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RESEARCH ARTICLE

CONCEPT OF FIXED DOSE COMINATION IN DEVELOPMENT OF DISPERSIBLE TABLETS OF TOLFENAMIC ACID AND PARACETAMOL

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ABSTRACT:

A fixed dose combination (FDCs) is a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. FDCs are the current hot topic of deliberations in the pharmaceutical industry, government (as regulators), NGOs and the pharmaceutical trade. Migraine is one of the most frequent disabling neurological conditions, which also impact the quality of life. There are server fixed dose combination are available in the treatment of migraine but having its own limitations. Existing fixed dose combination of Acetyl salicylic acid and caffeine is not recommended for pediatrics due to side effect of opoids in caffeine. Tolfenamic acid (TA) is one of the classes of non-steroidal anti-inflammatory drugs (NSAIDs). It 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 combination of Paracetamol with Tolfenamic acid can be used as next choice of drug due to lower side effects both the actives. The current research work was set to formulate a dispersible Tablets of Tolfenamic Acid and Paracetamol with application of solid dispersion and co-micronization for solubility enhancement and polymer coating for better taste masking. 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. The comparative evaluation of formulation A-2 with Crospovidone as disintegrant other formulations also showed better and acceptable organoleptic properties.

Keywords: Paracetamol, Tolfenamic Acid, Fixed Dose Combination, Solubility enhancement, Solid Dispersion, Co-micronization, Taste masking, Dissolution Profile, Dispersible Tablets.

Abbreviations: *TA shows Tolfenamic Acid, PA: Paracetamol, FDCs: Fixed Dose Combinations, IP: Indian Pharmacopoeia, BP: British Pharmacopoeia, EP: European Pharmacopoeia, SD: Solid Dispersion, RMG: Rapid Mixer Granulator, mm: millimeter, mg: milligram, RPM: Round per minute, RH: Relative Humidity, QS: Quantity as sufficient, w/w: weight by weight.*

1.0 INTRODUCTION

Fixed Dose Combination (FDCs) is the widely used approach due to its improved medical compliance of patients. A fixed dose combination (FDCs) is a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Recently in India, Fixed Dose Combination (FDCs) of drugs/medicines has drawn the attention of health service providers and the service recipients.[1] FDCs are the current hot topic of deliberations in the pharmaceutical industry, government (as regulators), NGOs and the pharmaceutical trade. Surprisingly, it is not so among the doctors who prescribe the medicines or the patients who consume. Technically, on one hand it increases patient compliance, but on the other hand there are chances of consuming medicines (FDCs available in market in India), more than what is required.[1, 2]

Advantages of Fixed Dose Combinations[2]

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes
- Prevents and/or slows attainment of antimicrobial resistance by eliminating monotherapy (i.e, one drug is never by itself in circulation)
- Allows for synergistic combinations (i.e., trimethoprim/ sulfamethoxazole combination allows each drug to se lectively 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 (single products may have different expiry dates).
- Potential for drug abuse can be minimized by using one drug of the combination for this purpose (i.e., excessive use of the antidiarrheal narcotic diphenoxylateis discouraged by side effects of atropine in the FDC atropine + diphenoxylate)
- Side effects are reduced by using one drug of the combination for this purpose

Disadvantages of Fixed Dose Combinations[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.

Fixed Dose Combination in Migraine Therapy

According to investigation of S. Evers et. Al., migraine is one of the most frequent disabling neurological conditions, which also impact the quality of life.[3, 4] According to migraine research foundation about 18 percent of women and 6 percent of men suffer from migraines. Migraine is also a major concern in pediatrics. About 10 percent of school-age kids get migraines; In fact, about 50 percent of the people who get migraines first experience them before they're 12.[5]

There are server fixed dose combination are available in the treatment of migraine. Caffeine and metoclopramide are used in combination with analgesics and ergotamine in the treatment of migraine attacks.[6] 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.[7, 8] Sumatriptan with combination of Naproxen is also effective in fixed dose combination for migraine.[9]

Rationale behind Selection of Tolfenamic Acid & Paracetamol as FDCs

Tolfenamic acid (TA) is one of the classes of non-steroidal anti-inflammatory drugs (NSAIDs). It is used to treat the symptoms of migraine. A study concludes, "Tolfenamic Acid was found significantly better than placebo in the subjective evaluation of drug efficacy ($p<0.001$) and in reducing the reported hangover symptoms in general ($p < 0.01$). In the Tolfenamic acid group, significantly lower symptom scores were obtained for headache ($p<0.01$), and for nausea, vomiting, irritation, tremor, thirst and dryness of mouth (all $p < 0.05$).[10] 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. [8, 11] Existing fixed dose combination of Acetyl salicylic acid and caffeine is not recommended for pediatrics due to side effect of opoids in caffeine.[4] The combination of Paracetamol with Tolfenamic acid is the next choice of drug due to lower side effects both the actives. 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 formulations in migraine therapy for pediatrics, so there is need to develop a formulation with effective taste masking.[12, 13] So the present study was designed with aim to formulate an effective fixed dose combination with rapid release profile to make more Pharmaco -dynamically active formulation.

