Available online at http://jddtonline.info

RESEARCH ARTICLE

OPTIMIZATION OF GRANULE SIZE AND DISINTEGRANTS ON FORMULATION OF RAPID DISPERSIBLE TABLETS OF TOLFENAMIC ACID

***Chinmay Anand[1], Gali Vidyasagar[2] Manisha Rajmane[3]**

[1]Department of Pharmacy, JJT University, Jhunjhunu, India

[2]Veerayatan Institute of Pharmacy, Jakhania, Kutch, India

[3]Research & Development, Elder Pharmaceuticals, Navi Mumbai, India

**Corresponding Author's E-mail: chinmay_anand@yahoo.com*

ABSTRACT:

Optimization of formulation is the backbone of any robust formulation. Tolfenamic Acid is an orally and parenterally administered Non-steroidal anti-inflammatory drug belonging to the fenamate group. As per the British pharmacopoeia, uniformity of dispersion and fineness of dispersion is the basic requirement of Orodispersible tablets. Delay in dispersion times, variation in dispersion, poor wetting tendency of formulation is some of the measurable factors showing insufficient optimization in formulation of rapid dispersible tablets. The size of granules plays a major role in disintegration and dispersion of rapid dispersible tablets. The present study was aimed to optimize the size of granules and selection of efficient disintegrants for rapid dispersible tablets of Tolfenamic acid. The present work studies effect of various size fractions of granules with superdisintegrants as Explotab, Ac di sol, Kyron T-314, Kollidon CL to determine the influence of disintegrant type and optimization of dispersion. Tolfenamic acid was co-micronized with microcrystalline cellulose and surfactants as sodium Lauryl sulfate. The formulation was than 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 with ac di sol and in first 5 minutes of time interval. The size of granules fraction also having a clear impact on dispersion and fineness of dispersion, the dispersion time was increasing with increasing the granules size fractions.

Keywords: Tolfenamic Acid, Co-micronization, Granules size fraction, Dissolution Profile, Dispersion and fineness of dispersion, Rapid Dispersible Tablets

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

1.0 INTRODUCTION:

The optimization of formulation is the backbone for any robust formulation. Formulation of an effective rapid dispersible tablet with ideal wetting and dispersion properties is required to achieve the rapid release profile of finished product. In preliminary work, the initial formulation was established to enhance the solubility and rapid release of Tolfenamic acid, but the optimization of size of granules and quantity of disintegrants was not the aim of experiment.[1] As per the British pharmacopoeia, uniformity of dispersion and fineness of dispersion is the basic requirement of Orodispersible tablets.[2] Delay in dispersion times, variation in dispersion, poor wetting tendency of formulation is some of the measurable factors showing insufficient optimization in formulation of rapid dispersible tablets.[3]

Granule size has an important role in compression and physical properties particularly disintegration and dispersion properties of tablets. Many workers have investigated the effect of granule size on disintegration and dispersion properties, Kassem et. al, 1972 using a lactose / starch / sodium alginate granulation found that as granule size decreased, the disintegration time increased and the coefficient of variation for disintegration time decreased.[4]

Femi-Oyewo & Adefesco (1993) studied the variation in drug content uniformity of tablets with granule size. The paracetamol content increased as the granule size decreased to the 710-500 µm size fraction, attributed to increased granule flow-rate and tablet weight. Further reductions in size produced lower drug contents, but with fluctuations.[5]

Leonard (1971) studied the influence of granule size on the disintegration time of wet granulated sulphadiazine: maize starch formulations. Three size fractions (1200-1000µm, 850-710 µm, 500-355 µm) were compared and individual tablets were externally lubricated to reduce the effect of magnesium Stearate.[6]

The size of granules plays a major role in disintegration and dispersion of rapid dispersible tablets. Still there is very limited work observed towards optimization of size of granules using various classes of disintegrants. The effect of granule size is dependent on the particular system and there is little work using super disintegrants. The present work studies effect of various size fractions of granules to determine the influence of disintegrant type and optimization of dispersion.

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. Microcrystalline cellulose, Sodium Lauryl sulfate, Povidone, Mannitol, Explotab, Ac di sol, Kyron T-314 and Kollidon CL were obtained from commercial sources.

3.0 METHOD OF MANUFACTURING:

3.1 SOLUBILITY ENHANCEMENT OF TOLFENAMIC ACID:

3.1.1 Co-micronization of Tolfenamic Acid for Solubility [7]

The co-micronization of Tolfenamic Acid and diluents as per the given details of formulation in Table -1 was done by using Air-jet mill (Shree Engineering). Total three cycle of micronization was completed to insure the proper particle size reduction of blend.

3.1.2 Physical evaluation of Co-micronization blend [8]

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.

3.2 MANUFACTURING OF BULK GRANULES: [9]

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. 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.

3.2.1 Separation of the Bulk Granules into different size fractions [10]

Different granule size fractions were obtained by sifting of granules using mechanical shifter. The respective size fraction of granules such as #20 mesh passing and #40 mesh retains were collected by passing the bulk granules on higher sieve size (#20 mesh) and retaining the granules on lower sieve size (#40 mesh). The same procedure was adopted in collection of remaining granules size fraction. The details of granules fraction with different disintegrants were summarized in Table – 2.0.

