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Original Article

Oral Disintegrating Minitablets: Mini Review

Deepak Garg[1], Vipin Saini[1], Sumeet Gupta[1], Deepak N. Kapoor[2], Lokesh Kumar Joshi[2]*

[1]M.M College of Pharmacy, Maharishi Markandeshwar University, Haryana, India
[2]School of Pharmaceutical Sciences, LFAMS, Lovely Professional University, Punjab, India
*Corresponding Author: lokeshkrjoshi@gmail.com

Abstract

The current review discusses the importance of oral disintegrating minitablets as a substitute to conventional oral dosage forms. ODMT's are dosage forms that disintegrate in mouth offering various advantages such as better mouth feel, dose accuracy, improved stability and convenient dosing as compared to oral liquids. The advantages, disadvantages, properties and key characteristics are discussed while emphasizing on various manufacturing techniques of ODMT's.

Introduction

In spite of incredible inventions in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, non-invasive method and ease of administration leading to high level of patient compliance for pediatrics as well as for geriatrics patients [1,2]. The commonly used formulation in, pediatrics are liquid dosage form that are safe and easily administered to children. However, in case of bitter drugs, taste masking presents serious challenge during formulation development of liquids. Other difficulties with liquid dosage forms are bulkiness, reduced stability, and incompatibilities [3]. Oral dosage form like mini tablets and mini pellets have been projected as a novel method of pediatric oral drug delivery, minitablets are compacts with diameters between 2 and 5 mm [4].

Oral dispersible tablets (ODTs) are the novel dosage form which rapidly disintegrates in the mouth (1-3 min) without chewing upon oral administration and without the need of water, unlike other conventional oral solid dosage form [5]. Oral Dispersible Tablets (ODTs) are also known as "fast-

dissolve", "rapidly disintegrating", "quick-dissolve", "crunch-melt", "bite-dispersible", "mouth-dissolve", and "orodispersible" tablets [6-7]. Oral dispersible minitablets (ODMTs) are more suitable for pediatric patients because of their small size, pleasant mouth feel and fast disintegration in mouth [8].

ADVANTAGES

Minitablets present many benefits over orally administered liquids (Alastair G. Sutcliffeet *et al.,* 2008) [9]:

a) Delivery of accurate dose vis-à-vis dose flexibility.
b) Require fewer or less problematic excipients.
c) Dry product formulation would improve drug stability.
d) Maintaining steady plasma levels [10].
e) From industry point of view the product is cost effective.
f) Defined sizes and strengths can be easily produced (Pich and Moest, 1989; Munday, 1994) [11].
g) Convenience of administration and accurate dosing as compared to liquids.
h) Good mouth feels property of ODTs helps to change the basic view of medication as "bitter pill", particularly for pediatric patients [12].
i) Rapid dissolution of drug and absorption which may produce rapid, onset of action [13].

DISADVANTAGES

a) High dose drugs could not be transformed into ODMTs.
b) Due to the small size these tablets powder blend more stick to the die or punch or the powder flow may get affected.

DESIRED CHARACTERISTICS OF ORAL DISINTEGRATING MINI TABLETS [14]:

- ODTs should disintegrate in the mouth without additional water.
- The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing.
- The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

- Because ODTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds.
- A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used.
- The taste-masking technology should also be compatible with ODT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation.
- Taste masking of bitter tasting drugs is critical to the success of the ODT formulations.
- For the ideal ODT technology, the drug properties should not significantly affect the tablet property.
- Because ODTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets.
- In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.
- A good package design or other strategy should be created to protect ODTs from various environmental conditions especially from moisture.

TECHNIQUES USED TO MANUFACTURE ODMTs:

Due to small dose and size of the tablet the manufacturing technique for ODMT's should carefully selected as because the amount of excipients used to manufacture the tablet is limited. There are four general techniques used to manufacture ODMTs. These are:

a) Direct compression technique

b) Dry granulation technique

c) Wet granulation technique

d) Melt-Extrusion method

1. Direct compression technique:

Direct compression is the process by which tablets are compressed directly from powder blends containing API and excipients (fillers, disintegrants, lubricants etc.). Stoltenberg *et al.,* 2011 directly compressed the powder blend into biconvex minitablet (Hydrochlorothiazide, HCT) of 2 mm diameter and a mass of approximately 6.5 mg. Compression forces (maximum upper punch forces) of 3 kN, 5.5 kN and 8 kN were applied for all of the ODMT formulations without API. The ODMTs obtained were de dusted for 1 min using an air jet sieve with a nominal mesh size of 125 µm and a pressure of 600 Pa.

2. Dry granulation technique:

Dry granulation is rational technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs. This technique employs processing equipment known as roller compactor or chilsonator. This machine compress as premixed powders between two counter rotating rollers under extreme pressure. The resultant material is in the form of a brittle ribbon, sheet, or piece-depending on the configuration of the roller. The compressed material is reduced to the proper size to form granules that are mixed with other in-active excipients and finally compressed on a rotary compression machine [17].

