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## DESIGN AND DEVELOPMENT OF ACECLOFENAC FAST DISSOLVING TABLETS BY AMORPHOUS SOLID DISPERSION TECHNIQUE USING MODIFIED AEGLE MARMELOS GUM

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### ABSTRACT

Aceclofenac is a non-steroidal anti-inflammatory, analgesic and antipyretic drug used in the treatment of rheumatoid arthritis, post-traumatic pain, musculo-skeletal and joint disorders. Problem with this drug is its poor solubility in water and hence poor bioavailability after oral administration. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. These drug molecules are often lipophilic and hence dissolution may be rate-limiting step in drug absorption from solid oral dosage forms. The increasing interest of the technology of dosage form with natural biopolymers has become the reason for undertaking present investigation on the possibility of Aegle marmelos gum (AMG) application in the preparation of oral solid dosage form of a poorly water-soluble drug. In the present study an attempt was taken to study the effect of AMG and modified Aegle marmelos gum (MAMG). MAMG was prepared using heat treatment technique. It was characterized for viscosity, swelling index and water retention capacity. The effect of polymer, its concentration and method of preparation on solubility enhancement were studied using solubility and dissolution studies. The result of solubility study showed increase in solubility of Aceclofenac with increase in concentration of AMG and MAMG, and change of technique from physical mixture to co-grinding to solid dispersion. The prepared SDS were characterized by FT-IR studies. The study confirmed that there was no interaction between drug and carrier. The results of present investigation indicated that solid dispersion of Aceclofenac with MAMG could be useful in developing fast dissolving tablets with increased solubility and hence improved dissolution and oral bioavailability of poorly water soluble drug.

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### Key Words

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Solubility enhancement.

## INTRODUCTION

Fast dissolving tablets are the novel dosage technology that involves the rapid disintegration or dissolution of dosage form, into a solution or suspension in the mouth without the need for water<sup>1-5</sup>. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30-50s after administration<sup>6</sup>. The solution containing the medicament is swallowed, and then the medicament is absorbed through the gastrointestinal epithelium to reach the target and produce the desired pharmacological action.

A survey of 6158 GP patients conducted in Norway indicated that approximately 26% of all patients do not take their prescribed medication as they encountered problems when swallowing conventional tablets<sup>7</sup>. This may be due to phagophobia, odynophagia and pseudodysphagia experienced by children and elderly patients<sup>8</sup>. FDTs will help to overcome some of these problems. In addition to improving patient compliance, FDTs have been investigated for their potential in increasing the bioavailability of poorly water-soluble drug through enhancing the dissolution profile of the drug<sup>9-10</sup>.

Product development scientists often encounter significant difficulties in solving the problem of poor water solubility of drug candidates in the development of pharmaceutical dosage forms. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water soluble or water-insoluble categories. More than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility<sup>11</sup>.

The rate at which poorly water-soluble drug dissolves is often the slowest step and therefore exerts rate-limiting effect on drug bioavailability. In case of drugs with the dissolution rate limited absorption, reduction in particle size often increases the rate of dissolution and the amount of drug absorbed. Many polymers have limitations in enhancing solubility of poorly water-soluble drugs due to their high viscosity. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of

polymers. Use of natural polymer is more beneficial because of their low cost, abundant availability, and biodegradability<sup>12</sup>.

Recently, many natural polymers have been evaluated for their use in new applications. The dissolution rate of drugs from the formulations containing viscous carriers is generally low due to the formation of gel layer on the hydrated surfaces, which prevents the drug release during dissolution. This can be overcome during tablet formulation by adding disintegrants. However, it is reported that the swelling ability of the carrier improves dissolution rate of poorly water-soluble drug. It is necessary to modify the gum in such a way that its swelling ability remains same and viscosity should be reduced. This can be achieved by heating method.

Aegle marmelos gum is obtained from the fruits of Aegle marmelos belonging to family Rutaceae is indigenous to India<sup>13</sup>.