Table 1: Formulation details Tolfenamic Acid Rapid Dispersible Tablets

Ingredients / Formulation Code	**Explotab**	**Ac-di-sol**	**Kollidon-CL**	**Kyron T-314**
	BG-1	**BG-2**	**BG-3**	**BG-4**
Co-micronization of Tolfenamic Acid				
Tolfenamic Acid	100.00	100.00	100.00	100.00
Microcrystalline Cellulose	80.000	80.000	80.000	80.000
Sodium Lauryl Sulfate	1.250	1.250	1.250	1.250
Granulation Stage				
Explotab	5.000	--	--	--
Ac-di-sol	--	5.000	--	--
Kollidon-CL	--	--	5.000	--
Kyron T-314	--	--	--	5.000
Povidone (PVP K-30)	2.500	2.500	2.500	2.500
Purified Water	QS	QS	QS	QS
Mannitol	50.000	50.000	50.000	50.000
Magnesium Stearate	1.250	1.250	1.250	1.250
Tablet Weight in mg	**240.00**	**240.00**	**240.00**	**240.00**

3.3 MANUFACTURING OF TABLETS: [9]

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.

Table 2: Separation of Bulk Granules in different size Granule Fractions (GF)

Description / Formulation Code	**Explotab**	**Ac-di-sol**	**Kollidon-CL**	**Kyron T-314**
	BG-1	**BG-2**	**BG-3**	**BG-4**
AGF = 1400 – 1000 µm #14/#18	AGF-1	AGF-2	AGF-3	AGF-4
BGF = 1000 – 710 µm #18/ #25	BGF-1	BGF-2	BGF-3	BGF-4
CGF = 710 – 500 µm #25/ #35	CGF-1	CGF-2	CGF-3	CGF-4
DGF = 500 – 250 µm #35/ #60	DGF-1	DGF-2	DGF-3	DGF-4

3.4 PHYSICAL EVALUATION OF GRANULES:

3.4.1 Loss on drying [10]

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.

3.4.2 Tapped and Untapped Density [10, 11]

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, 'ρb' 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.

3.4.3 Angle of Repose [10, 11]

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. 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.

Table 3: Interpretation of angle of repose for Flow Properties

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

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.

3.5.2 Weight Variation of tablets [11, 12]

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%.[12]

3.5.3 Hardness [11, 13]

The hardness of six tablets was determined using the Erweka type hardness tester and the average values were calculated for each formulation trials.

3.5.4 Thickness [13]

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.

3.5.5 Friability [11]

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. The tablets are then de dusted and reweighed. The percentage for friability than calculated using following formula,

$$Friability\ (\%) = \frac{\text{Initial weight of Tablets} - \text{Final weight of Tablets}}{\text{Initial weight of Tablets}} \text{X}100$$

As per the Indian pharmacopoeia the limit for friability tablets should not be more than 1% w/w.[17] The values for both Hardness & Friability can together indicate the mechanical strength of tablet.[14]

3.5.6 Disintegration Time [13, 15]

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.[2] Disintegration was carried out by using 600ml of disintegration media mentioning the temperature at 15^0C – 25^0C 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 [2, 16]

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 $37^0C + 1^0C$, the time required to disperse the tablets was determined.[17] The same dispersion was passed through a sieve screen with a nominal mesh aperture of 710 mm to confirm the fineness of dispersion.

3.6 ANALYTICAL EVALUATION OF TABLETS:

3.6.1 Assay of drug content in Tablets [2, 16]

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 50ml 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

The assay of each formulation was evaluated by taking twenty tablets and crushing the tablets by using Petri dish. 240 mg equivalent weight of powdered Tolfenamic acid was taken in to a 100 ml volumetric flask. Add 80 ml of 0.1 M NaOH. Shake for 30 minutes, dilute to 100 ml with 0.1 M NaOH. Filter, discarding the first few ml of the filtrate and dilute 1 ml of this solution to 100 ml with 0.1 M NaOH. Measure the absorbance of sample and standard preparation at 289 nm using 0.1 M NaOH as the blank with UV Spectrophotometer (Shimadzu). Calculate content of Tolfenamic acid per tablets, by following formula;

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

3.6.2 In-vitro drug release kinetics [2, 16]

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 Phosphate Buffer pH 7.2	:	1000 ml,
Temperature	:	37 ± 0.5 0C
Sampling Times (minutes) :		5, 10, 15, 30, 45, and 60

Preparation of Dissolution Medium

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.

Preparation of Standard solution

Weigh accurately & transfer about 100mg of Tolfenamic acid in a 500 ml volumetric flask. Dissolve in 250ml 0.1M NaOH & dilute up to mark with 0.1 M NaOH. Dilute 1ml of resulting solution to 25 ml with 0.1M NaOH.

Dissolution Procedure

Dissolution of tablets was initiated by placing one tablet in each of six vessels containing 1000 ml dissolution medium, using paddle apparatus at 100 rpm for 60 minutes. 5 ml of 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.

