REVIEW ARTICLE

FAST DISPERSION TECHNIQUES: APPROACHES AND RATIONALE FOR DEVELOPMENT OF FAST DISSOLVING TABLETS

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ABSTRACT

Pharmaceutical companies have introduced several drug delivery systems in the field of Pharmaceutical sciences that provide better and faster therapeutic response in patients to modulate pain and inflammation. In the present article a detail on fast dissolving technique and suitability of dexibuprofen as model drug for such rapidly disintegrating formulations has been addressed. This review articles focuses on all aspects taken into consideration regarding formulation development parameters, technologies used, role of superdisintegrants incorporated and the latest advancement in the improvement of aforementioned drug delivery system to increase the patient compliance.

Keywords: Drug delivery, Fast dissolving, Dexibuprofen, Superdisintegrants, Patient compliance

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INTRODUCTION

Pharmaceutical dosage forms and drug delivery systems are designed by formulation scientists as well as by various pharmaceutical manufacturing companies so that the required amount of the medicament can be delivered to the patients in a safer, precise and effective manner. For this reason several challenges and strategies are adopted and faced during the development phase of such formulations to make them targeted, efficient and stable throughout the shelf life period of the drug product.[1] Among all the drug delivery system presented in terms of oral solid dosage form tablets and capsules in the current era still have gained considerable importance and acceptance by the formulation scientists, physicians and the patients due to its numerous advantages which includes easy self-administration and cost effectiveness experienced by the patients.[2] However the drug delivery through the tablet dosage is no doubt, associated with potential drawbacks which include difficulty for the older and pediatric patients to swallow (dysphagia), low fraction of drug available for absorption in the bloodstream due to first pass hepatic effect, and a slower therapeutic outcome in patients.[3]

DISCUSSION

FAST DISSOLVING TABLETS

Fast and rapid drug delivery to the site of action with minimum side effects has attracted pharmaceutical industries to formulate and designed a tablet dosage form that can dissolve, disintegrate in the mouth cavity or disperses in water as quickly as possible. Thus readily absorbs in the bloodstream.[4] According to survey fifty percent of population belonging to the class of geriatric and pediatric population find difficult to swallow the tablet dosage form.[5] So for this purpose fast dissolving tablets have been emerged as a newer concept, in novel drug delivery systems that offers not only an alternative to conventional tablet dosage form, but also provide better therapeutic outcome ,ultimate solution and a better option for the problem faced by the patients of such age group and diseases.[6]

APPROACHES FOR DEVELOPMENT OF FAST DISPERSIBLE TABLETS

Following are the two approaches utilized:
1. Mouth dissolving tablets
2. Water dispersible tablets

1. Mouth Dissolving Tablets
This approach works by melting or disintegrating in the mouth cavity or by dissolving orally without the need of intake of water.[7]

2. Water Dissolving Tablets
This approach is designed and formulated in a way to disperse rapidly in water to form a homogenous dispersion.[8]

REASONS FOR FORMULATING FAST DISPERSIBLE TABLETS

•Taste masking by the incorporation of various flavoring and sweetening agents.
•Enhanced patient compliance due to acceptability by the patients.
•Faster rate of disintegration in a matter of seconds.
•Ease of manufacturing with low cost.
•Offers the advantage of being stable due to change in humidity and temperature. [9]
•Provides benefit in targeting pediatric and geriatric population to swallow both with and without the need of using water.[10]

POTENTIAL CANDIDATES FOR FAST DISSOLVING TABLETS

Following are the ideal characteristics which should be incorporated in formulation development of fast dissolving tablets.
•The drug should exhibit better solubility in both water and saliva as compared to others.
•The fast dissolving tablet must cross, diffuse and should be able to enter by means of partioning into the epithelial lining of upper part of GIT with (log P value be greater than one, or preferably greater than two).
•Must have shorter biological half-life and frequent dosing.
•It should be able to permeate the tissue of oral mucosa.
•Molecular weight of the drug must be moderate to smaller in size.[11]

FACTORS INFLUENCING FORMULATION DEVELOPMENT OF FAST DISSOLVING TABLETS

•Physical and chemical properties of active ingredient.
•Both the type and nature of active ingredient incorporated.
•Method employed during manufacturing.[12]
•The physical and chemical properties of the excipients which play an important role and therefore should be evaluated before formulation design and manufacturing.
•The design of formulation and the technique employed in manufacturing should be taken into consideration into order to avoid fluctuation in blood levels.