## MATERIALS AND METHODS

Aceclofenac was obtained as gift sample from Rantus pharma pvt ltd, Hyderabad, India. Fresh white gum of Aegle marmelos was collected from authenticated plant fruits in local area of Gulbarga district of Karnataka, India. CCS, MCC were obtained from Maple biotech pvt ltd, Pune, India. D.Mannitol, Talc and Magnesium stearate were purchased from S.D Fine chemicals ltd, Mumbai, India. All other chemicals were of analytical grade.

### Preparation and purification of Aegle marmelos gum (AMG)

The well-dried gum was powdered in mortar, passed through sieve no.80 and solubilised in distilled water. The concentrated solution was precipitated in acetone. The precipitate was separated and dried at 60°C. The dried gum was powdered and stored in tightly closed container for further usage<sup>13</sup>.

### Preparation of Modified Aegle marmelos gum (MAMG)<sup>14</sup>

Aegle marmelos gum (AMG) was powdered and placed in a porcelain bowl and heated on a sand bath for different time periods at different temperatures. The

results of swelling capacity and viscosity studies revealed that the modified gum is processed swelling property similar to AMG, but viscosity was decreased as a function of temperature and time period of heating. But the AMG samples were charred when heated at 135<sup>o</sup>C. In the preparation of modified form of AMG, no further change in viscosity of AMG was observed by heating it at 120<sup>o</sup>C for more than 2 hrs. Hence, the condition of heating at 120<sup>o</sup>C for 2 hrs were selected to prepare modified form of AMG (MAMG). The prepared MAMG was received (100 #) and stored in airtight container at 25<sup>o</sup>C.

#### Characterization of AMG and MAMG

##### Swelling Index (SI):

About 1.0g of AMG/MAMG powder was accurately weighed and transferred to a 100ml stoppered measuring cylinder. Initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100ml mark with distilled water. The volume occupied by the gum sediment was shaken gently and set aside for 24hrs at room temperature. The volume occupied by the gum sediment was noted after 24hrs. The swelling capacity of AMG/MAMG was expressed in terms of swelling index (SI). SI was expressed as a percentage and calculated from the following equation.

$$SI = \frac{(X_t - X_o)}{X_o} \times 100$$

Where X<sub>o</sub> is the initial height of the powder in graduated cylinder and X<sub>t</sub> denotes the height occupied by swollen gum after 24hrs<sup>15</sup>.

##### Water Retention Capacity:

The contents from the measuring cylinder from the above test were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100ml graduated cylinder. The volume of water collected was noted and the difference between the original volume of the mucilage and the volume drained was taken as water retained by the sample referred as water retention capacity or water absorption capacity of the gum.

##### Viscosity measurement:

The viscosity of 1% (w/v) AMG/MAMG solution was measured according to the US pharmacopoeia specification, using Brookfield viscometer.

##### Preparation of co-grinding mixer:

Co-grinding mixer (CG) of Aceclofenac and AMG and MAMG were done by grinding a physical mixer of Aceclofenac and/AMG or MAMAG in a 1:1.25 weight ratio for 20 min, in a ceramic mortar and sieved through 100#. To ascertain the effect of method, carrier or both on the dissolution rate of drug, Aceclofenac alone was grounded for 20minutes.

##### Preparation of physical mixers:

The physical mixers (PM) of Aceclofenac, AMG and MAMG were obtained by blending the Aceclofenac with AMG or MAMG in a 1:1.25 w/w ratio (Drug: polymer) in a double cone blender.

##### Preparation of solid dispersion of Aceclofenac with AMG and MAMG:

Aceclofenac was dissolved in Ethanol in a china dish with stirring. To this solution, AMG or MAMG were added at different ratio (1:0.5, 1:0.75, 1:1, 1:1.25). Then mixed well and solvent was evaporated at room temperature and dried in hot air oven at 50<sup>o</sup>c for 4 hrs. The resultant mass was passed through sieve no 60 and stored in desicator.