3.7 RESULT AND DISCUSSION:

3.7.1 Physical Evaluation of Granules

A – Loss on Drying

Loss on drying of lubricated blend of various size fractions were tabulated in Table – 4. Lubricated blend with similar size fraction such as AGF1, AGF2, AGF3, and AFG4 had very similar residual moisture contents. The loss of drying of smaller granule size fractions tended to be higher than for the larger fractions, this may be due to the greater surface area for moisture loss occurring during fractionation. This highlights a potential problem in fractionating granulations. Although loss was not major in this case, the effect may be more pronounced in formulations of active with greater hygroscopicity.

Table 4: Effect of Granules size fraction on loss on drying (n=3)

Form. Code/ LOD (%w/w)	Explotab	Ac-di-sol	Kollidon-CL	Kyron T-314
	1	2	3	4
AGF	1.50 ± 0.22	1.45 ± 0.26	1.58 ± 0.26	1.40 ± 0.15
BGF	1.65 ± 0.15	1.60 ± 0.19	1.69 ± 0.26	1.62 ± 0.22
CGF	1.72 ± 0.15	1.79 ± 0.35	1.74 ± 0.19	1.68 ± 0.16
DGF	1.80 ± 0.06	1.88 ± 0.10	1.82 ± 0.09	1.92 ± 0.12

B – Flow Properties of Granules

Untapped density, tapped density, compressibility index, Hausner ratio and angle of repose of each size fraction were tabulated in Table - 5.

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

Evaluation Parameter/ Formulation Code		Explotab	Ac-di-sol	Kollidon-CL	Kyron - T314
		1	**2**	**3**	**4**
Bulk density (gm/ml)	**AGF**	0.40 ± 0.01	0.42 ± 0.02	0.38 ± 0.01	0.36 ± 0.01
	BGF	0.43 ± 0.01	0.42 ± 0.02	0.42 ± 0.01	0.42 ± 0.01
	CGF	0.48 ± 0.01	0.45 ± 0.02	0.44 ± 0.01	0.47 ± 0.01
	DGF	0.52 ± 0.01	0.49 ± 0.01	0.53 ± 0.01	0.55 ± 0.01
Tapped density (gm/ml)	**AGF**	0.60 ± 0.02	0.58 ± 0.02	0.62 ± 0.02	0.64 ± 0.02
	BGF	0.65 ± 0.02	0.62 ± 0.01	0.65 ± 0.03	0.67 ± 0.01
	CGF	0.70 ± 0.02	0.68 ± 0.02	0.62 ± 0.02	0.69 ± 0.03
	DGF	0.79 ± 0.03	0.82 ± 0.01	0.75 ± 0.02	0.86 ± 0.02
Angle of Repose	**AGF**	Fair to pass	Good	Poor	Very Poor
	BGF	Good	Good	Fair to pass	Excellent
	CGF	Excellent	Excellent	Good	Good
	DGF	Fair to pass	Fair to pass	Poor	Fair to pass

Density of granules with different size fraction changes as per the change in the size of granules. The granules with coarser or larger particle size such as 14/18; 1400 – 1000 µm showing less density as compare to granules with less particle size such as 35/60; 500 – 250 µm. This may be due to less void space in granules with less particle size.

Lubricated blend with similar size fraction such as AGF1, AGF2, AGF3, and AFG4 had very similar flow properties. But significant changes observed with change in size fraction of granules. Granules with smaller size fraction (35/60; 500 – 250 µm) and larger size fraction (14/18; 1400 – 1000 µm) showing poor flow properties as compare to granules size fraction between 500 and 1000 µm (18/25; 1000 – 710 µm & 25/35; 710 – 500 µm).

On the basis of physical evaluation of granules with various size fractions it was clearly observed the impact of particle size of granules on the various physical parameters such as density and flow properties of granules.

3.7.2 Physical Evaluation of Tablets

The various physical evaluations for tablets with various size fraction of formulation were summarized in Table - 6.

A - Appearance of Tablets

The appearance of tablets found good without any significant defects for all formulations.

B - Weight Variation of Tablets

All weights falls within the range 240mg ± 7.5% . Lubricated blend with similar size fraction such as AGF1, AGF2, AGF3, and AFG4 had similar variation in weight. There were significant changes observed with change in size fraction of granules. Granules with smaller size fraction (35/60; 500 – 250 µm) showing higher side of variation during compression stage, this was probably due to poor flow properties of granules. Compression with medium size fraction of granules (25/35; 710 – 500 µm) showing less weight variation as compare to granules size fraction between 1000 and 1400 µm (14/18; 1400 – 1000µm). This was basically due to change in particle size and flow properties of granules during compression stage.

In agreement with others (Kassem et aI, 1972; Femi-Oyewo & Adefeso, 1993), weight variation decreased as the granule size decreased due to better die fill and closer, more uniform packing.[4, 5] Tablet weight did not increase with granule size because die fill was adjusted for each granule fraction to give the correct mean tablet weight. This was necessary to avoid increases in tablet crushing strength resulting from greater tablet weights which would complicate the interpretation of results.

C - Tablet Thickness and Hardness

The thickness of tablets with different size fraction was compressed at fixed thickness range to avoid any variation during compression stage. For all formulations and granule size fractions, tablet hardness / crushing strength increased with reducing the particle size fraction of granules. Disintegration time and tablet crushing strength may be directly related. [5] The increased inter particulate bonding makes particle separation in the deaggregation process more difficult. At the same compression force, granule size fractions containing intra-granular Explotab and Ac-Di-Sol tend to produce tablets of slightly higher crushing strengths than those Containing Kollidon-CL and Kyron K-314.

