Approach of Fixed Dose Combination in Formulation and Development of Dispersible Tablets for Migraine Therapy

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ABSTRACT:

Concept of fixed dose combination can be defined as formulation of two or more active ingredients formulated in a single dosage form. There are server fixed dose combination are available in the treatment of migraine but having its own limitations. Tolfenamic acid (TA) is used to treat the symptoms of migraine. Paracetamol (4'-hydroxyacetanilide, N-acetyl p-aminophenol, acetaminophen, PAR) is a widely used over-the-counter analgesic and antipyretic drug without any gastric irritation and ulcerative effects. The current research work was set to formulate a dispersible Tablets of Tolfenamic Acid and Paracetamol. Various formulations of FDCs were manufactured by using different disintegrants than taste masked by applying a thin layer of polymer coating. The formulation was than evaluated for various physical and analytical properties of dispersible tablets. Results obtained showed that there was a significant impact of disintegrants, and application of solubility enhancement by solid dispersion and co micronization used during formulation of FDCs.

Keywords: Superdisintegrants, Solubility Enhancement, Fixed Dose Combination, Tolfenamic Acid, Paracetamol, Co-micronization, Drug release, Dispersible Tablets.

1. INTRODUCTION

Concept of fixed dose combination can be defined as formulation of two or more active ingredients formulated in a single dosage form. Recently in our country, approach of Fixed Dose Combination (FDCs) of drugs/medicines has drawn the attention of health professional.¹ ² FDCs is emerges as the current hot topic of deliberations in the health care and medicine sector, government (as implementer), and the pharmaceutical trade. There are server fixed dose combinations available in the treatment of migraine. The combination of Paracetamol with Tolfenamic acid is the next choice of drug due to lower side effects of both the actives.³ ⁶ On the basis of literature and market survey it was observed that still it is rare to find any suitable fixed dose combination of rapid dispersible

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formulations in migraine therapy for pediatrics, so there is need to develop a formulation with effective taste masking.\textsuperscript{7,8}

**Advantages of Fixed Dose Combinations**\textsuperscript{2}

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes.
- Prevents and/or slows attainment of antimicrobial resistance by eliminating monotherapy.
- Allows for synergistic combinations (i.e., trimethoprim/ sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolisms.
- Eliminates drug shortages by simplifying drug storage and handling, and thus lowers risk of being “out of stock”
- Only 1 expiry date simplifies dosing.
- Side effects are reduced by using one drug of the combination for this purpose.

**Disadvantages of Fixed Dose Combinations**\textsuperscript{2}

- FDCs are (possibly) more expensive than separate formulations.
- Potential quality problems, especially with Rifampicin in FDCs for TB, requiring bio-availability testing.
- If a patient is allergic or has a side-effect to 1 component, the FDC must be stopped and replaced by separate tablets.
- Dosing is inflexible and cannot be regulated to patient’s needs (each patient has unique characteristics such as weight, age, pharmacogenetics, co-morbidity, that may alter drug metabolism and effect).
- Drug interactions may lead to alteration of the therapeutic effect.

**Availability of Fixed Dose Combinations in Migraine Therapy**

Caffeine and metoclopramide are used in combination with analgesics and ergotamine in the treatment of migraine attacks. As per the report of S. Evers et. Al. (2006), fixed combination of Acetyl salicylic acid, Paracetamol, and caffeine is effective in acute migraine treatment and is also more effective than the single substances or combinations without caffeine. Sumatriptan with combination of Naproxen is also effective in fixed dose combination for migraine.\textsuperscript{9-13}

2. **MATERIALS AND EQUIPMENTS**

Tolfenamic Acid, Paracetamol, Aspartame and Flavor Vanilla were a gift sample from Elder Pharmaceuticals Ltd, Navi Mumbai, India. Microcrystalline cellulose, Sodium Lauryl sulfate, Povidone, Mannitol, Eudragit-EPO, Polyethylene Glycol, Methanol, Hypromellose, Talc, Magnesium Stearate, Crospovidone and Ac-di-sol were obtained from commercial sources.