2.0 MATERIALS AND EQUIPMENTS

Tolfenamic Acid, Paracetamol, Aspartame and Flavor Vanilla was 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.

3.0 MANUFACTURING OF GRANULES AND TABLETS[14, 15, 16]

The basic aim of the study was to formulate a fixed dose formulation of Tolfenamic Acid and Paracetamol. Two separate granulation with different approaches were applied for manufacturing of Tolfenamic acid and Paracetamol granules. Manufacturing of Tolfenamic acid was prepared by using co-micronization technique.[14] The manufacturing of Paracetamol granules was prepared by using solid dispersion and wet granulation method.[15, 16] The basic aim behind using the novel technologies in development of fixed dose combination of Tolfenamic acid and Paracetamol were to improve the release profile of active for rapid action of formulation. The details of formulations were summarized in the Table 1.0.

3.1 Manufacturing of Granules

3.1.1 Manufacturing of Tolfenamic Acid Granules[17]

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/cm^2, secondary pressure 4.0-4.5 kg/cm^2, 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) 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 1.0 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.

3.1.2 Manufacturing of Paracetamol Granules[17, 18]

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 with continuous triturating to ensure proper mixing of dispersion solution, finally the mixture is allowed to dry at 60^{0}C for 8 hrs in Vacuum tray drier (Shree Engineering). The dried solid dispersion of Paracetamol was passed through #60 mesh to ensure the

uniform particle size for further processing at next stage such as formulation of Paracetamol granules.

B – Granulation of Paracetamol (SD) Granules [18]

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). Binder solution was prepared by dissolving the hypromellose in Luke warm purified water. The concentrations of binder used were kept at 6 % w/w to make uniform granule. The wet mass was granulated by passing them manually through a number 12 mesh sieve. Granules were dried at 60oc in vacuum tray dryer (Shree Engineering) again sizing through number 20 mesh sieve (Yayoi Kawano et al, 2010).[18]

Table 1: Formulation details of Tolfenamic Acid and Paracetamol Tablets

Ingredients/ Formulation Code	**Quantity in each tablets (mg/tabs)**			
	A-1	**A-2**	**A-3**	**A-4**
Part – 1 Tolfenamic Acid Granules				
Tolfenamic Acid	100.00	100.00	100.00	100.00
Microcrystalline Cellulose	50.00	50.00	50.00	50.00
Sodium Lauryl Sulfate	1.25	1.25	1.25	1.25
Povidone (PVP K-30)	2.50	2.50	2.50	2.50
Purified Water	QS	QS	QS	QS
Part – II Paracetamol Granules				
Paracetamol	125.00	125.00	125.00	125.00
Mannitol	125.00	125.00	125.00	125.00
Hypromellose	5.00	5.00	5.00	5.00
Eudragit – EPO	25.00	25.00	25.00	25.00
Polyethylene Glycol	5.00	5.00	5.00	5.00
Talc	5.00	5.00	5.00	5.00
Purified Water	QS	QS	QS	QS
Lubrication of Granules				
Ac-di-sol	25.00	--	25.00	--
Crospovidone	--	25.00	--	25.00
Aspartame	5.00	5.00	5.00	5.00
Flavor Vanilla	5.00	--	--	5.00
Flavor Strawberry	--	5.00	5.00	--
Magnesium Stearate	1.25	1.25	1.25	1.25
Tablet Weight in mg	**480.00**	**480.00**	**480.00**	**480.00**

C – Taste Masking of Paracetamol (SD) Granules[17]

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 (Dinkar Sharma et al, 2012). The loaded granules were coated in fluid bed processor using top spray granulation. The initial spray rate and air flow was kept slow to avoid any fines generation during polymer coating. The coated granules were additionally dried for 30 minutes at 60^0C for proper curing of taste masking granules of Paracetamol. The coated granules of Paracetamol was passed through #20 meshes and were mixed with disintegrants and than lubricated with Magnesium Stearate in Lab model Bin Blender (Solace Engineering).