D - Tablets Friability

Resistance to abrasion or friability is an important consumer attribute. It indicates how the tablet will withstand the tumbling effect encountered during manufacture, packaging, transport and handling. There is no clear relationship between granule size fraction and tablet friability. In all formulations friability decreased with decreasing size of granules, but again there were higher percentage of friability were observed in tablets with less size fraction of granules such as formulation DGF (35/60; 500 – 250 µm). However, friability does not appear to be simply a function of crushing strength. For example, tablets containing intra-granular Kyron T-314 tended to have lower crushing strength than those containing intra-granular Explotab and friability also tended to be lower. Tablet crushing strength, however,

does not necessarily reflect granule strength and this may explain the observed differences.[18]

E - Tablet Disintegration

The disintegration of tablets was checked as per the specification of disintegration for dispersible and Orodispersible tablets mentioned in British Pharmacopoeia were changes in disintegration time observed with change in type of disintegrant. So relationship between granule size and tablet disintegration and deaggregation is dependent on intra-granular disintegrant type. A graphical comparison of impact of particle size on tablet disintegration has shown in Graph- 1.

Ac-Di-Sol caused rapid tablet disintegration as compare to other intra-granular disintegrants. In tablets containing intra-granular Ac-Di-Sol, the time taken for disintegration or deaggregation was largely unaffected by granule size fraction. But the longer disintegration times were observed with increasing granule size fraction in case of Kollidon-CL and Kyron T-314. The higher disintegration of larger granules with Kollidon-CL, and Kyron T-314 was clearly observed due to slower bursting or deaggregation of granules during disintegration process. The larger granules fraction containing Kollidon-CL and Kyron T-314 was not able to pass the disintegrating sieves during disintegration resulted higher disintegration time.

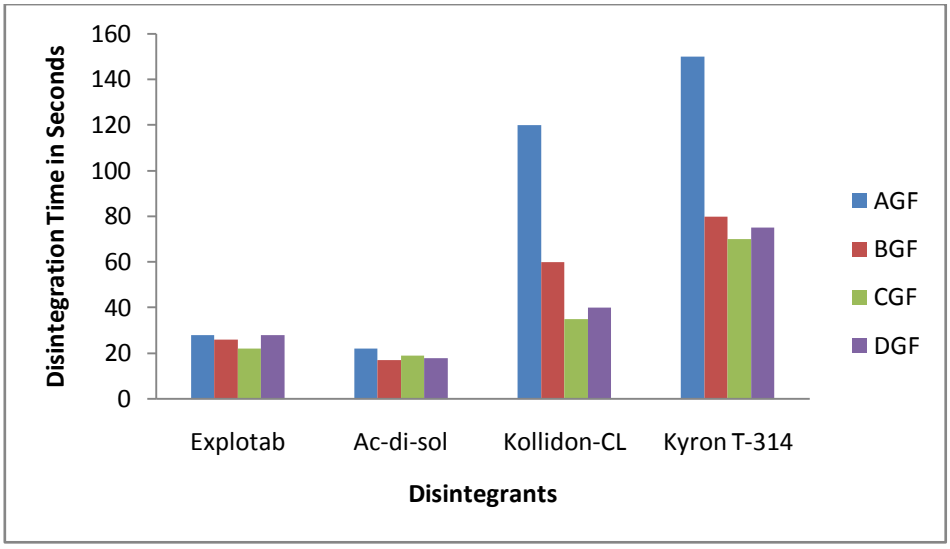
Table 6: Physical evaluation of tablets

Evaluation Parameters/ Formulation Code		A-1 Explotab	A-2 Ac-di-sol	A-3 Kollidon-CL	A-4 Kyron T-314
Appearance	**All**	Off-white colored, round flat faced tablet			
% Wt. Variation	**AGF**	240.62± 4.20	241.34± 3.89	240.36± 4.25	239.25± 3.98
	BGF	241.20± 2.35	239.96± 2.30	238.25± 2.10	242.36± 1.96
	CGF	238.65± 2.20	237.96± 1.65	241.01± 1.80	238.85± 1.56
	DGF	243.29± 3.68	240.62± 3.95	242.12± 4.05	241.20± 3.80
Avg. Hardness (in Newton)	**AGF**	25.20± 2.50	28.00± 2.32	20.30± 3.00	22.40± 3.12
	BGF	28.67± 2.45	27.50± 2.20	24.50± 2.10	26.20± 1.80
	CGF	30.67± 2.20	32.00± 2.18	28.20± 2.18	25.00± 1.96
	DGF	32.67± 1.80	35.00± 1.80	30.33± 1.75	28.10± 1.26
Avg. Thickness (in mm)	**AGF**	3.19± 0.05	3.18± 0.06	3.20± 0.04	3.19± 0.06
	BGF	3.19± 0.04	3.19± 0.08	3.19± 0.10	3.20± 0.08
	CGF	3.18± 0.02	3.21± 0.04	3.20± 0.06	3.19± 0.06
	DGF	3.20± 0.05	3.19± 0.06	3.18± 0.06	3.20± 0.05
Friability (in % w/w)	**AGF**	0.58	0.65	0.56	0.62
	BGF	0.43	0.38	0.32	0.45
	CGF	0.42	0.30	0.29	0.32
	DGF	0.62	0.52	0.48	0.49
Disintegration (in Seconds)	**AGF**	25-30	20-25	100-150	120-180
	BGF	25-30	15-20	45-70	60-100
	CGF	20-25	18-20	30-40	50-80
	DGF	22-30	15-22	35-45	60-90
Dispersion (in Seconds)	**AGF**	58.27± 4.12	53.67± 3.53	156.6± 12.3	180± 15.53
	BGF	60.29± 5.13	50.67± 4.06	110.23± 16.3	150.3± 12.65
	CGF	48.63± 3.65	40.67± 1.53	89.32± 12.63	90.67± 15.36
	DGF	50.26± 2.36	38.02± 1.60	120.3± 15.30	100.32± 9.63