3. **MANUFACTURING OF GRANULES AND TABLETS**\textsuperscript{14-16}

Two separate formulation with different approaches were applied in development of Fixed dose combination of Tolfenamic acid and Paracetamol granules. Tolfenamic acid part was prepared by using co-micronization technique.\textsuperscript{14} Paracetamol granules part was prepared by using solid dispersion and granulation method.\textsuperscript{15,16}
The concept of dual novel technologies in development of fixed dose combination of Tolfenamic acid and Paracetamol was basically adopted to improve the release profile of active for rapid drug release. Formulations details were summarized in Table 1.0.

3.1 Granulation of Fixed Dose Formulation

3.1.1 Manufacturing of Tolfenamic Acid Granules

A – Solubility Enhancement of Tolfenamic Acid
Solubility enhancement of Tolfenamic acid was done by using co-micronization technology. Co-micronization of TA with MCC was done by using Air-jet mill, total three cycle of micronization was completed to insure the proper particle size reduction of blend. Milling of blend was performed at primary pressure 4.5-5.0 kg/cm², secondary pressure 4.0-4.5 kg/cm², and screw feeder speed 6-7 rpm.

B – Granulation of Tolfenamic Acid
Co-micronized blend of Tolfenamic acid was mixed in rapid mixer granulator (HSMG-10, Kevin Machinery), 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. Granules were vacuum dried using vacuum dryer (Shree Engineering) at 55°C for 150 – 180 minutes. 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 1.0 using bin blender (Solace Engineering).

3.1.2 Manufacturing of Paracetamol Granules

A – Solubility Enhancement of Paracetamol
Solubility enhancement of Paracetamol was done by using solvent dispersion method. Solid dispersion of Paracetamol was prepared with dissolving Paracetamol with weighed quantity of Methanol, the solution was stirred for 3 hrs to make transparent solution of dispersion phase, the prepared solution than slowly dispersed on the solid material , finally the mixture is allowed to dry at 60°C for 8 hrs in Vacuum tray drier (Shree Engineering).

B – Granulation of Paracetamol (SD) Granules
Wet granulation method was adopted to manufacture Paracetamol (SD) granules. Granulation is required to make proper flow during compression stage. Solid dispersion blend of Paracetamol was granulated by using rapid mixer granulator (HSMG-10, Kevin Machinery). Granules were dried at 60oc in vacuum tray dryer (Shree Engineering) again sizing through number 20 mesh sieve.

C – Taste Masking of Paracetamol (SD) Granules
The dried granules than loaded in fluid bed processor (Pam Glatt), the taste masking polymer solution was prepared by adding Eudragit-EPO in purified water with continuous stirring, than Poly ethylene glycol , and talc was added in the coating solution to make dispersion of coating suspension. The loaded granules were coated in fluid bed processor using top spray granulation.
3.1.3 Lubrication of Granules
Lubrication of Tolfenamic acid and Paracetamol granules were done by mixing of Tolfenamic acid and Paracetamol granules in a suitable blender.

3.2 Manufacturing of Tablet
The compression of granules was completed by using Cadmach single rotary compression machine. Chrome plated punching tools was used to avoid any sticking problem during compression.

4. PHYSICAL EVALUATION OF GRANULES
4.1 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.

4.2 Tapped and Untapped Density
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 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, ‘Vp’ is final volumes of powder in cm\(^3\), ‘Vt’ is tapped volume of powder in cm\(^3\).

4.3 Compressibility Index
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:

\[ Carr’s \ Index \ (\%) = \frac{D_T - D_B}{D_T} \times 100 \]

\( D_T \) = Tapped Density
\( D_B \) = Bulk Density

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

\[ Hausner \ Ratio = \frac{D_T}{D_B} \]

Flow of granules was evaluated by using interpretation between Hausner Ratio and carr’s index as shown in Table – 2.0.