##### Solubility study:

The apparent solubility of Aceclofenac (A), co-grinded Aceclofenac alone (ACG), co-grinding of AMG (CGAMG), co-grinding of MAMG (CGMAMG), physical mixer of Aceclofenac with AMG (PMAMG), physical mixer of Aceclofenac with MAMG (PMMAMG), solid dispersions of Aceclofenac with AMG (A1-A4) and solid dispersion of Aceclofenac with MAMG (A5-A8) were determined in phosphate buffer pH 7.4 at 37<sup>o</sup>C. For each preparation, an equivalent of 100 mg of drug was added to 20 ml of buffer in a glass vial with caps. The vials were kept on a water shaker bath at 37 ± 0.5<sup>o</sup>C for 24hrs. Then, the solution was filtered through a 0.1mm whatman filter paper and the filtrate was assayed UV-Spectrophotometer at 274nm.

**Drug content of solid dispersions:**

150 mg of 1:0.5 (A1), 175 mg of 1:0.75(A2), 200 mg of 1:1(A3), 225 mg of 1:1.25(A4) solid dispersions were weighed and transferred to 250 ml volumetric flask and dissolved in phosphate buffer pH 7.4 and volume was made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically at 274 nm.

**Preparation of tablets containing solid dispersions of Aceclofenac:**

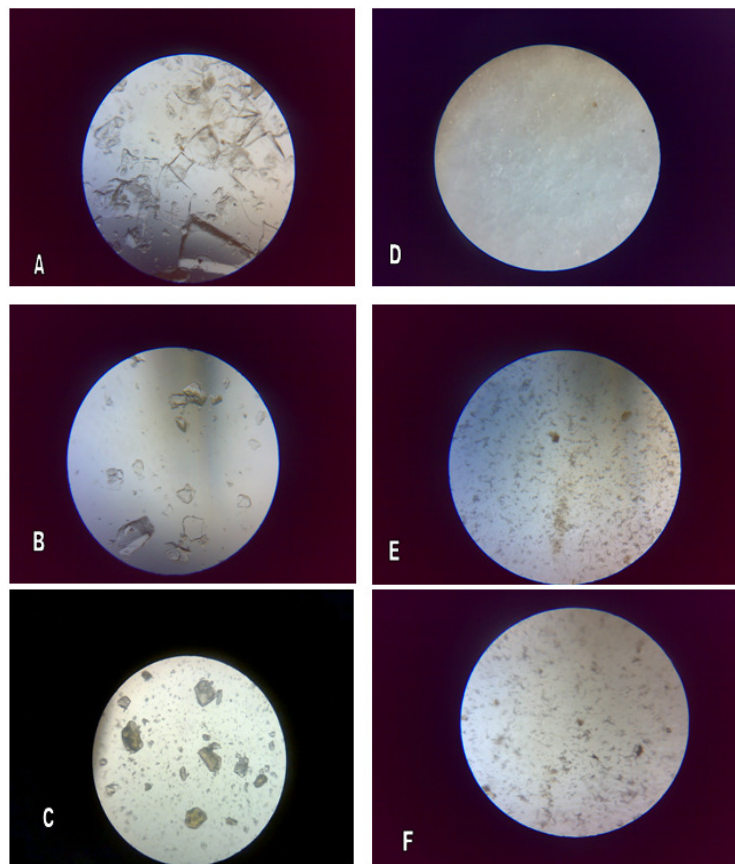
The solid dispersions equivalent to 100mg of aceclofenac were taken and prepared by direct compression method. The drug, diluent, superdisintegrant and sweetener were passed through sieve # 40. All the above ingredients were properly mixed together (in a Poly bag). Talc and magnesium stearate were passed through mesh no. 80, mixed and blended with initial mixture in a polybag followed by compression of the blend. The tablets were prepared by direct compression method using 8mm biconcave punches on a Rimek minipress 1 a 10 station rotary compression machine.