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[17]

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. 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. The relative humidity of the tabletting area monitored during compression of tablets. Limit of 50% RH was set as the maximum relative humidity at which tabletting was carried out.

4.0 PHYSICAL EVALUATION OF GRANULES

4.1 Physical evaluation of Co-micronization blend[19]

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.[19]

4.2 Loss on drying[20]

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,

$$\%\, LOD = \frac{\text{Weight of solvent in sample}}{\text{Total weight of initial sample}} \text{X}100$$

Approximately 2.0 gms of dried granules were placed on aluminum disk of IR moisture balance. The loss on drying was recorded at 105^0C for 10 minutes of time interval .[20]

4.3 Tapped and Untapped Density[20, 21]

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,

$$\rho b = \frac{M}{Vp}$$

$$\rho t = \frac{M}{Vt}$$

Where, 'ρ_b' is untapped bulk density, 'ρt' 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.

4.4 Compressibility Index[20, 21]

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,

$$Carr's\ Index\ (\%) = \frac{\text{Tapped Densit} - \text{Bulk Density}}{\text{Tapped Density}} X100$$

4.5 Hausner Ratio[20, 21]

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

$$Hausner\ Ratio = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

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

Table 2: Interpretation by Hausner Ratio

Hausner's Ratio	Interpretation	Equivalent Carr's Index
1.25	Good flow	20%
>1.25	Poor flow	33%

4.6 Angle of Repose[20, 21]

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). The diameter of pile formed was measured and angle of repose was calculated by using following formula,

$$\theta = \frac{h}{r}$$

Where, 'θ' 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.

Table 3.0: Interpretation of Angle of Repose

Flow Properties	Angle of Repose
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65

5.0 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[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[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[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[22, 23, 24]

It was intended to determine the loss of mass under defined conditions. The friability of uncoated tablets was determined by using Electro lab Friability Apparatus. 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). The tablets are then de dusted and reweighed. The percentage for friability than calculated using following formula,

$$Friability\ (\%) = \frac{\text{Initial weight of Tablets} - \text{Final weight of Tablets}}{\text{Initial weight of Tablets}} X100$$

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. [24]

5.6 Disintegration Time[22, 23, 18, 25]

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 600ml of disintegration media mentioning the temperature at 15^0C – 25^0C in disintegration basket.[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.[25]

5.7 In vitro dispersion Time and Fineness of Dispersion[22, 23, 26]

Fineness of dispersion is specified in the specification of dispersible tablets (British Pharmacopoeia 2010). 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 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 37^0C + 1^0C, the time required to disperse the tablets was determined.[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[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.[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. Total six tablets were used for the investigation of water absorption time and mean of water absorption time was calculated .[24]

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,

$$WAR\ (R) = \frac{\text{Weight of wetted tablets} - \text{Weight of dry Tablets}}{\text{Weight of dry Tablets}} X\ 100$$

6.0 ANALYTICAL EVALUATION OF TABLETS[23, 27]

6.1 Assay of Drug Content in Tablets[23, 27]

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.[23, 27]

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.
Retention time	:	Paracetamol: about 3.0 min. Tolfenamic Acid: about 8.0 min.
Standard Solution Preparation	:	Transfer an accurately weighed quantity of about 62.5 mg of Paracetamol WS and 50.0 mg of Tolfenamic Acid WS in a 100 ml volumetric flask. Add about 60 ml of mobile phase and sonicate for about 10 minutes to dissolve. Dilute up to the mark with mobile phase and mix well. Further dilute 5 ml of above solution to 50 ml with mobile phase. Use the filtrate for chromatographic injection.
Sample Preparation	:	Weigh and finely powder not less than 20 Tablets and transfer an accurately weighed quantity of powder equivalent to about 125 mg of Paracetamol & 100 mg of Tolfenamic Acid (one tablet) into a 100 ml volumetric flask. Add about 70 ml of mobile phase, and for about 20 minutes to dissolve. Dilute up to the mark with mobile sonicate phase and mix well. Filter the solution through 0.45 µ, filter discarding the first few ml of the filtrate. Further dilute 5 ml of above solution to 100 ml with mobile phase. Use the filtrate for chromatographic injection.

For Paracetamol

$$\frac{Ru \times Std.\ Wt \times 5 \times 100 \times 100 \times P}{Rs \times 100 \times 50 \times Spl.\ wt \times 5 \times 100} \times Avg.\ Wt.$$

Where,

Ru and Rs are peak responses of sample and std preparation in mg

P is the purity of Paracetamol WS on as is basis.