4.5 Angle of Repose
Angle of repose of samples were measured by employing fixed height method, the specific amount of sample was poured through the funnel from the height of 2cm anker GS et. Al 1987).

\[ \theta = \frac{h}{r} \]

Where, ‘\( \theta \)’ is angle of repose, ‘h’ is height, and ‘r’ is radius. The flow properties of granules were than interoperated by using Table as shown in Table 3.0.
5. PHYSICAL EVALUATION OF TABLETS

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.

5.2 Weight Variation of tablets\textsuperscript{22, 23}
Weight variation of tablets was calculated by weighing 20 tablets individually and determining the average weight. Tablet meets the test if not more than two of the individual weights deviate from percentage limits of 7.5% (Indian Pharmacopoeia, 2010).

5.3 Hardness\textsuperscript{22, 23}
The hardness of six tablets was determined using the Erweka type hardness tester and the average values were calculated for each formulation trials.

5.4 Thickness\textsuperscript{22, 23}
The Thickness of the tablets was determined by using Digital vernier calipers (Mitutoyo, Japan). Six tablets were used, and average values were calculated for each formulation trials.

5.5 Friability\textsuperscript{22, 23, 24}
The 20 pre weighed tablets were paced in friability apparatus and tested for the effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each operation for 100 revolutions (Indian Pharmacopoeia, 2010).

\[ Friability \% = \frac{WI - WF}{WI} \times 100 \]

\( W_I = \) Initial weight of Tablets
\( W_F = \) Final weight of Tablets

5.6 Disintegration Time\textsuperscript{22, 23, 18, 25}
Disintegration was carried out by using 600ml of disintegration media mentioning the temperature at 15\(^\circ\)C – 25\(^\circ\)C in disintegration basket.\textsuperscript{18} 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.

5.7 In vitro dispersion Time and Fineness of Dispersion\textsuperscript{22, 23, 26}
Fineness of dispersion is specified in the specification of dispersible tablets (British Pharmacopoeia 2010). This test 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 buffers. 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\(^\circ\)C + 1\(^\circ\)C, the time required to disperse the tablets was determined.\textsuperscript{26} The same dispersion was passed through a sieve screen with a nominal mesh aperture of 710 mm to confirm the fineness of dispersion.

5.8 Wetting Time and Water Absorption Ratio\textsuperscript{18, 24}
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.\textsuperscript{18} 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. 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,

\[ WAR (R) = \frac{W_{\text{wet}} - W_{\text{dry}}}{W_{\text{dry}}} \times 100 \]

\( W_{\text{wet}} \) = weight of wetted tablets
\( W_{\text{dry}} \) = weight of dry tablets

6. ANALYTICAL EVALUATION OF TABLETS

6.1 Assay of Drug Content in Tablets

The analysis for drug content of formulation was developed by HPLC method on the basis specification of individual active in pharmacopoeia and other physicochemical properties.

**Chromatographic condition**

Mobile Phase : Acetic Acid: Water: Ethanol (2:25:75), filter and degas.

HPLC Column : C18, 250 mm x 4.6mm, 5 µ or equivalent

Flow rate : 1.0 ml/min

Detector : 232 nm for Paracetamol & 285 nm for Tolfenamic acid

Injection vol : 10 µl

Run Time : 15 min.

6.2 In-vitro Drug Release Kinetics

In-vitro dissolution studies of all formulation were evaluated for the release profile of formulation. The separate dissolution for Tolfenamic acid and Paracetamol was performed as per the given method in British Pharmacopoeia.

**Dissolution of Tolfenamic Acid**

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

**Dissolution of Paracetamol**

USP dissolution apparatus : Type-II Paddle, 50 RPM

Dissolution Medium : 900 ml, Phosphate Buffer pH 5.8

Temperature : 37 ± 0.5 °C

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

**Dissolution Procedure**

Dissolution of tablets was initiated by placing one tablet in each of six vessels containing respective dissolution medium, using paddle apparatus at respective paddle rpm for 60 minutes.