**Infrared spectroscopic study:**

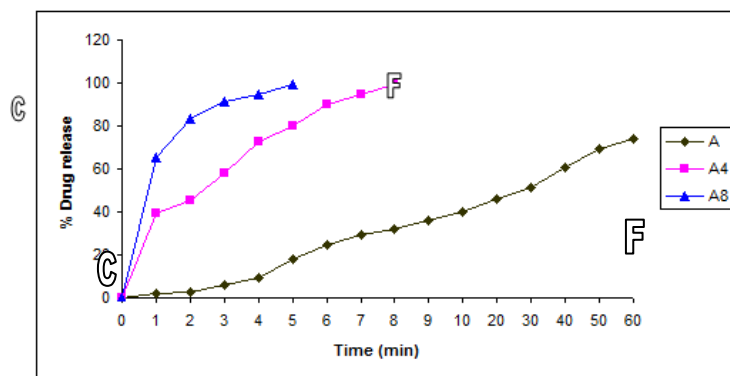
Fourier transformed (FTIR) spectrum of Aceclofenac, AMG, MAMG, PMANG, PMMAMG, CGAMG, CGMAMG and solid dispersion of Aceclofenac with AMG and MAMG were obtained on a FTIR (84005 Shimadzu Japan) using the KBr disk method. Results of this study are shown in Fig. 5 and 6.



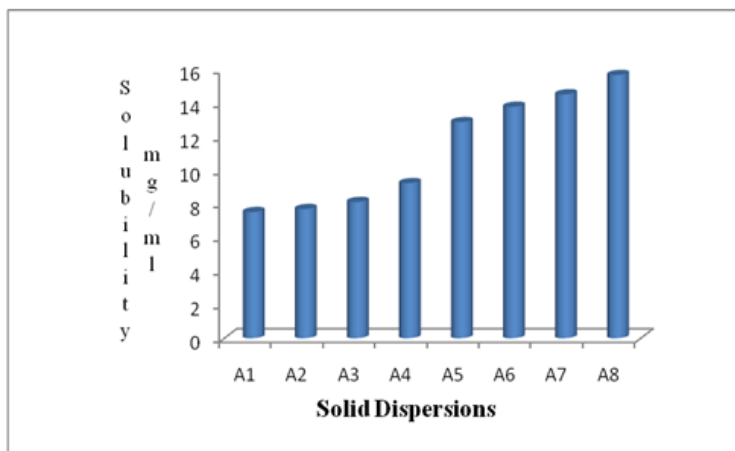
**Fig 1:** Fruits of AM (A) and Gum of AM (B)



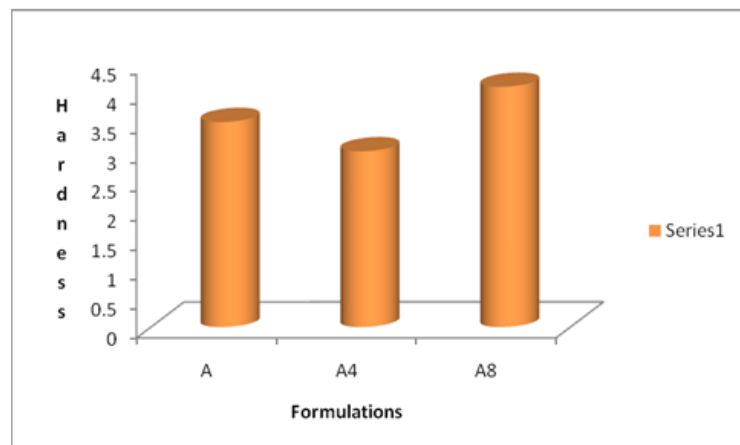
**Fig2:** Microscopical images of Aceclofenac pure drug (A), pure AMG (B), pure MAMG (C), Co-grounded Aceclofenac (D), solid dispersion of Aceclofenac with AMG (E), solid dispersion of Aceclofenac with MAMG (F)