SALIENT FEATURES AND DEVELOPMENTAL CHALLENGES IN DEVELOPMENT OF FAST DISSOLVING TABLETS

1.TASTE MASKING
The unpleasant or bitter taste of the drug is a critical factor as the drug after disintegration into fine particles or granules in the oral mucosa is exposed to the taste buds. Hence, taste is one of the key parameter taken into account in development phase of fast dissolving drug delivery system. It is difficult to mask the bitter taste by the incorporation of sweetening agents alone readily available in the market. Therefore, in the recent years advancement in the technology has led to make improvement in such situations using combination of sweeteners with encapsulation and utilizing the technique of coating and making granules.[13, 14]

2.MOISTURE SENSITIVITY
Various fast dissolving tablets are moisture sensitive and are unstable to maintain the desired characteristic features of the drug under conditions of optimum humidity and controlled temperature. Therefore, several strategies are taken into consideration such as addition of additives (water soluble) to accelerate the dissolving ability and also to enhance taste. Addition of these additives imparts a serious damaging affect therefore; incorporation of suitable desiccants besides taking precautionary steps can prevent the deleterious effect of the hazards associated with the environment.[15, 16]

3.MOUTH FEEL
Fast dissolving tablets must not break into granules into the mouth cavity. Therefore, particle size in the smaller range is preferred for formulation development. In addition, the property of mouth feel can be achieved by the addition of cooling and flavoring agents that could result in enhanced patient compliance.[17]

4.MECHANICAL STRENGTH AND DISINTEGRATION TIME
Since faster and quick disintegration activity with rapid onset of action has always been demanded by the patients. Several means in the past few decades were adopted to formulate it using different techniques like freeze drying, wet mass compression and molding that result in formation of highly porous mass.[18, 19] During the formulation development binder is added to provide mechanical strength and several water soluble polymers like gelatin, dextran and maltodextrin incorporated to maintain the shape. Secondly, agents like sucrose and mannitol facilitates the disintegration activity of the matrix supporting mediator.[20]

5.TABLET SIZE
The patient compliance is also dependent on the size of the tablet which in turn related to the patient comfort in intake of dosage form. Research reported that the size of the tablet easier for the patient to swallow is 7-8 mm while the size preferred

to handle is found to be larger 8 mm. Therefore, both parameters tablet size that encompasses both easy swallowing and easy manufacturing are so far, quite problematic to accomplish.[21]

METHODS

FAST DISSOLVING PRODUCT MANUFACTURING TECHNIQUES

1. DIRECT COMPRESSION

Direct compression is the most preferable, demanding and simplest technique employed to manufacture a solid oral dosage form. Minimum number of steps involved, low cost of equipment utilized and commonly used excipients are the topmost features in selection of tablet manufacturing by direct compression technique.[22] The technique involves a two step process in which the active (API) and excipients is mixed together and compacted using tableting machine.[23]

2. SUBLIMATION

Sublimation technique involves the formation of pores through the use of several volatile substances like thymol, camphor and menthol. The porous network of the matrix created results in quick water uptake which is due to the wicking action, hence faster rate of disintegration achieved.[24, 25]

3. MOULDING

It is another method to manufacture tablet in which either heat or solvent is used. The advantage of this method is better taste masking and quicker breaking up of tablet into fine particles or granules. However, these features are enhanced when porous mass of such tablets is produced using various physically modified components utilized in the procedure. The porous network created in the tablet is one of the major steps in providing faster dissolution. However, several drawbacks associated using this technique is poor mechanical strength that results in difficulty in handling. [26, 27]

5. FREEZE DRYING

Freeze drying is also known as "Lyophilization". In this process the solvent (water) is removed from a solution or suspension form of a drug along with the carrier incorporated. Tablets manufacturing by freeze drying produces tablets of high porosity and therefore, offers faster dissolution and disintegration. The medicament is released immediately as soon as it is kept in the oral cavity. The process is carried out at a temperature not high enough so as to reverse the affect produce by heat on the drug product, which will eventually improve the stability of the product. However the major drawback of this technique is high cost involve and also the product manufacture through freeze drying is difficult to maintain the optimum feature of humidity and temperature.[28]

6. MELT GRANULATION

It is a process of manufacturing tablets in which powder mass is agglomerated using a binder that melts. The technique offers the advantage that no water or organic solvents is required .Since no drying step is involved, the process is less tedious, and therefore less energy than other granulation techniques are needed. It is a versatile technique to improve the dissolution profile of drugs.[29]

SUPERDISINTEGRANTS USED IN FAST DISSOLVING TABLETS

Disintegrants play a pivotal role in facilitating the breaking up of a tablet into fine particles or granules when exposes to the medium (water). Hence, promote the water molecules to enter into the tablet and thus, mechanism of disintegration is achieved.[30] The general mechanism of tablet disintegration is as follows.[31]

1. Wetting down of tablet.
2. The liquid to be dissolved enters into the crevices or pores.
3. The added disintegrant swells due to absorption of water.
4. Due to swelling, tablet disintegrates into powder particles or granules.