7. ORGANOLEPTIC EVALUATION

The objective of this study is to conduct and evaluate the Palatability of different formulations of Tolfenamic Acid and Paracetamol Dispersible Tablets. Paracetamol is bitterer as compare to Tolfenamic Acid, so the taste evaluation also designed to check the bitterness of Paracetamol in FDCs. The taste score between 1 and 5 was given to evaluate the taste of formulation. The mean observation was recorded in the evaluation sheet.
8. STABILITY STUDIES\textsuperscript{18,19}

Stability studies are essential to every phase of drug life-cycle. The objective of the current study was to perform the various physical and analytical properties of finished product at specified temperature and humidity for a definite time interval.

9. RESULT AND DISCUSSION

9.1 Physical Evaluation of Granules

A – Co-micronization blend of Tolfenamic Acid

The average particle size which is the mean particle size of 90\% (\(d_{0.90}\)) of particle in sample was recorded for evaluation ad tabulated in the Table 4.0 Graph 1.0. The average particle size of all formulation A-1 to A-4 showing similar particle size profile, which was reflecting an effective and reproducible results of co-micronization processing of Tolfenamic acid using Air jet mill.

B – Physical Evaluation of Granules

The various physical evaluation of lubricated blend such as loss on drying, tapped and untapped density, compressive index, Hausner ratio, and angle of repose for formulation A-1 to A-4 were summarized in Table 5.0.

Since there was not any major difference up to drying step in all formulation, so the physical properties of granules was found similar to each other. The loss of drying for formulation A-4 was 1.96 \% w/w, which was on higher side as compare to remaining formulation such as A-1, A-2, and A-3 as 1.63\% w/w, 1.73\% w/w, 1.49\% w/w respectively. The variation in moisture may be due to uptake of water during granulation stage. Compressive index (Carr’s Index) of blend was found as 18.32\%, 22.64\%, 19.34\%, and 25.33\% for formulation A-1, A-2, A-3, and A-4 respectively. On the basis of compressive index, flow properties of blend indicating fair to poor flow of granules, the poor flow of granules probably due to higher moisture content of formulation A-4.

There were various reasons other than compressibility index of granules such as density profile, angle of repose playing a significant role in flow of granules, so the correlation of all the physical parameters needs to be considered during compression stage. Angle of repose of granules was also evaluated to confirm the flow of granules, the values of angle of repose was found in the range of 34 – 36 indicating a fair to good flow of granules.

9.2 Physical Evaluation of Tablets

The various physical evaluation for tablets of formulation A-1 to A-4 were summarized in Table -6.0. The appearance of tablets found good without any significant defects. 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 Dispersible tablets. The thickness of tablets was also within limit.

The average disintegration time for formulation A-1, A-2, A-3, and A-4 was 85, 65, 90, and 55 second respectively. The changes in disintegration time reflecting the impact of disintegrants during compression stage. 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-3 as compare to formulation A-2 and A-4. The rapid dispersion and wetting reflects the effect of super disintegrants in lubrication stage of granulation. Use of Crospovidone showing rapid bursting and wetting effect as compare to Ac di sol during compression stage. Micronization of Tolfenamic acid during granulation stage also one of the reason behind rapid dispersion of tablets. Same phenomenon of rapid dispersion and wetting reflects in water absorption ratio. The water absorption ratio for formulation A-2 and A-4 was found higher as comparison to remaining formulation. So there is clear impact of disintegrants in enhancement of physical properties of formulations. The comparative evaluation of disintegration, dispersion and wetting time between different formulations were also shown in Graph 2.0.

There were no significant changes observed due to combination of Tolfenamic acid and paracetamol in FDC. The basic requirement of rapid disintegration and dispersion with acceptable hardness also achieved in formulation of the FDCs of Tolfenamic acid and Paracetamol tablets. The diagrammatic presentation of dispersion tendency of tablets is shown in Figure – 1.0.

