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A Review: Formulation and Characterization of Fast Dissolving Tablet of Carvidilol

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ABSTRACT

Carvedilol a poorly water soluble drug undergoes extensive first pass metabolism, which reduces its bioavailability to 25-30%. Fast dissolving tablets of Carvedilol were prepared with the purpose of delivering the drug directly into the systemic circulation and bypassing the hepatic first pass metabolism with a concomitant increase in bioavailability. The solubility of Carvedilol was improved by forming inclusion complex with cyclodextrin which was then further used for the formulation of Fast dissolving tablet.

Keywords: Carvedilol, Superdisintegrats, Fast dissolving Tablets and FDTs.

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1. INTRODUCTION

Carvedilol is indicated for the treatment of mild to severe chronic heart failure, Left ventricular dysfunction following myocardial infraction in clinically stable patients and hypertension. Carvedilol is a poorly water-soluble oral antihypertensive agent, with problems of variable bioavailability and bio-equivalence related to its poor water-solubility. In present work attempt will be made to design and evaluation of Fast dissolving tablets of Carvedilol for the effective management of angina pectoris, hypertension etc. [1] In view of substantial first pass effect and its shorter plasma half life therefore is an ideal drug candidate for Fast dissolving drug delivery system. [2] To formulate the fast dissolving dosage form of Carvedilol to Improve patient compliance, Ease of administration, Increase bioavailability of drug and avoid first pass effect.[3]

Fast Dissolving Tablet is solid unit dosage form which disintegrates or dissolves rapidly in the mouth without chewing and water. To design fast dissolving oral tablet of Carvedilol in order to improve bioavailability, ease of administration and patient compliance. In the present study, fast dissolving tablet of Carvedilol was attempted with the aim to develop a dosage form that was easy to administer, provided fast release of drug and also enhanced bioavailability of the drug. Pregastric absorption through mouth, pharynx and oesophagus, could enhance the bioavailability by suitable formulation approaches and also provide local action, as the drug releases in saliva and passes down in to the stomach. The market survey revealed that the conventional tablets are available. Hence it was thought to formulate novel and convenient solid dosage form i.e. fast dissolving tablet. Carvedilol was selected as a drug candidate for the formulation of fast dissolving tablet for the following reasons, It is practically insoluble in water therefore taste related problems can be avoided. It is chemically stable. Having $t^{1/2}$ of – 7 to 10 hrs. In view of substantial first pas effect and its shorter plasma half life, therefore is an ideal drug candidate for fast dissolving tablet. Appropriate disintegrating agents and highly hydrophilic excipients are the main ingredients of fast dissolving tablets.

2. IDEAL CHARACTERISTICS Of FDT [4,5]

It should require no water for administration

It should dissolve/disperse in mouth within few seconds

It should have pleasant mouth feel

Ability to permeate to mucosal layer

Compatibility of drug with taste masking agent

It should leave minimum or no residue after oral administration

Manufacturing should involve easy conventional techniques.

3. ADVANTAGES OF FDT [6-9]

FDT can be easily administered to pediatric and geriatric patients

Safest route of administration

Rapid onset of action

Enhancement in bioavailability

High drug loading can be achieved

Economic drug delivery system

4. DISADVANTAGES OF FDT [6,7]

FDTs usually possesses insufficient mechanical strength

In some cases taste masking agents make FDTs as expensive

5. DRUGS SUITABLE FOR FDT [8, 9]

Drugs which are having less dose

Stable in water and saliva

Bitter drugs are not suitable for FDT. But by using taste masking agent's bitter drugs can be formulated as F.

6. TECHNOLOGIES USED FOR MANUFACTURING OF MDTS

In the recent past, several new advanced technologies have been introduced for the manufacturing of FDTs with ideal properties like less disintegration time, pleasant mouth feel, exceptional taste masking and sugar free tablets for diabetic patients. The technologies used for manufacturing of FDTs broadly classified in two category one is patented another one is nonpatented technologies.