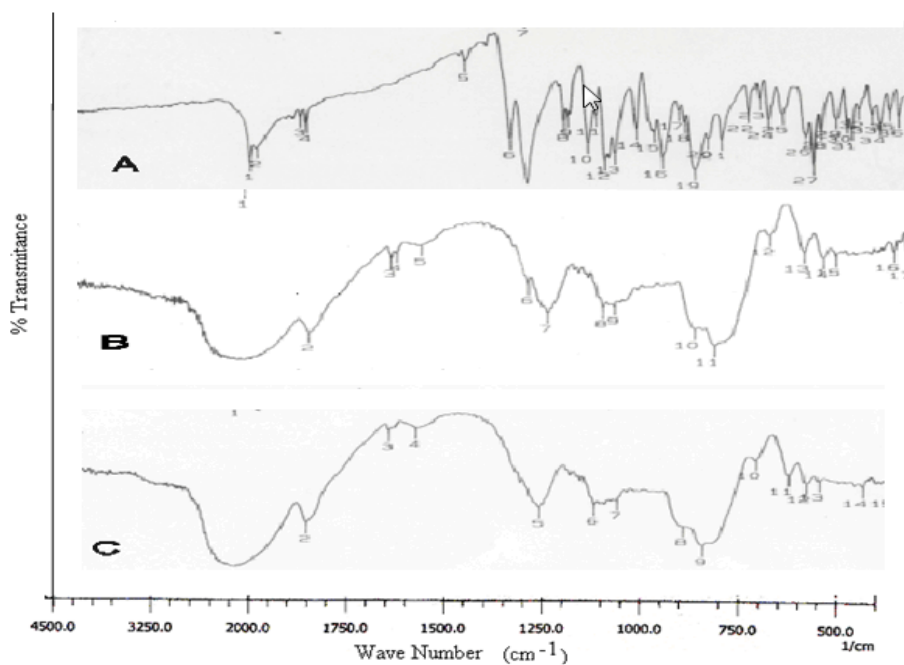
**Fig. 3.** Dissolution profile of Aceclofenac tablets



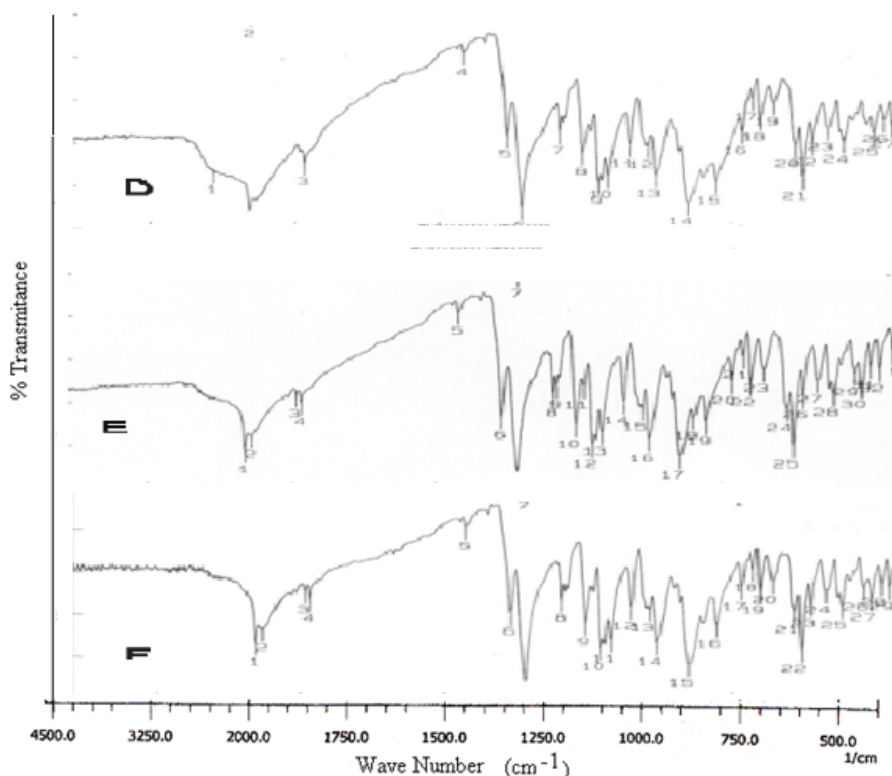
**Fig. 4** Graphical representation of solubility study of different solid dispersions



**Fig 5:** Graphical representation of hardness of the formulations



**Fig. 6.**IR spectrum of Aceclofenac (A), AMG, (B) MAMG (C)



**Fig:7.** IR spectrum of Physical mixture of drug+MAMG (D), Solid dispersion of drug +AMG (E), Solid dispersion of drug +MAMG (F)

#### Evaluation of powder blends<sup>16-17</sup>:

##### Angle of repose

Angle of repose ( $\theta$ ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height ( $h$ ) was obtained. The radius of the heap ( $r$ ) was measured and angle of repose was calculated.