9.3 Analytical Evaluation of Tablets
The assay of drug content and in vitro drug release profile for tablets of formulation A-1 to A-4 were summarized in Table – 7.0 and Graph 3.0 and 4.0. The drug content of Tolfenamic Acid for all formulation A-1 to A-4 was well within the limits. There was no significant variation observed in the assay of Tolfenamic acid in all formulations. There was no significant variation observed due to co-micronization and solid dispersion for improvement of solubility on finished formulation of dispersible tablets.

The rate of drug release was also evaluated to check the impact of combination of two active in FDCs. The release profile Tolfenamic acid in first 5 minutes time interval was found 70, 76, 68, and 78 % for formulation A-1, A-2, A-3, and A-4 respectively. The release profile of Tolfenamic Acid after 15 minutes for formulation A-1, A-2, A-3, A-4 were 87, 90, 89, and 92 % respectively. The release profile of Tolfenamic acid after 30 minutes for formulation A-1, A-2, A-3, and A-4 were 95, 97, 94, and 98 respectively. There were significant differences observed in release profile of Tolfenamic acid at initial phase but it was found similar at later stage. Among all formulation A-2 and A-4 showed more than 90% release of active within first 15 minutes of dissolution as compare to remaining formulation A-1 and A-3. The use of Crospovidone showing better release as compare to ac di sol in existing system.

The release profile Paracetamol in first 5 minutes time interval was found 28, 30, 29, and 32 % for formulation A-1, A-2, A-3, and A-4 respectively. The release profile of Paracetamol after 15 minutes for formulation A-1, A-2, A-3, A-4 were 87, 82, 85, and 80 % respectively. The release profile of Paracetamol after 30 minutes for formulation A-1, A-2, A-3, and A-4 were 90, 88, 93, and 90 respectively. The
release profile of Paracetamol remains same in all formulation, which showing minor impact of disintegrants during lubrication stage. The solubility of paracetamol already has enhanced by solid dispersion may be one of the reason behind no change in release profile of paracetamol.

10. ORGANOLEPTIC EVALUATION
The organoleptic evaluation (Sensory Taste) such as taste of tablets was evaluated for all four formulation trials. The results of Tablet Sensory Test on taste were summarized in Table 8.0. On the basis of evaluation the range of mean value was found between 4.0 and 5. There were no bitterness in formulation observed in combination of Tolfenamic acid and Paracetamol.

11. STABILITY STUDIES
Optimized formulation (A-2) on the basis of physical, analytical and organoleptic evaluation was kept in stability at accelerated (40±2°C & 75±5% RH) and intermediate storage condition (30 ±2°C & 65±5% RH). Various physical and analytical parameters were evaluated as per the given stability protocol and summarized in Table 9.0. There were no significant changes observed in drug content of Tolfenamic Acid and paracetamol on both storage conditions.

12. CONCLUSION
On the basis of various physical and analytical evaluations formulation of FDCs of Tolfenamic Acid and Paracetamol can be successfully implemented in dispersible dosage form. The disintegration and dispersion properties of finished formulation also fulfill the regulatory requirement (European Pharmacopoeia) in the given formulation. The usage of Crospovidone shows promising effect on disintegration and dispersion of formulation. The fineness of dispersion also comply the specification. The usage of disintegrants improves the release profile of co-micronized Tolfenamic acid but do not have any impact on solid dispersion of paracetamol in FDCs. The rapid release of formulation which was the basic requirement of dispersible tablets also achieved without any changes in fixed dose combination of Tolfenamic acid and paracetamol.

The stability profile of formulation at accelerated conditions such as 40°C temperature and 75% relative humidity for 3 months does not have significant effect on physical and analytical properties of finished product.

13. ACKNOWLEDGEMENT
We are very grateful to Elder Pharmaceuticals for providing Tolfenamic acid, Paracetamol and polymers and Cadila Pharmaceuticals for providing excipients. Authors wish to thank the faculty of Pharmacy JJJT University and Veerayatan Institute of Pharmacy.

