzed for the evaluation of release kinetics.

**USP dissolution apparatus** : Type-II Paddle, 100 RPM

**Dissolution Medium** : 1000 ml, Phosphate Buffer pH 7.2

**Temperature** : 37 ± 0.5°C

**Sampling Times (minutes)** : 5, 10, 15, 30, 45, and 60

**Preparation of Dissolution Medium**

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the sample solution was withdrawn from the dissolution beaker as per the given time interval and replacing the same volume by addition of dissolution media. The absorbance of sample solution and standard solution was measured by using UV Spectrophotometer (Shimadzu) at the maximum about 289 nm using 0.1M NaOH as blank.

4.0 RESULT AND DISCUSSION

4.1 Physical evaluation of Co-micronization blend

<table>
<thead>
<tr>
<th>Table - 5: Particle size distribution after micronization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>A-1</td>
</tr>
<tr>
<td>A-2</td>
</tr>
<tr>
<td>A-3</td>
</tr>
<tr>
<td>A-4</td>
</tr>
</tbody>
</table>

4.2 Physical Evaluation of Granules

The various physical evaluation for granules of formulation A-1 to A-4 is summarized in table - 6.

<table>
<thead>
<tr>
<th>Table – 6: Physical properties of granules (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Properties</td>
</tr>
<tr>
<td>Qty of water uptake during granulation (ml)</td>
</tr>
<tr>
<td>Loss on drying (% w/w)</td>
</tr>
<tr>
<td>Bulk density (gm/ml)</td>
</tr>
<tr>
<td>Tapped density (gm/ml)</td>
</tr>
<tr>
<td>Hausner’s Ratio</td>
</tr>
<tr>
<td>Angle of Repose</td>
</tr>
</tbody>
</table>

Discussion

The additional quantity of water during granulation was noted in all four formulations, 10, 14, and 17 ml additional uptake of water was required in formulation A-2, A-3, A-4. This might be due to increased surface area of particle due to co-micronization of Tolfenamic acid, and Tolfenamic acid with diluents. The same tendency of additional drying was observed during drying of granules, the loss on drying for formulation A – 3 & A – 4 was 1.60 and 1.64 % W/W, as compare to loss on drying of formulation A – 1, and A – 2; 1.42 and 1.513 % w/w.

Angle of repose was evaluated to confirm the flow of granules, the values of angle of repose was found in the range of 30 – 36 indicating a fair to good flow of granules. The effect of micronization clearly reflecting in the compressibility index of granules, which is the basic requirement of compression, the co-micronization processing of formulation A-3 and A-4 showed good compressibility index in the range of 15 – 16. The same observation also reflecting in housner’s Ratio of granules.

So on the basis of various physical properties of granules; it was clearly indicating the justified selection of intragranular diluents such as microcrystalline cellulose and wet granulation of co-micronized granules to avoid any weight variation problem, die filling problem, and flow problem during compression of tablets.

4.3 Physical evaluation of tablets

The various physical evaluation for tablets of formulation A-1 to A-4 is summarized in table - 7.

<table>
<thead>
<tr>
<th>Table 7: Physical evaluation of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation Parameters</td>
</tr>
<tr>
<td>Appearance</td>
</tr>
<tr>
<td>Weight Variation (%)</td>
</tr>
<tr>
<td>Hardness (Newton) n=6</td>
</tr>
<tr>
<td>Thickness (mm) n=6</td>
</tr>
<tr>
<td>Friability (% w/w)</td>
</tr>
<tr>
<td>Disintegration (Seconds)</td>
</tr>
<tr>
<td>Dispersion (Seconds) n=3</td>
</tr>
<tr>
<td>Wetting Time (Seconds) n=3</td>
</tr>
<tr>
<td>Water Absorption Ratio</td>
</tr>
</tbody>
</table>
Discussion

The appearance of tablets found good without any significant defects (figure – 1). Weight variation data for all the formulations batches indicated no significant difference in the weight of individuals tablets from the average value and weight variation were found to be within limits. The value of hardness friability of tablet showed good strengths in all formulation, which is an essential parameter for formulation of rapid dispersible tablets. The thickness of tablets was also within limit.

Disintegration time for all formulation was in range between 15 and 22 seconds, which is required to formulate ideal rapid dispersible tablets. There was some significant difference observed in dispersion and wetting time of formulation, the dispersion time and wetting time was higher for formulation A-1 and A-2 as compare to formulation A-3 and A-4. The rapid dispersion and wetting reflects the effect of co-micronization of blend during granulation stage. The co-micronization of blend was increasing the surface area of compressed blend during dispersion and wetting. The dispersion and wetting time was lowest for the formulation A-4, indicating the clear impact of wetting properties of sodium Lauryl sulfate in formulation. The co-micronization of sodium Lauryl sulfate with active and diluents increasing the wetting properties of granules. Same phenomenon of rapid dispersion and wetting reflects in water absorption ratio of formulation A-4. The water absorption ratio for formulation A-4 and A-3 was very less as compare to A-1 and A-2. So there is clear impact of co-micronization in enhancement of physical properties of formulations. Since the present study was focused on the enhancement of release profile of formulation, still there were possibilities of enhancing the dispersion and wetting time by using more concentration of superdisintegrants. The diagrammatic presentation of dispersion and wetting of tablets is shown in figure – 2 and 3.

4.4 Analytical Evaluation of Tablets

The assay of drug content and in vitro drug release profile for tablets of formulation A-1 to A-4 is summarized in table – 8 and 9.
Table 8: Assay of drug content in tablets

<table>
<thead>
<tr>
<th>Evaluation Parameters</th>
<th>A-1</th>
<th>A-2</th>
<th>A-3</th>
<th>A-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Content (%) n=3</td>
<td>100.97± 1.75</td>
<td>100.30± 1.97</td>
<td>100.80± 1.73</td>
<td>100.33± 1.63</td>
</tr>
<tr>
<td>Content Uniformity ( %) n=10</td>
<td>Passed</td>
<td>Passed</td>
<td>Passed</td>
<td>Passed</td>
</tr>
</tbody>
</table>

Discussion

The drug content of tablets and content uniformity of tablets for all formulation A-1 to A-4 was well within the limits.

There was no significant variation observed due to co-micronization and simple mixing of blend at granulation stage.

CONCLUSION

On the basis of various physical and analytical evaluation of formulation the rapid dispersion and wetting of formulation can easily achieved by simple incorporation of micronization of active with diluents. The co-micronization showed a promising effect in the particle size reduction of Tolfenamic acid and providing more surface area in enhancement of wetting and dispersion properties of formulations. The comparative evaluation of formulation A-1 (as reference formulation without micronization of active) proved the concepts of co-micronization in the Tolfenamic acid rapid dispersible tablets. The rapid release of formulation which was the basic requirement of rapid dispersible tablets also achieved by using co-micronization approach during manufacturing of granules.

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