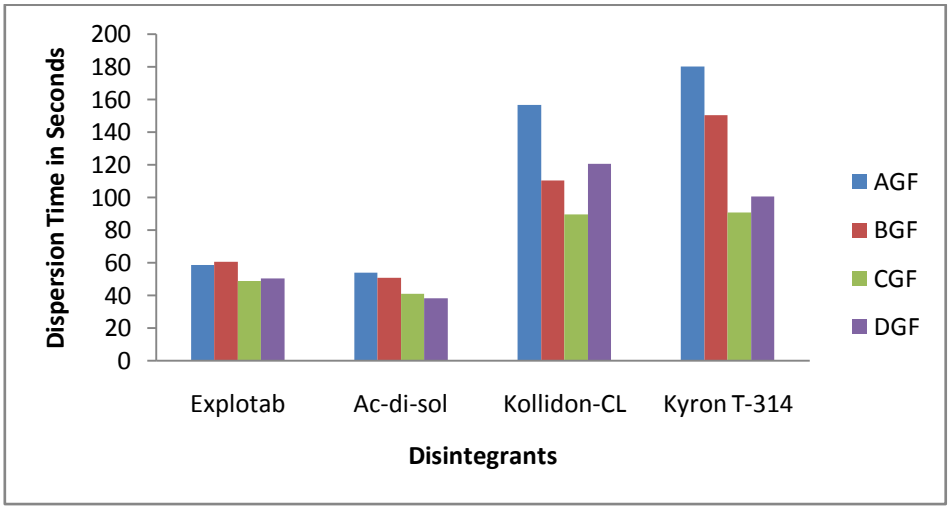
There were very minor differences observed in disintegration time of smaller granules fraction, but the overall disintegration time does not show the significant changes. Poorer disintegrant efficiency means that size reduction of granules is more dependent on dissolution and therefore larger granules tend to exhibit longer disintegration times.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Disintegrant efficiency of Ac-Di-Sol is higher than Explotab and Kyron T-314 because whereas the latter two mainly cause disintegration by swelling, Ac-Di-Sol combines high swelling activity with wicking properties.[19] Wicking activity causes rapid penetration of water into the tablet and allows intra-granular Ac-Di-Sol to function effectively in a tablet without extra-granular disintegrant.[20, 21]



Graph 1: Effect of particle size fraction and various disintegrants on Disintegration Time of Tablets



Graph 2: Effect of particle size fraction and various disintegrants on Dispersion Time of Tablets

F - Tablet Dispersion and Fineness of dispersion

The dispersion of the tablets provides the effective evaluation of the dispersion and deaggregation of granules in to fine particle which can be correlated for in-vivo release of formulations. A graphical comparison of impact of particle size on tablet dispersion and fineness of dispersion has shown in Graph - 2.

In tablets compressed from all granule size fractions, the disintegration times remained the same but a significant changes was observed in dispersion time and fineness of dispersion. The dispersion time with Ac-di-sol and Explotab taking less time as compare to formulation containing Kyron T-314, and Kollidon-CL. Ac-Di-Sol caused rapid tablet dispersion, which is hardly affected by granules size fraction. Explotab functioned less efficiently than Ac-Di-Sol. Increasing granule Size and hardness adversely affected the dispersion of tablets containing intra-granular Explotab. Dispersion time increased with granule size and the fineness of dispersion also showing the same tendency.

Generally, tablets made from the larger granules (1400-1000µm) had a marbled surface, probably indicating higher inter-granular porosity due to the lack of fine particles to fill inter-granular spaces. These granules when tested for fineness of dispersion, shows retention of particle instead of rapid dispersion of granules (with Ac-di-sol and Explotab). The same tendency also observed in case of smaller granule size fraction (500-250µm) with Kollidon-CL and Kyron T-314. This is due to overall reduction in tablet porosity because of fine material contained in the particular granules size fraction. Dispersion of tablets with granules size fraction between 500 and 1000 µm (18/25; 1000 – 710 µm & 25/35; 710 – 500 µm) showing excellent dispersion without any retention, the effect of disintegrants respect to final dispersion also not observed during dispersion study of tablets. Overall the tablets formulated with Ac di sol

showing better dispersion as compare to other disintegrants used in formulation.

