Journal of Advances and Scholarly Researches in Allied Education
Vol. 20, Issue No. 1, January-2023, ISSN 2230-7540

A Study of Co-Micronization In Formulation of Rapid Dispersible Tablets

Azharuddin[1]*, Dr. Abhay Gupta[2]

[1] Research Scholar, Lords University, Chikani, Alwar

[2] Professor, Faculty of Pharmacy, Lords University, Chikani, Alwar

Abstract - The concept of rapid dispersible, fast dissolving, quick dissolving, and Orodispersible tablets dosage forms have acquired great importance in recent years due to their unique properties and advantages over other available dosage forms. The micronization of TA and diluents was done by using Air-jet mill. The comicronization of formulation was done as per the given details in table. Total three cycle of micronization was completed to insure the proper particle size reduction of blend. There is no micronization of formulation F-1 was done; it was basically used as reference to check the impact of micronization and co-micronization. But sifting of Tolfenamic acid (non-micronized) of Formulation F-1 was done through #60 meshes to insure the uniformity of Tolfenamic acid in blend. The micronization of TA and diluents was done by using Air-jet mill. The comicronization of formulation was done as per the given details in table. Total three cycle of micronization was completed to insure the proper particle size reduction of blend. There is no micronization of formulation F-1 was done; it was basically used as reference to check the impact of micronization and co-micronization. But sifting of Tolfenamic acid (non-micronized) of Formulation F-1 was done through #60 meshes to insure the uniformity of Tolfenamic acid in blend.

Keyword - Tolfenamic, Tolfenamic acid, Drug

----------X----------

INTRODUCTION

Several strategies, including solid dispersion, particle size reduction, micronization, the direct compaction method, melt granulation techniques, and solvent deposition inclusion, have garnered significant attention in recent years as potential means of modifying drug release. We used some complex formulation techniques. Creating an appropriate formulation that allows for the quick release of medications that aren't water-soluble is the driving force behind all of these advances. [1]

Almost a third of all medications in development cannot be dissolved in water, and half of those fail clinical testing due to poor pharmacokinetics. In a similar vein, Tolfenamic Acid presents a similar issue in formulation due to its low solubility. Probably due to challenges in making tablets having a decent size and quick breakdown of active in compressed dosage form, with adequate size that can be readily ingested by patients, Tolfenamic acid was first created as hard gelatin capsules. There are a number of methods published in the literature and patents for enhancing the release profile of Tolfenamic acid, including solid dispersion and size reduction. Tolfenamic acid (TA) and polyvinylpyrrolidone K-30 solid dispersions were used to increase the release rate of poorly soluble TA, and this formulation was created. He used the spray drying method to create a stable Tolfenamic acid dispersion in solid form. Tolfenamic acid's dissolution profile was shown to be improved in all solid dispersion formulations, according to dissolution experiments. Tolfenamic acid was maintained in its amorphous form throughout the stability test in the solid dispersion with a high concentration of PVP. Tolfenamic acid solubility increase using various surfactants was studied by Raunio et al. in 1982. Tolfenamic acid's solubility improved linearly with the addition of Brij and polysorbate 80 to an aqueous solution. An increase in the fraction of hydrophobic region of surfactant molecules was connected with a rise in solubility. Using Brij 58 as surfactants resulted in the most optimal formulation release profile. The quick release formulation of Tolfenamic acid was developed by Gebhard et al. in 2000 through the particle size reduction or micronization technology. Micronizing Tolfenamic acid, he discovered, improves both its release profile and bioavailability. According to his research, using a pharmaceutically acceptable salt like alginic acid and a superdisintegrant like sodium starch glycolate may help make Tolfenamic acid into particles that are on average 8 m in size. [2-3]

LITERATURE REVIEW

Hannan et al., (2016) A dosage form is a vehicle for administering medication to a living organism. The medicine has to be administered to the site of action at a pace and concentration that maximizes therapeutic benefit while minimizing harm. Inasmuch as the oral method remains popular despite the fact that many people have trouble swallowing pills, capsules, and lozenges. This is why there is so much focus on developing cutting-edge methods of administering medicines. This review is about oral dispersible tablets a novel approach in drug delivery systems that are now a day's more focused in formulation world, and laid a new path that, helped the patients to build their compliance level with the therapy, also reduced the cost and ease the administration especially in case of pediatrics and geriatrics. Quick absorption, fast start of action and decrease in drug loss qualities are the fundamental benefits of this dosage form. [4]