Calculate the % labeled amount, since label claim of Paracetamol is 125 mg/tablets.

For Tolfenamic Acid

$$\frac{Ru \times Std.\ Wt \times 5 \times 100 \times 100 \times P}{Rs \times 100 \times 50 \times Spl.\ wt \times 5 \times 100} \times Avg.\ Wt.$$

Where,

Ru and Rs are peak responses of sample and std preparation in mg

P is the purity of Tolfenamic Acid WS on as is basis.

Calculate the % labeled amount, since label claim of Tolfenamic Acid is 100 mg/tablets.

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. 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 : $37 \pm 0.5\ ^0C$

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 : $37 \pm 0.5\ ^0C$

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.

7.0 ORGANOLEPTIC EVALUATION [18]

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. All four formulations were selected for taste evaluation study with a team of 10 members for taste evaluation. The taste score between 1 and 5 was given to evaluate the taste of formulation. Namely, the scores were set as follows: 1 (Distasteful, equivalent to Paracetamol taste), 2 (Slightly taste, Paracetamol taste remaining fairly), 3 (Mean, Paracetamol taste remaining to some extent), 4 (slightly tasty, Paracetamol taste slightly remaining), 5 (Tasty, no taste of Paracetamol). The mean observation was recorded in the evaluation sheet.

8.0 STABILITY STUDIES [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. It is also required to understand any significant physical and analytical changes in the product, with time under the influence of variety of environmental factors to which drug product may be exposed during its shelf life.

9.0 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.

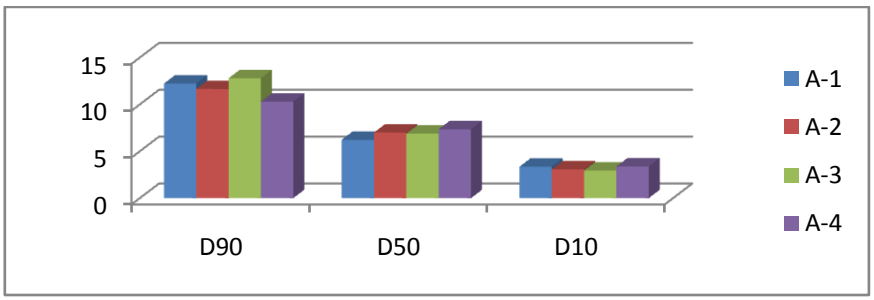
Table 4: Particle size distribution of Co-micronized blend of Tolfenamic Acid

Formulation	Average Particle Size (d-0.90) in µm	Particle Size (d-0.50) in µm	Particle Size (d-0.10) in µm
A-1	12.23	6.23	3.36
A-2	11.65	7.01	3.08
A-3	12.80	6.90	2.96
A-4	10.29	7.36	3.39

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. There were some variation observed in the density profile of lubricated blend but it was not having any significant impact on the properties of granules. 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. So on the basis of various physical properties of granules; it was clearly indicating the justified selection of intra granular diluents such as microcrystalline cellulose and mannitol during wet granulation stage of individual formulations.



Graph 1: Particle size distribution of Co-micronized blend of Tolfenamic Acid

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

Physical Properties	A-1	A-2	A-3	A-4
Loss on drying (%w/w)	1.63 ± 0.06	1.73 ± 0.06	1.49 ± 0.08	1.96 ± 0.06
Bulk density (gm/ml)	0.47 ± 0.03	0.45 ± 0.03	0.50 ± 0.02	0.40 ± 0.16
Tapped density (gm/ml)	0.58 ± 0.02	0.59 ± 0.03	0.62 ± 0.03	0.54 ± 0.01
Carr's Index (%)	18.32 ± 1.52	22.64± 1.47	19.34 ± 1.14	25.33 ± 1.48
Hausner's Ratio	1.23 ± 0.02	1.34 ± 0.03	1.24 ± 0.02	1.29 ± 0.02
Angle of Repose	35.53 ± 0.50	36.66 ± 0.58	34.00 ± 1.00	35.53 ± 0.50

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. On the basis of comparative evaluation of hardness of tablets with friability, friability of tablets was increasing with reducing the hardness of tablets.

