Design, Development and Evaluation of Rapidly Disintegrating Tablets

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Abstract

Recent advances in novel drug delivery system aims to enhance safety and efficacy by the formulating a convenient dosage form for administration to achieve the better patient compliance. One of the approaches is formulation of rapidly disintegrating tablets. These are useful for pediatric, geriatric and also dysphagic patients, leading to improved patient compliance. These dosage forms dissolve or disintegrate rapidly in the oral cavity within a matter of seconds without the need of water. Combination of solid dispersion and natural super disintegrants is a promising approach to prepare efficient rapidly disintegrating tablets of poor water-soluble drugs.

INTRODUCTION

In the all the dosage forms taken orally, the tablet is one of the most used dosage forms. Disintegrants are substances integrated to tablet and some encapsulated formulations to enhance the breakup of the tablet and capsule "slugs" into more small particles in an aqueous environment thereby increasing the available effective surface area and increasing a more rapid release of the substance. These substances increase moisture entry and breaking of the tablet matrix. Tablet disintegration had received considerable attention and it is an main step in getting fast drug release. The accentuation on the better availability of drug in the dosage form is the important in the rapid disintegration of a tablet as a criterion for ascertaining uninhibited drug dissolution character. Number of factors influences the disintegration replace of tablets. The disintegrants have the important function to retard the efficiency of the tablet binder and the attractive forces that act during compression to make the tablet. The stronger the binder, the great efficacious must be the disintegrating agents in the release its medication. Ideally, it is responsible for the disruption, not only into the granules from which it was made, but additionally into powder form from which the granulation was done.

Literature Review

Ahmed IS, *et al.*, 2006 prepared Ketoprofen fast dissolving tablet by lyophilization technique. The Tablets was prepared by dispersing the drug in an aqueous solution of highly water-soluble carrier materials consisting of gelatin, glycine, and sorbitol. The mixture was dosed into the pockets of blister packs and then was subjected to freezingand lyophilization. The saturation solubility and dissolution characteristics of ketoprofen from the LT were investigated and compared to the plain drug and the physical mixture (PM). Results obtained showed that the increase in solubility of ketoprofen from LT matrix, nearly three times greater than the solubility of the plain drug, was due to super saturation generated by amorphous form of the drug. Results
obtained from dissolution studies showed that LT of ketoprofen significantly improved the dissolution rate of the drug compared with the PM and the plain drug. More than 95% of ketoprofen in LT dissolved within 5 min compared to only 45% of ketoprofen plain drug dissolved during 60 min. Initial dissolution rate of ketoprofen inLT was almost tenfold higher than that of ketoprofen powder alone. The lyophilized tablets were evaluated for solubility & dissolution and compared with plane drug as well as physical mixture. The results revealed that lyophilized tablets showed improved dissolution than plane drug and physical mixture.

Sarasija Suresh, *et al.*, 2007 formulated salbutamol sulphate mouth dissolving tablets by sublimation technique using sublimed components. The formulation containing microcrystalline cellulose as filler showed minimum disintegration time which could be attributed towards disintegrating property of microcrystalline cellulose. However, the formulations containing mannitol as filler showed longer disintegration time,which could be, attributed to slower dissolution characteristics of mannitol. The tablets containing a combination of mannitol and camphor or tablets containing microcrystalline cellulose and camphor showed longer disintegration time while the combination comprising of mannitol and ammonium bi carbonate or microcrystalline cellulose and ammonium bicarbonate showed least

disintegration time, indicating that the disintegration properties of tablets were influenced by the presence of the type of volatilizable component and filler used. However, all the prepared tablets were found to disintegrate fast showing disintegration time of less than a minute. Amongst the prepared formulations, F_3 was found to have the minimum disintegration time of 5 seconds. Formulations tested for all the official tests for tablets and were found to be within limits. Thus, it can be concluded that fast dissolving can be prepared with a view of obtaining faster action of the drug and would be advantageous in comparison to the currently available conventional forms. The technique adopted was found to be economical and industrially feasible. Stability studies conducted for optimized formulation. All batches of tablets were evaluated and concluded that, tablets prepared with microcrystalline cellulose and ammonium bicarbonate showed very lessdisintegration time.

Excipients Used in Rapidly Disintegrating Tablets

Excipients balance the properties of the actives in fast melting tablets. This demands athorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of Rapidly disintegrating tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Tablet Moulding

Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly. Following are the different tablet moulding techniques Compression Moulding Process.

This manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mould plates to form a wetted mass compression moulding. The solvent is then removed by air drying, a process similarto the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

Durasolv Technology:

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity.

These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

CIMA labs have developed Orasolv Technology. In this system active medicament is taste

Orasolv Technology:

Compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

Flash Dose Technology:

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared byflash heat processing.