Prasad et al., (2015) purpose of this research was to create and perfect an ibuprofen tablet formulation that could be taken orally. Crospovidone, sodium starch glycolate, croscaramelose sodium, and sodium carboxy methylcellulose were used as superdisintegrants in concentrations of 5, 7.5, and 10% w/w, respectively, and mannitol was used as a diluent to prepare orodispersible tablets via the direct compression technique. Pre-compression parameters such as FTIR spectroscopy, DSC, and micromeritics are applied to the powder mixtures. The formulations were tested to see how they performed in terms of tablet weight variation, hardness, friability, wetting time, absorption ratio, drug content, in vitro dispersion time, in vitro disintegration time, and in vitro drug release studies. Micromeritics investigations showed that all formulations had flowability that was acceptable to excellent. When compared to the control (D5 min = 18.29%), the 10% w/w concentration (F3) of crospovidone exhibited the shortest in vitro disintegration time (38 seconds), an acceptable hardness (3.93 kg/cm3), friability (0.652%), and dissolution profile (D5 min = 95.89%). The optimum recipe demonstrated 90% To sum up, we find that a 10% w/w (F drug release of 2.6 minutes) concentration of crospovidone yields the best results. No drug-excipient interactions were detected in the FTIR and DSC studies performed on the optimised formulation. [5]

Vora, et al., (2014) Oral dispersible tablets are a popular pharmaceutical delivery system. Since their inception in the 1980s, ODTs have become one of the fastest growing divisions of the oral drug delivery business, with an ever-expanding product pipeline. Only a small number of nonprescription and prescription drugs are available in the dose form of an orally disintegrating tablet (ODT) or orodispersible tablet (ODT). ODTs are one such unique strategy since they may be self-administered without water or chewing and disintegrate or dissolve swiftly in the mouth (saliva) within a few seconds, which might boost consumer acceptability. Besides generating enormous profits via the expansion of their product lines, they also provide a number of benefits to their patients. Patients of all ages, including children, the elderly, and those confined to bed, may benefit from the oral dispersible tablets that have been developed thanks to their increased therapeutic effectiveness and patient compliance even in the absence of water. Several different formulations provide a chance to expand the product range, particularly for the elderly, who may have trouble swallowing or consuming typical oral dose forms due to hand tremors, dysphasia, or other conditions. This article provides a brief review of the ideal properties, significance, characteristics, limitation, choice of drug candidates, challenges in formulation, the fabrication of Oro-dispersible tablets, and a detailed concept of fabricating technologies, patented technologies, emerging trends, and evaluation tests of ODTs. [6]

Singh et al., (2014) To boost bioavailability and patient compliance, orodispersible drug delivery systems are increasingly used. Orodispersible tablets (ODTs) have emerged as a popular replacement for traditional tablets and capsules over the past three decades thanks to their high patient compliance, high solubility, and high stability. This article aims to discuss the potential benefits of ODT technology for pharmaceutical uses. The direct compression method, freeze drying, spray drying, tablet moulding, sublimation, and mass extrusion are all methods used to create ODTs. Patients in the categories of paediatrics, the elderly, the bedridden, the postoperative, and those who may have difficulty swallowing conventional tablets and capsules may benefit from ODTs. ODTs, or orally disintegrating tablets, are solid dosage forms that dissolve quickly (typically within seconds) when placed on the tongue. Increased patient compliance and greater bioavailability and stability contribute to ODTs' greater acceptability. This article provides a summary of current research and development efforts devoted to ODTs, as well as a discussion of recent advances in ODTs technologies, drug candidate suitability, and ODT characterization. Orodispersible tablets. [7]

Heer (2013) Interest in the fast dissolving drug delivery system (FDDDS) is rising quickly among the various novel drug delivery systems. As an alternative to the more commonplace pill, capsule, and syrup forms, FDDDS were created. Fast dissolving tablets (FDTs) and fast dissolving oral films are two common delivery systems for these (FDOFs). These dissolve or disintegrate in under a minute without the need for water or chewing, which increases the possibility of improved compliance in paediatric and geriatric patients who have trouble swallowing tablets or liquids. Fast disintegrating oral films (FDOFs) are a convenient alternative to fast dissolving tablets (FDTs), which dissolve instantly once placed on the tongue and allow for rapid drug absorption and instant bioavailability. These films have been used for both local and systemic drug delivery via intragastric, sublingual, and buccal routes of administration. This article compares and contrasts two types of fast dissolving tablets/films

and discusses the formulation considerations, methods of preparation, applications, and limitations of each. [8]