Table 6: Physical Evaluation of Tolfenamic Acid and Paracetamol Tablets

Evaluation Parameters	A-1	A-2	A-3	A-4
Appearance	Off-white colored, Caplet shape tablet			
Weight Variation (%)	482.36± 2.35	480.96± 1.93	479.36± 2.46	478.39± 2.29
Hardness (Newton) n=6	39.59± 2.50	35.26± 2.10	40.03± 2.16	30.00± 1.26
Thickness (mm) n=6	3.22± 0.04	3.20± 0.06	3.19± 0.04	3.21± 0.05
Friability (% w/w)	0.65	0.76	0.60	0.82
Disintegration (Seconds)	80 – 90	60 – 70	85 – 95	50– 60
Dispersion (Seconds) n=3	115.00± 5.00	74.33± 4.00	105.00± 5.00	62.33± 2.50
Wetting Time (Seconds) n=3	125.00± 5.00	79.00± 3.61	111.67± 2.89	62.67± 6.81
Water Absorption Ratio	43.57	47.49	43.89	47.61

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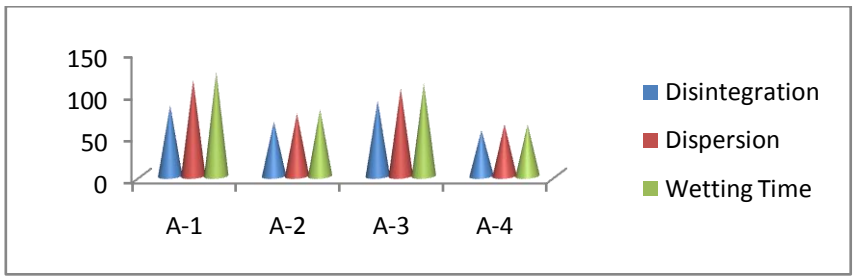
The average disintegration time for formulation A-1, A-2, A-3, and A-4 was 85, 65, 90, and 55 second respectively. The changes in disintegration time reflecting the impact of disintegrants during compression stage. There was some significant difference observed in dispersion and wetting time of formulation, 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. Higher wetting tendency of tablets during dispersion of tablets may also due to usage of sodium lauryl sulfate during granulation 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.

Since the present study was focused on the combination of two actives such as Tolfenamic Acid and Paracetamol in formulation of FDCs, the rapid dispersible granules were utilized in formulation of dispersible tablets. There were no significant changes observed due to combination of Tolfenamic acid and paracetamol in fixed dose combination. 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.



Graph 2: The comparative evaluation of disintegration, dispersion and wetting time between different formulations

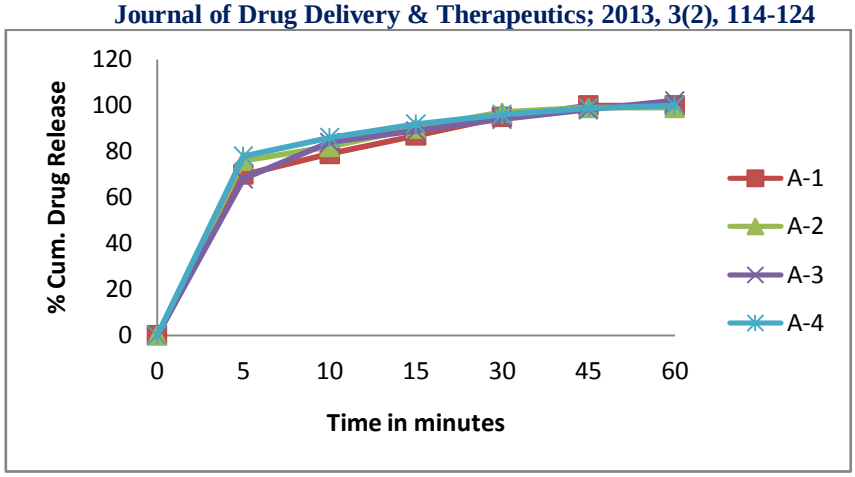
Figure 1: Dispersion of Tolfenamic Acid and Paracetamol Tablets

9.3 Analytical Evaluation of Tablets

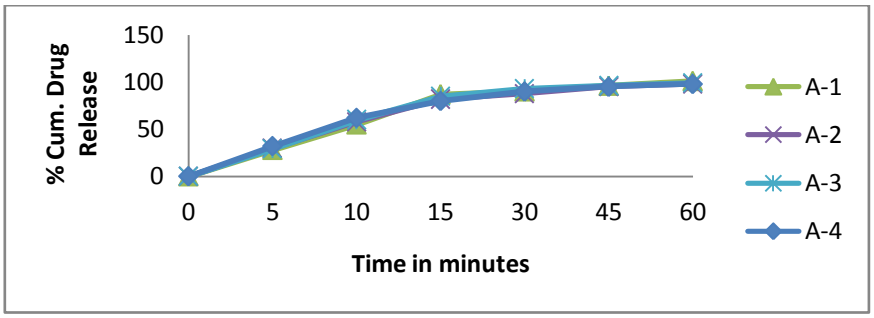
The assay of drug content and in vitro drug release profile for tablets of formulation A-1 to A-4 were summarized in Table – 7.0 and Graph 3.0 and 4.0.