$$\theta = \tan^{-1} h/r$$

##### Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility that is calculated as follows:

$$C = (\rho_t - \rho_b) / \rho_t \times 100$$

$\rho_t$  - Tapped density,  $\rho_b$  - Untapped bulk density

##### Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

$$\text{Hausner's ratio} = \rho_t / \rho_b$$

$\rho_t$  - Tapped density,  $\rho_b$  - Untapped bulk density

#### Evaluation of Aceclofenac fast disintegrating tablets<sup>18-19</sup>

##### Weight variation test

Weight variation test was done by weighing 20 tablets individually, by using Sartorius balance (Model CP- 224 S). Calculating the average weight and comparing the individual tablet weight to the average weight.

##### Tablet thickness

The thickness was measured by placing tablet between two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

##### Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

##### Tablet friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai).

Tablets of a known weight ( $W_o$ ) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed ( $W$ ) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = 100 (W_o - W) / W_o$$

#### **In-vitro disintegration time**

The disintegration time of tablets was determined at  $37 \pm 1^\circ\text{C}$  according to the method described in the British Pharmacopoeia, 1998.

#### **Dissolution study:**

*In-vitro* release of Aceclofenac FDTs was monitored by using 900 ml phosphate buffer pH 7.4, at  $37^\circ \pm 0.5^\circ\text{C}$  and 50 rpm using programmable dissolution tester [paddle type, Model DR-6, Cambell Electronics Mumbai, India]. Aliquots were withdrawn at one-minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions were assayed spectrophotometrically [UV-T80, PG Instruments Ltd JAPAN ] at 274 nm.

## **RESULTS AND DISCUSSION**

Evaluation of fast dissolving tablets:

**Table 1:** Characterization of AMG and MAMG

Product	Viscosity (cps)	Swelling index (%)	Water retention capacity(ml)
AMG	2672 $\pm$ 30.52	26.50	8.34
MAMG	725 $\pm$ 27.30	42.68	11.73

**Table2:** Formula used in the preparation of Aceclofenac solid dispersion With AMG and MAMG

Carrier Type	A1 (1:0.5)	A2 (1:0.75)	A3 (1:1)	A4 (1:1.25)
Aceclofenac: AMG	100:50	100:75	100:100	100:125
	A5(1:0.5)	A6(1:0.75)	A7(1:1)	A8(1:1.25)
Aceclofenac: MAMG	100:50	100:75	100:100	100:125

The results of solubility study data of all products were shown in Table 3. The solubility of Aceclofenac in co-grinding with AMG, MAMG and drug alone was increased then its physical mixer with AMG and MAMG and pure drug. Solubility of drug was increased with solid dispersion technique. It was observed that, as the concentration of gum increases, the solubility of

Tablets were evaluated for weight variation, hardness, friability, thickness; disintegration time<sup>20</sup> and wetting time<sup>21</sup> and results were shown in Table 6. All post compressional parameters results were within the acceptable range of fast dissolving tablets.

Pharmaceutical solid dispersion technology is generally accepted as a technique to enhance the dissolution characteristic of drugs with poor water solubility. The drug substance is dispersed in a water-soluble inert polymer matrix, sometimes at the molecular level, and the higher surface area due to the presence of polymer may increase the drug solubility and dissolution. If the drug is not dispersed on a molecular scale, it is often physically modified from its crystalline to amorphous form during processing. The presence of high energy amorphous state leads to enhanced dissolution rate and hence bioavailability owing to the lack of crystalline lattice.

The results of the characterization of AMG and MAMG are given in Table 1. The results shows that the viscosity of MAMG was markedly lower than AMG but its swelling index and water retention capacity were increased. It may be due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution.

Aceclofenac increased. Solid dispersion of Aceclofenac with AMG in the ratio 1:1.25 and with MAMG in the same ratio were increased significantly then other solid dispersions. So these two solid dispersions (A4 and A8) only selected for preparation of Fast Dissolving Tablets.