REFERENCES


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Table 1: Formulation details of Tolfenamic Acid and Paracetamol Tablets

<table>
<thead>
<tr>
<th>Ingredients/ Formulation Code</th>
<th>Quantity in each tablets (mg/tabs)</th>
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<th>A-2</th>
<th>A-3</th>
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Table 2: Interpretation by Hausner Ratio

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<th>Hausner’s Ratio</th>
<th>Interpretation</th>
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<tr>
<td>1.25</td>
<td>Good flow</td>
<td>20%</td>
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<tr>
<td>&gt;1.25</td>
<td>Poor flow</td>
<td>33%</td>
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Table 3: Interpretation of Angle of Repose

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<th>Flow Properties</th>
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<td>Good</td>
<td>31-35</td>
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<tr>
<td>Fair-aid not needed</td>
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<td>Passable-may hang up</td>
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<td>Poor-must agitate, vibrate</td>
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<td>Very poor</td>
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Table 4: Particle size distribution of Co-micronized blend of Tolfenamic Acid

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<th>Formulation</th>
<th>Average Particle Size (d-0.90) in µm</th>
<th>Particle Size (d-0.50) in µm</th>
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<tr>
<td>A-1</td>
<td>12.23</td>
<td>6.23</td>
<td>3.36</td>
</tr>
<tr>
<td>A-2</td>
<td>11.65</td>
<td>7.01</td>
<td>3.08</td>
</tr>
<tr>
<td>A-3</td>
<td>12.80</td>
<td>6.90</td>
<td>2.96</td>
</tr>
<tr>
<td>A-4</td>
<td>10.29</td>
<td>7.36</td>
<td>3.39</td>
</tr>
</tbody>
</table>

Table 5: Physical properties of Granules (n=3)

<table>
<thead>
<tr>
<th>Physical Properties</th>
<th>A-1</th>
<th>A-2</th>
<th>A-3</th>
<th>A-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss on drying (%w/w)</td>
<td>1.63 ± 0.06</td>
<td>1.73 ± 0.06</td>
<td>1.49 ± 0.08</td>
<td>1.96 ± 0.06</td>
</tr>
<tr>
<td>Bulk density (gm/ml)</td>
<td>0.47 ± 0.03</td>
<td>0.45 ± 0.03</td>
<td>0.50 ± 0.02</td>
<td>0.40 ± 0.16</td>
</tr>
<tr>
<td>Tapped density (gm/ml)</td>
<td>0.58 ± 0.02</td>
<td>0.59 ± 0.03</td>
<td>0.62 ± 0.03</td>
<td>0.54 ± 0.01</td>
</tr>
<tr>
<td>Carr’s Index (%)</td>
<td>18.32 ± 1.52</td>
<td>22.64 ± 1.47</td>
<td>19.34 ± 1.14</td>
<td>25.33 ± 1.48</td>
</tr>
<tr>
<td>Hausner’s Ratio</td>
<td>1.23 ± 0.02</td>
<td>1.34 ± 0.03</td>
<td>1.24 ± 0.02</td>
<td>1.29 ± 0.02</td>
</tr>
<tr>
<td>Angle of Repose</td>
<td>35.53 ± 0.50</td>
<td>36.66 ± 0.58</td>
<td>34.00 ± 1.00</td>
<td>35.53 ± 0.50</td>
</tr>
</tbody>
</table>
Table 6: Physical Evaluation of Tolfenamic Acid and Paracetamol 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>Appearance</td>
<td>Off-white colored, Caplet shape tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Variation (%)</td>
<td>482.36± 2.35</td>
<td>480.96± 1.93</td>
<td>479.36± 2.46</td>
<td>478.39± 2.29</td>
</tr>
<tr>
<td>Hardness (Newton) n=6</td>
<td>39.59± 2.50</td>
<td>35.26± 2.10</td>
<td>40.03± 2.16</td>
<td>30.00± 1.26</td>
</tr>
<tr>
<td>Thickness (mm) n=6</td>
<td>3.22± 0.04</td>
<td>3.20± 0.06</td>
<td>3.19± 0.04</td>
<td>3.21± 0.05</td>
</tr>
<tr>
<td>Friability (% w/w)</td>
<td>0.65</td>
<td>0.76</td>
<td>0.60</td>
<td>0.82</td>
</tr>
<tr>
<td>Disintegration (Seconds)</td>
<td>80 – 90</td>
<td>60 – 70</td>
<td>85 – 95</td>
<td>50 – 60</td>
</tr>
<tr>
<td>Dispersion (Seconds) n=3</td>
<td>115.00± 5.00</td>
<td>74.33± 4.00</td>
<td>105.00± 5.00</td>
<td>62.33± 2.50</td>
</tr>
<tr>
<td>Wetting Time (Seconds) n=3</td>
<td>125.00± 5.00</td>
<td>79.00± 3.61</td>
<td>111.67± 2.89</td>
<td>62.67± 6.81</td>
</tr>
<tr>
<td>Water Absorption Ratio</td>
<td>43.57</td>
<td>47.49</td>
<td>43.89</td>
<td>47.61</td>
</tr>
</tbody>
</table>