NATURAL SUPERDISINTEGRANTS FOR RAPIDLY DISINTEGRATING TABLETS

Disintegrating agents are substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as “Super disintegrants”. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the super disintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations

containing high-dose drugs. The natural super disintegrants involve various natural substances like gums, mucilage's, and other substances of natural origin which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Some natural substances like gum karaya, modified starch and agar have been used in the formulation of RDTS. Mucilage of natural origin ispreferred over semi synthetic and synthetic substances because they are comparativelycheaper, abundantly available, nonirritating and nontoxic in nature **(Allen LV, *et al.*, 1997)**.

EQUIPMENTS

The following equipments are used for the development of Rapidly Disintegratingtablets. Table Equipment's used in the research work

S.No.	Equipments	Source
1	Digital Weighing balance	Contech CA-123 , Mumbai
2	FTIR Spectrophotometer	Compact Raman analyser, Mumbai
3	Vibratory Sifter	Remi motors, Mumbai
4	Bulk Density apparatus	Adarsh motors, Mumbai
5	Infra-Red Moisture analyzer	Shimadzu, japan
6	Tablet Compression machine	Kambert-KMP-D-8, Mumbai
7	Vernier calipers	Today tech solution, Mumbai
8	Friability apparatus	020334 -Veego Digital, Mumbai
9	Tablet Hardness tester	Monsanto hardness tester
10	Disintegration apparatus	Electrolab, ED-2L, Mumbai
11	Dissolution test apparatus	Lab India, TDT-06, Mumbai
12	HPLC	Shimadzu, japan
13	UV Visible spectrophotometer	Elico SL 196 Spectrophotometer, Mumbai
14	Stability Chamber	Today tech solution, Mumbai
15	Drying oven	Today tech solution, Mumbai
16	Centrifuge	Today tech solution, Mumbai
17	Glassware	Today tech solution, Mumbai
18	Vacuum oven	Today tech solution, Mumbai
19	pH meter	Systronics µ pH System 335, Japan
20	Micro pipette	Today tech solution, Mumbai

Applications in pharmaceutical formulation or technology: Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily usedas a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Applications in pharmaceutical formulation or technology: Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask someunpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in thebody and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal).

Preparation of Rapidly Disintegrating Tablets

The Rapidly Disintegrating Tablets can be prepared for selected solid dispersionpreparations by direct compression method. The solid dispersion powder equivalent toamount of drug and other excipients were passed through mesh no. 60 #. The powdered solid dispersion was mixed with proper portion of natural superdisintegrants. Then excipients other than glidant and lubricant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with talc and magnesium stearate for another 5 min and the resultant mixture was directly compressed into tablets by 8 mm round, flat punches using rotary tablet machine.

Evaluation of tablets for Post Compression Parameters

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Dissolution studies of Rapidly Disintegrating Tablets

The release studies can be carried out using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L). The rotation speed was 50 rpm and temperature was set at 37±0.5 °C. The drug release studies were carried out in phosphate buffer (900 ml). An aliquot was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed by using double beam UV spectrophotomer.

Dissolution studies of Rapidly Disintegrating Tablets

The release studies can be carried out using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L). The rotation speed was 50 rpm and temperature was set at 37±0.5 °C. The drug release studies were carried out in phosphate buffer (900 ml). An aliquot was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed by using double beam UV spectrophotomer.

PHARMACOKINETIC STUDIES OF THE OPTIMIZED TABLETS IN RABBITS

The objective of the *in vivo* studies in rabbits was to demonstrate the improvement of bioavailability of poorly soluble drugs by solid dispersion technology. The major goal to conduct the pharmacokinetic studies in rabbits was to describe the time course of drug concentrations in blood in mathematical expressions.

Exploration on the pharmacokinetics of drugs from their dosage forms is a significant and essential part of research studies and provides the key information related to bioavailability of the newly developed formulations. So the present study was aimed to conduct *in vivo* pharmacokinetic studies to prove the improvement in bioavailability of drug from the optimized formulation.

The institutional animal ethical committee (IAEC) of Chaitanya College of Pharmacy Education and Research, hanamkonda, Warangal agreed the proposed protocol of bioavailability study of Rapid Disintegrating Tablets of Flurbiprofen. The approval was recorded and protocol approval number was 02/IAEC/CCPER/CPCSEA/2017.

Twelve male albino rabbits weighing 1.9±0.2 kg were used for this study. In the present study, a crossover study was followed in which twelve male albino rabbits were participated and divided into two equal groups (group I and group II). In the firstphase of study, group I (n=6) received a control tablet (dose 50 mg) whereas group II (n=6) received FF6 rapidly disintegrating tablet (dose 50 mg). The animals were fasted and had free access to water from twelve hours before the experiment. The rabbit‟s mouth was opened, tongue was elevated and tablet was placed. Small amount of water was added to surface of the tablet before administering. The mouth was closed for 2 min to avoid chewing or swallowing of the tablet. Two millilitres of water was administered after dosing. In the second phase of the study, after 35 days washout period, group I received FF6 rapidly disintegrating tablet and group II received control tablet. Blood samples were collected at 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing from marginal vein.