**Table3:** solubility study data

Product	Solubility (mg/ml)
A	0.0816(0.008)
ACG	0.0820(0.009)
CGAMG	0.0958(0.003)
CGMAMG	0.1022(0.007)
PMAMG	0.1037(0.005)
PMMAMG	0.1058(0.004)
A1	7.50(0.39)
A2	7.68(0.27)
A3	8.10(0.50)
A4	9.22(0.48)
A5	12.85(0.27)
A6	13.76(0.37)
A7	14.50(0.32)
A8	15.65(0.46)

**Table 4:** Drug content data of solid dispersions.

Solid dispersions	Drug content (%), ( $\pm$ SD), n=4
A1	99.25(1.64)
A2	98.34(1.25)
A3	98.57(3.36)
A4	100.00(1.32)
A5	97.50(1.85)
A6	99.37(1.50)
A7	100.20(2.50)
A8	100.12(0.92)

**Table5:** Formula used in preparation of tablets  
Using AMG and MAMG solid dispersions.

Ingredients mg/tab	A	A4	A8
Aceclofenac	100	-	-
Amt of SD Equivalent to 100mg drug	-	225	-
	-	-	225
Ccs	-	24	24
D.Mannitol	179	30	30
Aspartame	15	15	15
Talc	3	3	3
Mg.Stearate	3	3	3

**Table6:** post compressional parameters of tablets.

Parameters	Formulations		
	A	A4	A8
Hardness (Kg/cm <sup>2</sup> ) ( $\pm$ SD),n=10	3.50(0.52)	3.00(0.68)	4.10(037)
Friability (%) ( $\pm$ SD),n=10	0.39(0.04)	0.22(0.06)	0.40(0.08)
Thickness (mm) ( $\pm$ SD),n=10	4.65(0.06)	4.67(0.05)	4.66(0.12)
Weight variation (mg) ( $\pm$ SD),n=10	301 $\pm$ 1.00	302 $\pm$ 2.00	301 $\pm$ 2.00
Disintegration time (sec) ( $\pm$ SD), n=10	150 $\pm$ 2.00	18 $\pm$ 1.00	16 $\pm$ 1.500
Wetting time (Sec) ( $\pm$ SD), n=3	220 $\pm$ 3.00	28 $\pm$ 2.00	25 $\pm$ 1.00

**Infrared spectroscopic study:**

The prominent IR absorption peaks of Aceclofenac showed at 3319 and 3267 these broad peaks may be due to OH hydrogen bonding. 2970 is NH aromatic stretching, peaks near 2937 including 1921

may be due to CH stretching of CH<sub>2</sub> groups, carbonyl group vibration at 1770 and 1716. Peaks at 1589, 1577 and 1508 indicates the presence of C=C ring stretching. All these principal IR peaks of Aceclofenac were present

in all formulations. This clearly indicates that there is no interaction between drug and carrier.

Improvement in dissolution rate of Aceclofenac FDTs (A8) prepared by solid dispersions using MAMG compared with Aceclofenac FDTs (A4) prepared by solid dispersion using AMG and Aceclofenac conventional tablets (A). This may be due to the solubilization effect and wetting ability of the MAMG. Due to the hydrophilic nature of the carrier hydrodynamic microenvironment around the particles was changed. When a drug-carrier particle comes in contact with the dissolution fluid, seeping of dissolution medium into the drug-carrier particles takes place, which initiates the formation of a stagnant gel layer of carrier around the particles.

The viscosity of 1% w/v solution of MAMG at 28<sup>o</sup> C was 725cps, which is about 4 times lower than that of AMG. Hence, the dissolution rate of formulation A4 is low, because it was prepared by using high viscous AMG, resulted in the formation of lumps of drug-carrier particles during dissolution, where as Aceclofenac-MAMG particles dispersed rapidly.

#### CONCLUSION:

From the results of solubility and dissolution rate it can be concluded that MAMG could be used as a potential carrier in the solubility and dissolution rate enhancement of poorly soluble drug. The dissolution rate of formulation A4 was low when compared with the formulation A8. Increased wettability, dispersibility, surface area and solubilization effect of AMG and MAMG enhances the solubility of water insoluble drugs.