3.7.3 Analytical Evaluation of Tablets

A - Assay of drug content in Tablets

Assay of tablets for various formulations were summarized in Table - 7. For tablets containing Ac-Di-Sol, Explotab, Kollidon-CL, and Kyron T-314 the active drug content of the different granule fractions were similar. There were some variation observed in the assay of tablets with smaller granules size fractions, but practically the differences were small. So there were no significant effects of granules size fraction on active content of formulations.

Table 7: Effect of Granule size fraction on Drug Content of Tablets

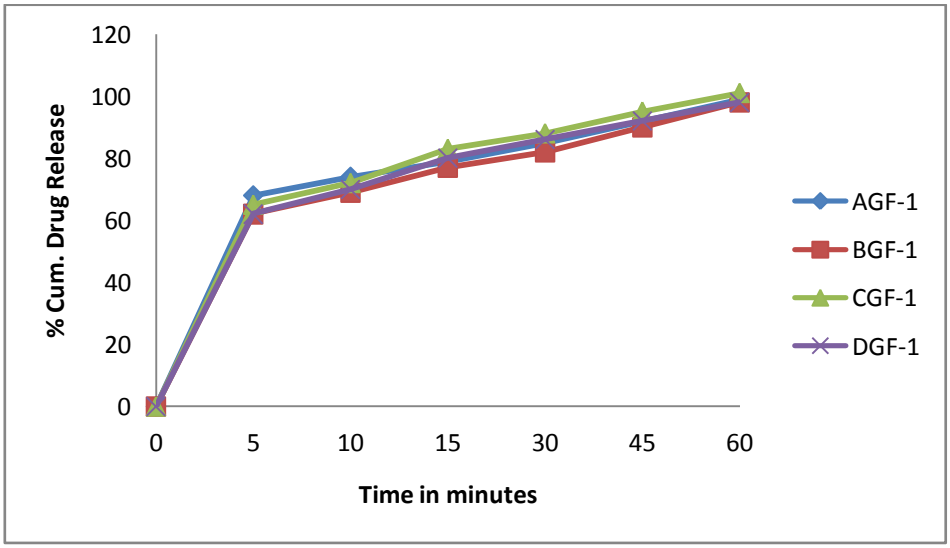
Formulation Code	Explotab	Ac-di-sol	Kollidon-CL	Kyron T-314
	1	2	3	4
AGF	99.50± 1.20	100.23± 1.25	101.20± 1.96	97.89± 1.96
BGF	100.20± 1.35	98.63± 1.10	102.3± 1.20	100.96± 1.23
CGF	101.23± 1.35	100.96± 1.25	97.25± 1.39	98.96± 1.96
DGF	100.20± 1.05	100.35± 1.09	100.23± 1.95	100.23± 1.20

B - In-vitro Drug Release Profile

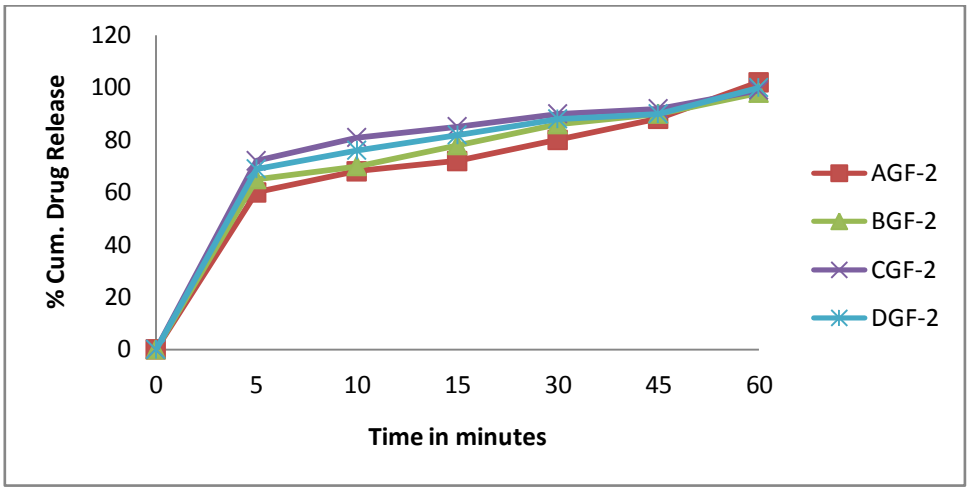
The release profile of various formulations was analyzed to evaluate the actual effect of disintegrants and granules size fraction and summarized in Graph - 3 to 6. The release profile of Ac-di-sol with higher granules size fractions (1400 – 1000, 1000 – 710 µm) showing similar but slow release profile in first 5 minutes time profile as compare to lower granules size fraction (710 – 500, 500 – 250 µm). There was no impact of size fraction at later stage in release profile of tablets. The basic properties of prompt release which is also basic requirement in formulation of rapid dispersible tablets can be easily achieved by using the optimized size of granules in development of rapid dispersible tablets.