Parkash et al., (2011) Demand for fast dissolving tablets (FDTs) has skyrocketed over the last decade, making this a dynamically expanding sector of the pharmaceutical business. Many medications are still most often given to patients by oral administration. With the advent of new technologies, researchers have been motivated to create FDTs that are more user-friendly and effective. These tablets are designed to dissolve or disintegrate in the mouth upon introduction, making it unnecessary to need extra water for dosing. Several FDT technologies have been developed as a consequence of the formulation's widespread acceptance and practical use. Freeze-dried tablets (FDTs) are a kind of solid UDF that dissolve quickly in the mouth without the need for chewing or water. People of all ages, but especially young children and the elderly, may have trouble swallowing regular tablets and capsules, but FDTs, or orally disintegrating tablets, solve this problem. This article discusses the many methods and technologies that have been created to make tablets dissolve quickly in the mouth. Methods for improving FDT qualities, such as spray drying and the application of disintegrants, are also discussed in depth, along with FDT technologies based on lyophilization, moulding, sublimation, and compaction. We also talk about how to hide flavours, how to time how long it takes for something to dissolve in the lab, and how to make something dissolve faster in the body. [9]

Pilgaonkar et al (2010) Acetaminophen Oro dispersible tablets were developed using the Rubi Oro dispersible technology. Compared to other pain relievers, paracetamol has an extremely harsh taste and poor solubility. Various soluble and insoluble polymers have been tried to disguise drug flavors and improve the medication's solubility. In instance, coating with water-insoluble polymers accomplishes the necessary flavor masking but leads to delayed medication release. Based on the results of these tests and investigations, he designed an aqueous coating method for taste masking that is safe for the environment and allows for rapid (at least 85%) medication release within 15 minutes. Acetaminophen granules of the appropriate size were employed, and an aqueous coating solution was applied to them using a fluidized bed coater. The coating system, coating procedure, and coating thickness were all improved. Additional granular additives including Pan Excea ODT, disintegrants, flavours, sweeteners, etc. were compacted into a quickly dissolving formulation utilizing RubiODT technology to conceal the granules' original tastes. Multiple aspects of the produced formulation were tested and found to be satisfactory: how well it dissolves, how long it takes to dissolve, how long it takes to disintegrate, and how it tastes in the mouth. [10]

METHODOLOGY

This research was examining the characteristics of both active ingredients after examining preformulation experiments of various formulations of tolfenamic acid, paracetamol, and tolfenamic acid and paracetamol (FDCs). Tolfenamic Acid's solubility improvement research was use a comicronization strategy for a formulation with a quick release profile. During the research, the impact of particle size, surfactants, and co-micronization of the active with the surfactant will be examined. The influence of temperature and humidity at certain times was examined as part of the stability study of the improved formulation. The impact of granule size and intra-granular disintegrant type on tablet qualities, especially dispersion and wetting properties of formulation, was researched.

Paracetamol's solubility was improved by employing a variety of solid dispersion techniques to improve the release profile of the active ingredient and formulation with the right excipients. The use of polymer coating was used to try to disguise the paracetamol's taste. The integration of two technologies into a single formulation was examined to assess the formulation's taste and release kinetics. Dispersible tablet formulation will examine the fixed dosage combination concept. Tolfenamic acid and paracetamol were combined in an effort to treat migraines in children as well as possible. For enhanced patient compliance, the formulation was also undergoing an organoleptic evaluation. According to ICH requirements, the stability study of the improved formulation was also being assessed.

DATA ANALYSIS

Manufacturing of Co-micronization Blend

Air-jet mill was used to micronize the TA and diluents. As shown in the accompanying table, the formulation was co-micronized. The right amount of particle size reduction of mix was ensured by completing a total of three cycles of micronization. Formulation F-1 was not micronized, but rather served as a control against which the results of micronization and co-micronization could be compared. Formulation F-1's non-micronized Tolfenamic acid, on the other hand, was sifted through #60 meshes to ensure a consistent mix. The granulation of these formulations also made use of the same co-micronized mixes. The Table detailed the steps involved in preparing co-micronization.