Table 7: 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>98.65± 1.30</td>
<td>100.69± 1.97</td>
<td>102.25± 1.30</td>
<td>100.05± 1.24</td>
</tr>
<tr>
<td>(Tolfenamic Acid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Content (%) n=3</td>
<td>97.80± 1.52</td>
<td>99.20± 1.20</td>
<td>99.69± 1.10</td>
<td>99.95± 1.19</td>
</tr>
<tr>
<td>(Paracetamol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Organoleptic Evaluation of FDCs of Tolfenamic Acid and Paracetamol dispersible tablets

<table>
<thead>
<tr>
<th>Organoleptic Evaluation</th>
<th>A-1</th>
<th>A-2</th>
<th>A-3</th>
<th>A-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Value</td>
<td>4.50</td>
<td>5.0</td>
<td>4.75</td>
<td>4.00</td>
</tr>
</tbody>
</table>
Table 9: Stability Compilation for FDCs of Tolfenamic Acid and Paracetamol

<table>
<thead>
<tr>
<th>Test Parameters</th>
<th>Acceptance criteria</th>
<th>Initial results</th>
<th>Condition - 40°C &amp; 75% RH</th>
<th>Condition - 30°C &amp; 65% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>1M</td>
<td>2M</td>
</tr>
<tr>
<td>Appearance</td>
<td>White off white colored round flat faced tablets</td>
<td>Complies</td>
<td>Complies</td>
<td>Complies</td>
</tr>
<tr>
<td>Average weight (mg)</td>
<td>480.00± 5.00%</td>
<td>480.05</td>
<td>481.20</td>
<td>480.56</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>Not less than 20 N</td>
<td>35</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Disintegration Time (Sec)</td>
<td>Not more than 3 minute</td>
<td>60</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>Fineness of Dispersion</td>
<td>To comply as per BP</td>
<td>Complies</td>
<td>Complies</td>
<td>Complies</td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td></td>
<td>1M</td>
<td>2M</td>
</tr>
<tr>
<td>Tolfenamic Acid</td>
<td>90-110% of the labelled amount</td>
<td>100.69</td>
<td>98.20</td>
<td>99.63</td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
<td>99.20</td>
<td>98.36</td>
<td>98.10</td>
</tr>
</tbody>
</table>

Graph 1: Particle size distribution of Co-micronized blend of Tolfenamic Acid
**Graph 2:** The comparative evaluation of disintegration, dispersion and wetting time between different formulations

**Graph 3:** Comparative Release Profile of Tolfenamic Acid in Formulation of FDCs
Graph 4: Comparative Release Profile of Paracetamol in Formulations of FDCs

Figure 1: Dispersion of Tolfenamic Acid and Paracetamol Tablets