Table 7: Assay of Drug Content in Tablets

Evaluation Parameters	A-1	A-2	A-3	A-4
Drug Content (%) n=3 (Tolfenamic Acid)	98.65± 1.30	100.69± 1.97	102.25± 1.30	100.05± 1.24
Drug Content (%) n=3 (Paracetamol)	97.80± 1.52	99.20± 1.20	99.69± 1.10	99.95± 1.19



Graph 3: Comparative Release Profile of Tolfenamic Acid in Formulation of FDCs



Graph 4: Comparative Release Profile of Paracetamol in Formulations of FDCs

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. The drug content of Paracetamol was found lower side as compare to content of Tolfenamic acid but the loss was not significant to make any major impact on formulation. 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 release profile of Tolfenamic acid was influenced by using disintegrants. 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 by using disintegrants.

10.0 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 The taste of formulations containing strawberry flavor shown pleasant effect as compare to formulation containing vanilla flavor. There was no effect of disintegrants on the taste of formulations, but formulation containing Crospovidone shown rapid wetting tendency in saliva as compare to formulation containing ac di sol as disintegrants.

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

Organoleptic Evaluation	A-1	A-2	A-3	A-4
Median Value	4.50	5.0	4.75	4.00

11.0 STABILITY STUDIES

Optimized formulation (A-2) on the basis of physical, analytical and organoleptic evaluation was kept in stability at accelerated (40±2^{0}C & 75±5% RH) and intermediate storage condition (30 ±2^{0}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. The hardness and dispersion of tablets increased during accelerated storage condition but well within specification. There were no significant changes observed on physical parameters of tablets at intermediate storage condition. The higher humidity condition may be one of the reasons behind moderate changes in dispersion time. Moisture absorbing tendency of dispersible tablets also one of the reasons behind retarded dispersion of tablets. So tablets to be kept at closed and moisture protective containers to avoid any effect of moisture during long term storage. The implementation of alu -alu blister packing also eliminates the permeation of moisture during storage of dispersible tablets.

Table 9: Stability Compilation for FDCs of Tolfenamic Acid and Paracetamol

Test Parameters	Acceptance criteria	Initial results	Condition - 40°C & 75% RH		
			1M	2M	3M
Appearance	White to off white colored round flat faced tablets	Complies	Complies	Complies	Complies
Average weight (in mg)	480.00± 5.00%	480.05	481.20	480.56	479.63
Hardness (in N)	Not less than 20 N	35	30	35	32
Disintegration Time (Sec)	Not more than 3 minutes	60	65	62	70
Fineness of Dispersion	To comply as per BP	Complies	Complies	Complies	Complies
Assay Tolfenamic Acid Paracetamol	90-110% of the labeled amount	 100.69 99.20	 98.20 98.36	 99.63 98.10	 97.20 96.25
			Condition - 30°C & 65% RH		
Appearance	White to off white colored round flat faced tablets	Complies	--	--	Complies
Average weight	480.00± 5.00%	480.05	--	--	482.10
Hardness	Not less than 20 N	35	--	--	38
Disintegration Time	Not more than 3 minutes	60	--	--	65
Fineness of Dispersion	To comply as per BP	Complies	--	--	Complies
Assay Tolfenamic Acid Paracetamol	 90-110% 90-110% of the labeled amount	 100.69 99.20	 --	 --	 99.60 99.63

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. There was no interaction between two active such as Tolfenamic acid and Paracetamol in fixed dose formulation. 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 positive taste results during organoleptic evaluation of FDCs also showing promising acceptance of FDCs in pediatrics and geriatric patient. There was no bitterness of active observed during organoleptic evaluation of tablets. The wetting properties of formulation showed pleasant mouth feeling in case of formulation containing Crospovidone.

The stability profile of formulation at accelerated conditions such as 40^{0}C temperature and 75% relative humidity for 3 months does not have significant effect on physical and analytical properties of finished product. So the product found stable on specified storage and packaging.

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CONFLICTS OF INTEREST: Nil

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