Table 1: Formulation Details of Rapid Dispersible Tablets of Tolfenamic Acid

Ingredients	Quantity available in each tablets (mg/tabs)			
	F-1	F-2	F-3	F-4
Intra-granular				
Tolfenamic Acid	100.00	100.00	100.00	100.00
Microcrystalline Cellulose	80.000	80.000	81.250	80.000
Sodium Lauryl Sulfate	1.250	1.250	--	1.250
Povidone (PVP K-30)	2.500	2.500	2.500	2.500
Purified Water	QS	QS	QS	QS
Extra-granular				
Mannitol	45.000	45.000	45.000	45.000
Sodium Starch Glycolate	2.500	2.500	2.500	2.500
Magnesium Stearate	1.250	1.250	1.250	1.250
Aspartame	5.000	5.000	5.000	5.000
Flavor Vanilla	2.500	2.500	2.500	2.500
Tablet Weight in mg	**240.00**	**240.00**	**240.00**	**240.00**

Physical Evaluation of Co-micronization Blend

The mean particle size of 90% (d-0.90) of particles in the sample was measured and collated for analysis (average particle size). Particle size was effectively reduced by employing an Air jet mill, with the average particle size of the reference formulation (un-micronized) formulation F-1 being 161.625 µm and the average particle size of the micronized and co-micronized blend for formulations F-2, F-3, and F-4 being about 10 µm.

Table 2: **Particle Size Distribution after Micronization**

Formulation	Average Particle Size (d-0.90) in	Particle Size (d-0.50) in µm	Particle Size (d-0.10) in µm
F-1	161.625	53.675	9.621
F-2	10.926	6.256	3.256
F-3	9.856	6.958	3.125
F-4	10.214	5.935	2.968

Physical Evaluation of Granules

Granules' physical properties are listed in Table, from F-1 through F-4 formulations. Granulating all four formulations needed more water than expected; specifically, formulations F-2, F-3, and F-4 absorbed an extra 10, 14, and 17 ml of water, respectively. Tolfenamic acid with diluents and Tolfenamic acid co-micronization may account for this phenomenon by increasing the particle's surface area. Drying granules showed a similar trend toward further drying, with a higher loss on drying for formulations F-3 and F-4 (1.60 and 1.64% W/W) compared to formulations F-1 and F-2 (1.42 and 1.513% W/W).

The flow of the granules was confirmed by measuring the angle of repose, and the results showed that the values were in the range of 30 and 36, suggesting a reasonable to excellent flow. Compressibility index of granules, which is the fundamental condition of compression, clearly exhibiting the influence of micronization; co-micronization processing of formulation F-3 and F-4 exhibited excellent compressibility index in the range of 15 to 16. Similar results may be seen in housner's Ratio of granules.

Table3 : **Physical Properties of Granules (n=3)**

Physical Properties	F-1	F-2	F-3	F-4
Qty of water uptake during granulation (ml)	Nil	10	14	17
Loss on drying (%w/w)	1.42	1.513	1.640	1.600
	± 0.312	± 0.031	± 0.050	± 0.020
Bulk density (gm/ml)	0.55	0.500	0.523	0.530
Tapped density	0.683	0.637	0.627	0.623
Carr's Index (%)	19.500	21.481	16.448	14.968
Hausner's Ratio	1.242	1.274	1.197	1.176
Angle of Repose	33.33	36.667	31.667	30.333

To prevent issues with weight variation, die filling, and tablet compression flow, granules' varied physical qualities pointed to the need of using intra-granular diluents such microcrystalline cellulose and wet granulation of co-micronized granules.

Physical Evaluation of Tablets

Table summarizes the results of several physical evaluations performed on tablets of formulations F-1 through F-4. There were no major flaws discovered in the tablets' look. It was determined that there was not a statistically significant difference between the average and individual tablet weights, and that the weight variance for all batches of the formulations was well within acceptable ranges. An key criteria for the development of rapidly dispersible tablets, the value of hardness friability of tablet showed excellent strengths in all formulations. Tablet thickness was likewise well within acceptable ranges.

All formulations achieved the 15–22 second disintegration time window necessary for creating optimal quick dispersible tablets. The dispersion time and wetting time of formulation F-1 and F-2 were longer than those of formulations F-3 and F-4. Co-micronization of the mix during granulation is shown in the quick dispersion and wetting. Compressed blend's surface area was increased by co-micronization during dispersion and wetting. Formula F-4 had the fastest dispersion and wetting times, demonstrating the significant influences of the wetting qualities of sodium Lauryl sulphate in formulation. Improved granule wetting is achieved by co-micronization of sodium Lauryl sulphate with the active and diluents. Formulation F-4 has the same quick dispersion and wetting phenomena in its water absorption ratio. Formulations F-4 and F-3 have a

significantly lower water absorption ratio compared to F-1 and F-2. Thus, co-micronization has an observable effect on improving the formulations' physical qualities. Although this investigation aimed to improve the formulation's release profile, it was possible to improve the dispersion and wetting time by increasing the concentration of superdisintegrants.