6.1 Lyophilization or Freeze-drying:

Formation of porous product in freeze-drying process is exploited in formulating FDTs. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives.[8] Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has Rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug. However, the FDTs formed by lyophilization have low mechanical strength, poor stability at higher temperature, and humidity [8]

6.2 Molding:

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydroalcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying .Molded tablets are very less compact than compressed tablets. These posses porous structure that increase dissolution[9]

6.3 Cotton candy process:

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process[10] involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDTs.

6.4 Spray drying:

This technology produces highly porous and fine powders as the processing solvent is evaporated during the process[11.] In this method to prepare FDTs hydrolyzed and nonhydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent and sodium starch glycolate or crosscarmellose sodium as superdisintegrant. Disintegration and dissolution were further increased by adding acidic substances like citric acid or alkali substance like sodium bicarbonate. This formulation technique gives porous powder and disintegration time < 20 sec [12, 13].

6.5 Mass extrusion: This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets[14]

6.6 Melt granulation:

In this process, FDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate is a waxy material with an m. pt. of 33- 37°C and a hydrophilic- lipophilic balance of[9]. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of FDTs by melt granulation method where granules are formed by the molten form of this material [15]

6.7 Phase transition process:

Kuno *et. al.*,[16] investigated processes for the disintegration of FDTs by phase transition of sugar alcohols using erythritol (m. pt. 122°C), xylitol (m. pt. 93-95°C), trehalose (97°C), and mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

6.8 Sublimation: The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of FDTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet[17]. Developed FDTs utilizing camphor, a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

6.9 Direct compression methods:

This technique is easy way to formulate FDTs since limited number of processing steps, low manufacturing cost and also accommodate high dose the final weight of tablet can easily exceed that of other production method[18].

The disintegration and dissolution of directly compressed tablets depends on single or combined effect of disintegrant, water soluble excipients and effervescing agents. Disintegrant efficacy is strongly affected by tablet size and

hardness. Disintegration properties can be optimized by medium or low tablet size, low hardness and low physical resistance .It is essential to choose a suitable and an optimum concentration of disintegrant to ensure fast disintegration and high dissolution rates[18,19]. The addition of water soluble excipients or effervescent agent can further increase dissolution or disintegration properties. Super disintegrants provide fast disintegration due to combine effect of swelling and water absorption. As an effect of swelling of super disintegrant the wetted surface of the carrier increase, which promotes wettability and dispersibility of the system and thereby increase the disintegration and dissolution [20, 21, 22].

The optimum concentration of superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration the tablet disintegration time is inversely proportional to the concentration of superdisintegrant, where as if concentration of superdisintegrants incorporated in tablet is above the critical concentration, the disintegration time remains approximately constant or even increases.

7. PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS

7.1 Zydis Technology:

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze-drying process or long-term storage.[23] Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

7.2 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 tabletting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters.[24] Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

7.3 Orasolv Technology:

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct 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.[24]

7.4 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 by flash heat processing.[24]

7.5 Wow tab Technology:

Wow tab technology is patented by Yamanouchi Pharmaceutical CoWOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides).[24]

8. EVALUATION OF MOUTH DISSOLVING TABLET

FDTs formulations have to be evaluated for the following evaluation test [25,26.]

8.1 Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled. Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

8.2 Uniformity of weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Average weight of Tablets (mg) Maximum percentage difference allowed 130 or less 10 130-324 7.5 More than 324 5.

8.3 Tablet hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

8.4 Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre weighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as; In-Vivo.

8.5 Disintegration test:

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

8.6 Wetting time:

The method reported by Yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined. In vitro dispersion time: In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

9. CONCLUSION

The FDTs have potential advantages over conventional dosage forms, with their improved patient compliance, convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. FDTs formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. These FDTs can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently. They remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. As they have significant advantages as both solid and liquid dosage forms, FDTs may be developed for most of the available drugs in near future.

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