The release profile of Explotab with different granules size fraction shows significant changes with change in size of granules. The release profile of smaller granules fraction (500-250µm) is lower as compare to remaining granules size fractions. This may be due to high swelling of Explotab during deaggregation. [19] The increase compressibility and hardness also may be the reason for slower release of smaller granules size fraction. There was lowest release of active was observed in first five minutes with disintegrants such as Kollidon-CL, and Kyron T-314, the same phenomenon also observed during dispersion of tablets. The slow release was basically due to slower bursting effect of tablets at initial time points during dissolution study. The release profile at later stages was same but low as compare to Explotab and Ac di sol.

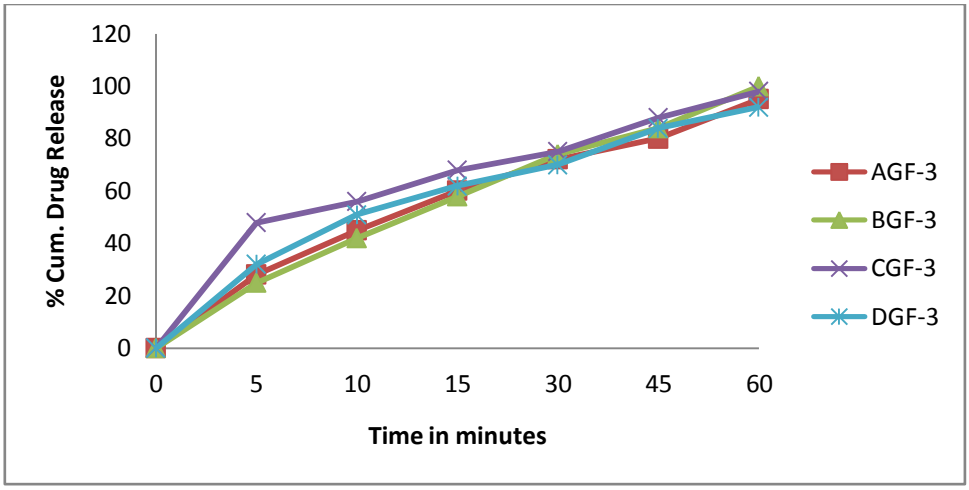
On the basis of overall evaluation of release profile of tablets compressed with various size fractions of granules the formulation having Ac di sol and Explotab shows better release profile in first 5 minutes of release kinetics. The tablets compressed with granules size fraction between 500 and 1000 µm (1000 – 710, 710 – 500 µm) showing better release profile with all disintegrants used in formulation of rapid dispersible tablets.



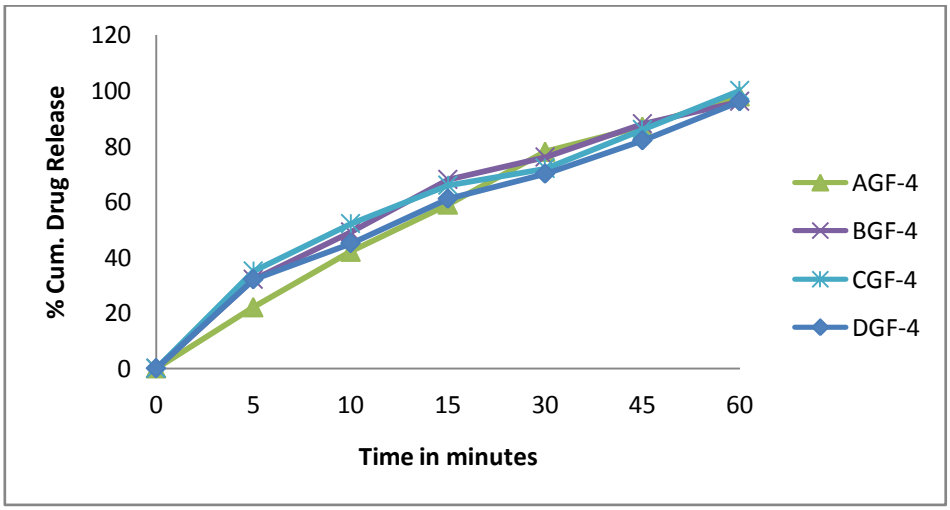
Graph 3: Effect of Granule Size Fraction on In-vitro drug release profile of Tablets with Explotab as disintegrant



Graph 4: Effect of Granule Size Fraction on In-vitro drug release profile of Tablets with Ac di sol as disintegrant



Graph 5: Effect of Granule Size Fraction on In-vitro drug release profile of Tablets with Kollidon-CL as disintegrant



Graph 6: Effect of Granule Size Fraction on In-vitro drug release profile of Tablets with Kyron T-314 as disintegrant

CONCLUSION:

There was a clear effect of various disintegrants with different granules size fraction was observed on disintegration, dispersion and fineness of dispersion of rapid dispersible tablets. The rate and variability of dispersion was greatly influenced by intra-granular disintegrant type, which had a greater influence on dispersion and disintegration properties of tablets. Tablets containing Ac-Di-Sol disintegrated most rapidly with least variability. The dispersion characteristics of tablets containing intra-granular Explotab / Kyron T-314 are less

 ISSN: 2250-1177 CODEN (USA): JDDTAO

consistent. Used alone intra-granular, disintegrants efficiency can be summarized as:

Ac-Di-Sol > Explotab > Kyron T-314 > Kollidon-CL

The size of granules fraction also having a clear impact on dispersion and fineness of dispersion, the dispersion time was increasing with increasing the granules size fractions.