In order to produce robust tablets with desired properties of lesser disintegration and faster dissolution time particles of cohesive nature are required. The incorporated medicament must diffuse, dissolve and so a strong tablet resists dissolution. Tablet breaking agents added in the formulation to aid in the process of tablet disruption and fragmentation when exposes to water.[32] Researchers has studied the effect, concentration and activity of disintegrants and superdisintegrants on disintegration time. According to Rudinic and Schwartz, The concentration of starch suggested is 5% but this concentration can be increased by up to 15% if a drug has to been quickly disintegrated.[33] In other study Davies studied the affect of hydrophobic lubricant on the activity of disintegrant added.[34]

MECHANISM OF DISINTEGRANT ACTIVITY:

1. WATER WICKING

Wicking through crospovidone is one of the effective mechanisms of disintegration and is defined as the ability of the disintegrant to penetrate water uptake into the tablet matrix resulting in the displacement of trapped air.[35] However, porous tablets impart a significant effect in the disintegration pathway. The fluid enters into the crevices of the tablet matrix by means of capillary action and disrupts the interparticulate

bond through which the tablet breaks.[36]

2. SWELLING

Swelling is the mechanism of tablet deaggregation in which water uptake is facilitated in to the tablet matrix that causes disintegrants to swell and breaks.37 The porosity and packing fraction also imparts a significant impact on the disintegration behavior therefore, powder with poor porosity exhibits poor disintegration time.[38]

3. REPULSION

According to the theory based on the mechanism of particle repulsion tablet disintegration is also caused by particles that do not have the ability to swell. However, the tablet deaggregation mechanism depends on the forces of repulsion that exists between the powder particles. Hence researchers concluded that wicking is thought to be the primary mechanism of tablet breakup besides repulsion.[39]

4. PARTICLE DEFORMATION

Disintegrants during the compression phase of tableting under deformation and particles return to their precompression shape upon wetting with water. Hence the mechanism of tablet deaggregation is achieved as number of deformed particle increases.[40]

5. EFFERVESCENCES

Tablet disintegration by effervescence involves the expulsion of carbon dioxide gas when chemical reaction between citric and tartaric acid with bicarbonates and carbonates takes place. This favors the faster rate of dissolution with an added advantage of being good mouth feel.[41]

6. ENZYMATIC REACTION

Human body has several enzymes. These Enzymes help to break the bonds that exist between the primary powder particles. Hence, facilitates in the deaggregation mechanism of tablets.[42, 43]

Table 1: Types of Superdisintegrants.

	SUPERDISINTEGRANTS	PROPOSED MECHANISM OF ACTION
i.!	Cross-linked sodium Carboxymethyl cellulose	Swelling and wicking
ii.!	Cross-linked polyvinylpyrrolidon/ Cross-linked PVP	Swelling, wicking and deformation recovery
iii.!	Modified starches/ Cross-linked starch.	Swelling with rapid uptake of water
iv.!	Cross-linked Alginic Acid	Swelling or wicking action
v.!	Calcium Silicate	Wicking
vi.!	Gellan gum	Swelling with rapid uptake of water
vii.!	Xanthan gum	Swelling

DEXIBUPROFEN

Ibuprofen in its racemic form exhibits analgesic activity to reduce pain. However, this racemic form contains the same quantity of R (-) ibuprofen and S (+). This S (+) form of ibuprofen is known as Dexibuprofen. The chemical formula is $C_{13}H_{18}O_2$ with (2S)-2-[4-(2-methylpropyl) phenyl] propionic acid being the chemical name. However, this newly derived molecule possesses different physicochemical characteristic features than rac form of ibuprofen. According to literature it is found that Dexibuprofen and racemic form of ibuprofen are entirely two different chemical molecules that differ in their physical state. [44, 45]

Dexibuprofen has proven to be a safer and new pharmacological molecule that imparts better safety and efficacy as compared to the conventional NSAIDS prescribed. Biopharmaceutical classification system has categorized it under class II drug that favors low solubility in the aqueous phase. Due to the low solubility exhibited by the drug in water favors its absorption.[46]

MECHANISM OF ACTION

Inflammation, swelling and fever produced in the body are due to the activity of Prostaglandins. NSAIDS like dexibuprofen acts by the blocking of cyclo-oxygenase (COX) enzyme and inhibition of prostaglandin synthesis. Resultant decrease in prostaglandin concentration thus improves the inflammatory conditions and pain.[47]

CLINICAL INDICATIONS

Dexibuprofen is the most widely and newly prescribed therapeutic NSAID used to treat conditions associated with various types of pain which includes arthritis of joint and knee, pain related to skeletal muscles, conditions of postoperative pain. It works as an agent that reduces the inflammation in fever also.[48, 49]

CONCLUSION

The concept of fast dissolving drug delivery system

emphasizes in fulfilling the need of patient in terms of providing faster onset of action. Because of such reasons patients found conventional drug delivery system less easy, less effective that result in decrease compliance issues related to swallowing. Hence, the concept of fast dissolving drug delivery has been found as a newer approach that produces significant impact in providing profitability and improving the life cycle of the drug product. It is therefore, expected that newly design future trends in such a drug delivery system will hopefully provide several different disciplines of current technology that would help to mitigate patients suffering from serious pain conditions.

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