Preparation of Rapidly Disintegrating Tablets of Flurbiprofen

- Flurbiprofen, natural superdisintegrants, microcrystalline cellulose, Mannitol were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with magnesium stearate and talc and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using 12mm round flat faced punch of Rotary tableting machine.

- Compression force was kept constant for all formulations.

Table 4.2 Formulae of Rapidly Disintegrating Tablets of Flurbiprofen with Natural Superdisintegrants

S.No.	Ingredients (mg)	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9	FF10	FF11	FF12
1	Flurbiprofen FS5 (Solid dispersion equivalent to 50 mg of Pure drug)	300	300	300	300	300	300	300	300	300	300	300	300
2	MCC PH 102	q.s	q.s	q.s	q.s.	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
3	Mannitol	35	35	35	35	35	35	35	35	35	35	35	35
4	Mango peel pectin	9	18	27	36	_	_	_	_	_	_	_	_
5	Banana powder	_	_	_	_	9	18	27	36	_	_	_	_
6	Orange peel pectin	_	_	_	_	_	_	_	_	9	18	27	36
7	Aspartame	6	6	6	6	6	6	6	6	6	6	6	6
8	Magnesium stearate	6	6	6	6	6	6	6	6	6	6	6	6
9	Talc	3	3	3	3	3	3	3	3	3	3	3	3
	Total Tablet Weight	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**

Subjects and Study Design

Twelve male albino rabbits weighing 1.9±0.2 kg were used for this study. In the present study, a crossover study was followed in which twelve male albino rabbits were participated and divided into two equal groups (group I and group II). In the firstphase of study, group I (n=6) received a control tablet (dose 50 mg) whereas group II (n=6) received FF6 rapidly disintegrating tablet (dose 50 mg). The animals were fasted and had free access to water from twelve hours before the experiment. Small amount of water was added to surface of the tablet before administering. The mouth was closed for 2 min to avoid chewing or swallowing of the tablet. Two millilitres of water was administered after dosing. In the second phase of the study, after 35 days washout period, group I received FF6 rapidly disintegrating tablet and group II received control tablet. Blood samples were collected at 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing from marginal vein.

Characterization of physicochemical parameters of tablets

a) Hardness test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge.

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablet was determined as per IP procedure. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by, % Friability of tablets less than 1% is considered acceptable.

$$F = \frac{Wi - wf}{wi}$$

Uniformity of weight

The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

Uniformity of drug content

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of Aceclofenac was extracted into distilled water and liquid was filtered (0.22 □ m membrane filter disc (Millipore Corporation). The Aceclofenac content was determined by measuring the absorbance at 275 nm (using UV-Vis spectrophotometer, Shimadzu 1700) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

***f. In- Vitro* Dispersion Time[19]**

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at37±0.5ºC and the time required for complete dispersion was determined.

STUDIES ON RAPIDLY DISINTEGRATING TABLETS OF FLURBIPROFEN

Preformulation study

Preformulation studies were primarily performed to investigate the physico chemical properties of drug and to establish its compatibility with polymers and other excipients.

Hardness and Friability of the tablets

All the formulations was checked using Monsanto hardness tester, the results obtainedare given in table. the average hardness of all the batches is in the range 3.01 to 3.21 kg/cm2.the hardness of all formulations was found to be in acceptable range, because these formulations are meant to be disintegrated or dispersed on tongue between fifteen seconds to three minutes, so excessive hardness is not favored for them. The hardness of formula KF12 was found to be highest and for formula KF9 was found to be the least. The friability test is designed to evaluate the ability of the tablet to with stand abrasion in packaging, handling, and shipping. The percentage friability for all the formulations lies in the range of 0.36 % to 0.52%.

Conclusion

The study performed on "formulation and evaluation of rapidly disintegrating tablets of Flurbiprofen using natural super disintegrants "reveals the following conclusions:

- The solid dispersions of Flurbiprofen could be prepared with carrier PEG 6000 using acetone as solvent by solvent evaporation method.
- Rapidly disintegrating tablets of Flurbiprofen could be prepared with Mango peel pectin, Dehydrated banana powder and Orange peel pectin were used as natural superdisintegrants by using direct compression technique.
- The evaluation parameters of all Rapidly Disintegrating Tablets of Flurbiprofen were shown satisfactory results.
- The Rapidly disintegrating tablets of Flurbiprofen to FTIR study suggested there was no drug interaction.
- The prepared Rapidly Disintegrating Tablets of Flurbiprofen of Flurbiprofen were stable.
- The results of the pharmacokinetic study revealed that the FF6 rapidlydisintegrating tablets containing PEG6000 solid dispersion enhances the bioavailability of poorly soluble Flurbiprofen.

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