On the basis of various physical and analytical investigations formulation containing Ac-di-sol (Formulation BGF-2 and CGF-2) was the most suitable candidate to use as disintegrants in this particular system. The choice of most suitable granules fractions was observed between 500 – 1000µm to formulate rapid dispersible tablets in this particular system.

ACKNOWLEDGEMENT:

We are very grateful to Elder Pharmaceuticals for providing Tolfenamic Acid and Cadila Pharmaceuticals Limited for providing excipients. Authors wish to thank the faculty of Pharmacy JJT University and Veerayatan Institute of Pharmacy.

CONFLICTS OF INTEREST: Not applicable.

REFERENCES

1. Chinmay Anand, Gali Vidyasagar, Manisha Rajmane, Vijay Agrawal, Shubhangi Sawant (2012): "Approach of Co-micronization in Solubility Enhancement and Release Profile of Rapid Dispersible Tablets of Tolfenamic Acid", Journal of Drug Delivery & Therapeutics; 2012, 2(6), pp. 29-36.
2. British Pharmacopoeia 2010 Edition, (2010): London, UK.
3. Do-Soon Kim, Tae Young Kim, Jong Nam Lee, Ki Hwan Hwang, Yong Sang Lee (2006): Optimization of self-dispersible floating granule (UG) of Flucetosulfuron and its herbicidal performance, The Korean Journal of Pesticide Science Vol. 10, No. 1. , pp.28 – 35.
4. Kassem, A. M., Sakr, A. M. & Mesha, H. S. (1972): "Effect of granule size on physical standards of tablets", Mfg. Chern. Aerosol News, 43: pp. 24-27.
5. Femi-Oyewo, M. N. & Adefeso, A. (1993): "Influence of granule size on paracetamol granule and tablet properties: Effect of surfactant incorporation." Pharmazie, 48: pp. 120-123.
6. Leonard, G. S. (1971): "The effect of disintegrating agents on some properties of compressed tablets". PhD Thesis, University of London.
7. Kaur Jaspreet, Singh Gurpreet, Saini Seema, Rana AC, "Particle Size Reduction Of Aceclofenac by using Surfactants And Micronization For Nanocarrier Entrapment", Journal of Drug Delivery & Therapeutics; 2012, 2(5), 42-44.
8. Betz G, "The role of drug solubility in formulation development." In: Rong Liu, ed. Water-insoluble Drug Formulation, CRC; Press Taylor and Francis Group, 2008,615, 19-9c22.
9. Dinkar Sharma, Reetika Chopra And Neena Bedi, "Development And Evaluation of Paracetamol Taste Masked Orally Disintegrating Tablets Using Polymer Coating Technique", Int. J. Pharm. Pharm. Sci, Vol 4, Suppl 3, 129-134.
10. Christine Elizabeth Strachan (2000): "The Formulation Technology of dispersible Tablets", School of Pharmacy, Liverpool John Moores University.
11. Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman H.A, Kanig JL, The Theory and Practice of Industrial Pharmacy, 3rd Ed, Varghese publishing house, Bombay. 1987, 293-345.
12. Indian Pharmacopoeia, (2010): Ministry of Health and Family welfare, Government of India, Controller of Publication, New Delhi, India.
13. Yayoi Kawano, Akihiko Ito, Masanaho Sasatsu, Yoshiharu Machida, and Hiraku Onishi, "Preparation and Evaluation of Taste Masked orally disintegrating tablets with granules made by wet granulation method." The Pharmaceutical Society of Japan, 2010, Vol 130 (12), 1737-1742.
14. Jyoti Singh and Meenakshi Bajpai, "Effect of superdisintegrants in the formulation of taste-masked orodispersible tablets of Tizanidine HCl," Journal of Pharmacy Research 2011,4(7), 2175-2178.
15. Wells JI, "Encyclopedia of Pharmaceutical Technology." Swarbrick J, Boylan, JC (Eds.), 1996, 401.
16. European Pharmacopoeia, 7th Ed., 2010. Council of Europe, Strasbourg, France.
17. Bi YX, Sunada H, Yonezawa Y, Danjo K, "Evaluation of rapidly disintegration tablets by direct compression method." Drug Develop Ind Pharm, 1999, 25, 571-81.
18. Wells, J. I. & Walker, C. V. (1983): "The influence of granulating fluids upon granule and tablet properties: the role of secondary binding". Int. I. Pharm., 15: pp. 97-111.
19. Caramella, C., Ferrari, F., Conte, D., Gazzaniga, A., La Manna, A. & Colombo, P. (1989): "Experimental evidence of disintegration mechanisms". Acta. Pharm. Techno., 35: pp. 30-33.
20. Gissinger, D. & Stamm, A. (1980): "A comparative evaluation of the properties of some tablet disintegrants". Drug Dev. Ind. Pharm., 6: pp. 511-536.
21. Gordon, M. S., Chatterjee, B. & Chowhan, Z. T. (1990): "Effect of the mode of croscarmellose incorporation on tablet dissolution and friability". 1. Pharm. Sci., 79: pp. 43-48.