Table 4 : Physical Evaluation of Tablets

Evaluation Parameters	F-1	F-2	F-3	F-4
Appearance	Off-white colored, 9.0± 0.1 mm, round flat faced tablet			
Weight Variation (%)	241.56± 2.35	241.34± 1.93	241.01± 2.46	240.85± 2.29
Hardness (Newton) n=6	28.67± 2.50	30.00± 2.10	33.33± 2.16	35.00± 1.26
Thickness (mm) n=6	3.20± 0.01	3.18± 0.02	3.20± 0.02	3.19± 0.02
Friability (% w/w)	0.65	0.68	0.72	0.69
Disintegration (Seconds)	15 – 20	18 – 22	15 – 20	17– 22
Dispersion (Seconds) n=3	50.67± 1.15	43.67± 1.53	43.67± 1.00	40.00± 3.00
Wetting Time (Seconds) n=3	65.00± 3.00	55.00± 2.00	43.67± 1.53	40.00± 2.00
Water Absorption Ratio	53.17	55.79	61.82	66.08

CONCLUSION

Strategies for the Systematic Exploration and Development of Dissolvable Tablets, New to the Indian and worldwide markets is the unique solid oral dose form Rapid Dispersible Tablets, which have been shown to increase patient compliance while maintaining the active drug's therapeutic efficacy. As part of this research, we will investigate the formulation factors that affect the efficiency and efficacy of quick dispersible tablets manufactured using commercially available excipients. That's why we're doing this research: to discover and improve the efficacy of novel formulation technology principles for the development of dispersible tablets. This research uncovered two innovative technologies, co-micronization and an efficient combination of dual technology (Solid dispersion and polymer coating), that show promise in addressing the fast dispersion and release profile with appropriate flavour masking.

REFERENCE

1. Yayoi kawano, akihiko ito, masanaho sasatsu, yoshiharu machida, and hiraku onishi, (2010) “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.
2. Warren kaplan, (2003): “effect of fixed-dose combination (fdc) drugs on development of clinical antimicrobial resistance: a review paper”; [last cited on 2012 sep 06]. Available from: http://whqlibdoc.who.int.
3. 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.
4. P. A. Hannan*, j. A. Khan, a. Khan and s. Safiullah (2016) on “oral dispersible system: a new approach in drug delivery system” doi: 10.4103/0250-474x.180244
5. Ranjit prasad swain, p. Satish, b. B. Subudhi, satyajit panda(2015) on “ormulation and optimization of orodispersible tablets of ibuprofen” international journal of pharmacy and pharmaceutical sciences issn- 0975-1491 vol 7, issue 2, 2015.
6. Harsh vora, et al ,. (2014) on “oral dispersible tablet: a popular growing technology” asian journal of pharmaceutical research and development vol.1 (6) nov. – dec. 2013: 138-155 harsh vora et al www.ajprd.com 138 asian journal of pharmaceutical research and development (an international peer-reviewed journal of pharmaceutical research and development) www.ajprd.com issn 2320-4850
7. Rewar s* , singh c j et al., (2014) on “oral dispersible tablets: an overview; development, technologies andevaluation” international journal of research and development in pharmacy and life sciencesavailable online at http//www.ijrdpl.comoctober - november, 2014, vol. 3, no.6, no.4, pp 1223-1235issn (p): 2393-932x, issn (e): 2278-0238
8. Deepak heer (2013) on “recent trends of fast dissolving drug delivery system - an overview of formulation technology” pharmacophore 2013, vol. 4 (1), 1-9 issn 2229 – 5402 usa coden: pharm7 pharmacophore (an international research journal) available online at http://www.pharmacophorejournal.com/
9. Parkash v, maan s, deepika, yadav sk, hemlata, jogpal v.(2011)fast disintegrating tablets: opportunity in drug delivery system. J adv pharm technol res. 2011 oct;2(4):223-35. Doi: 10.4103/2231-4040.90877. Pmid: 22247889; pmcid: pmc3255350.
10. Pilgaonkar p. S., m. T. Rustomjee , a. S. Gandhi , h. M. Kanekar, s. Bhattacharya, (2010): “development of taste masked acetaminophen rapidly disintegrating formulations with improved in-vitro dissolution using rubi odt technology”, the american association of pharmaceutical scientists journal , abstracts, 2010, w5067

Corresponding Author

Azharuddin*

Research Scholar, Lords University, Chikani, Alwar