#### REFERENCES

1. M. Ciper and R. Bodmeier, Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity, *Eur. J. Pharm. Biopharm.* 62 (2006), pp. 178–184.
2. T. Mizumoto, Y. Masuda, T. Yamamoto, E. Yonemochi and K. Terada, Formulation design of a novel fast disintegrating tablet, *Int. J. Pharm.* 306 (2005), pp. 83–90.

3. H. Seager, Drug delivery products and the Zydis fast dissolving dosage form, *J. Pharm. Pharmacol.* 50 (1998).
4. S.V. Sastry, J.R. Nyshadham and J.A. Fix, Recent technological advances in oral drug delivery: a review, *Pharm. Sci. Technol. Today* 3 (4) (2000), pp. 138–145.
5. EU Pharmacopoeia, Published by the Directorate for the Quality of Medicines of the Council of Europe (EDQM), second ed., Strasbourg, France, 2002a.
6. L. Dobetti, Fast-melting tablets: developments and technologies, *Pharm. Technol. N. Am. Suppl.* (2001), pp. 44–50.
7. Rahul c, Zahra H, Farhan A, Alan M.S, Afzal R.M. The role of formulation excipients in the development of lyophilised fast-disintegrating tablets. *Eur. J. Pharm. Biopharm.* 72 (2009), pp. 119–129.
8. Shapiro J, Franko D.L, Gange A. Phagophobia: a form of psychogenic dysphasia. A new entity: *Ann otol rhinol laryngol* 1997; 106:206-290.
9. Ahmed and M. Aboul-Einien, In vitro and in vivo evaluation of a fast disintegrating lyophilised dry emulsion tablet containing griseofulvin, *Eur. J. Pharm. Sci.* 32 (2007), pp. 58–68.
10. S. Corveleyn and J. Remon, Formulation of a lyophilised dry emulsion tablet for the delivery of poorly soluble drugs, *Int. J. Pham.* 166 (1998), pp. 65–74.
11. Aulton M.E. *pharmaceutics- the design and manufacture of pharmaceuticals*, 2007, 3rd ed; 286-303.
12. G.V.Murali Mohan babu, D.S.prasad, and K.V. Raman Murthy. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug nimodipine. *Int.J.Pharm.* 234: 1-17(2002).
13. Patil D.N, Kulkarni A.R, Hatapakki B.C, Patil B.S. preparation and Evaluation of Aegle marmelos gum as tablet binder. *Int.J.pham, Bio, sci.* 1 (1) 2010-5.
14. Manjil patel, Avinash Tekade, surendra gattani, Sanjay surana. Solubility enhancement of

- lovastatin by modified locust bean gum using solid dispersion techniques. *Aaps pharm sci tech*, 9(2008) 1262-1269.
15. Shah viral, Patel dhiren, sandeep mane, upadhyay umesh. solubility and dissolution rate enhancement of Licofelone by using modified guar gum. *Int.jr.pharm Tech. Res.2* (2010), 1847-1854.
  16. Martin A. Diffusion and Dissolution. In: *Physical pharmacy*. 3<sup>rd</sup> ed. Philadelphia: Lea and Febiger; 1983; 399-444.
  17. Fiese EF, Hagen TA. Preformulation. In: Lachman L, Lieberman HA, Kanig JL. editors. *The theory and practice of industrial pharmacy*. 3rd ed. Mumbai: Varghese Publishing House; 1987; 182-184.
  18. Banker GS, Anderson NR. In: Lachman L, Lieberman HA, Kanig JL. *The Theory and Practice of Industrial Pharmacy*. 3rd ed. Mumbai: Varghese Publishing House; 1987; 293-399.
  19. Mohapatra A, Parikh RK, Gohel MC. Formulation, development and evaluation of patient friendly dosage forms of metformin, Part-I: Orally disintegrating tablets. *AAPS*. 2009; 167-171.
  20. United States pharmacopoeia. Rockville.MD: 27th revision. USP convention, Inc, 2004.2302.
  21. Sunada H, Bi YX, Yonezawa y, Danoj k. preparation, evaluation and optimization of raoidly disintegrating tablets. *powder Technol* 2002; 122:188-198.

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