≈ **Slugging:**

There is another method instead of making brittle ribbon sheets, the slugs can be formed by forcing the initial blend of powders into the dies of a large capacity tablet press and is compacted by means of flat faced punches. The formed compacted masses are called ‘slugs’ and the process is referred as ‘slugging’. The slugs are then screened or milled to produce granules. These granules are mixed with other excipients and finally subjected to compression. A thorough schematic representation is mentioned in fig.1 which is described below.

Peter Kleinebudde *et al.,* developed the mini tablet of size 1 mm and 2 mm of diameter using roller compactor/dry granulation as a strategic technique by choosing three model drug *i.e.* quinine hydrochloride, ibuprofen and spray dried gentian extract. Depending on the individual drug substance, mini-tablets were produced by direct compression or after roll-compaction/dry granulation. With dry granulation a specific compaction force of 2 kN/cm was applied for quinine hydrochloride and tabletting mixtures containing quinine hydrochloride. The speed of rolls was set to 3 rpm and the gap between the

rolls was kept constant at 2.0 mm. Ibuprofen and the ibuprofen mixture were dry granulated with a specific compaction force of 3 kN/cm, the gap between the rolls was kept constant at 3.0 mm and speed of rolls was set to 2 rpm.The prepared ribbons were dry granulated using a star granulator with a 1.0 mm sieve. For the first time 1 mm mini-tablets could be successfully produced by direct compression (90% quinine hydrochloride; 90% dried gentian extract) and after roll compaction (70% ibuprofen). Depending on the applied compression pressure, 1 mm mini-tablets with quinine hydrochloride exhibited robust mechanical properties (*e.g.* median tensile strength of 2.02 N/mm2) with equal or lower variance of distributioncompared to the 2 mm compacts [18].

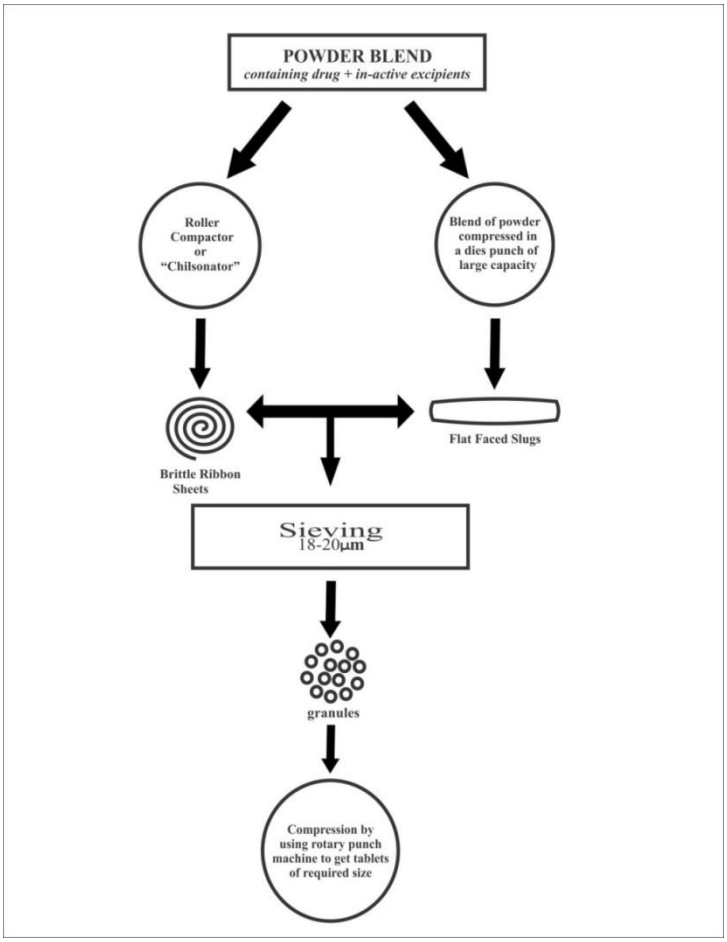

Fig. 1: *Schematic Representation of Dry Granulation Technique.*

3. Wet granulation technique:

Mirelabodea *et al*., identified the critical formulation variables for obtaining the metoprolol tartarate mini-tablets using wet granulation as a principal technique. In this process, the granulation is achieved in

a fluid system using polyvinyl pyrrolidone k-30 (PVP K30) as a chief binder in a blend [19]. The obtained granules were milled in an Erweka FGS oscillator mill (sieve 0.6 mm). Particle size distribution of the blend was performed using dry sieving method with a set of 6 sieves: 600, 500, 400, 315, 200 and 125 µm (for 100 g of blend). In order to improve tabletting properties of metoprolol granules, the extra granular ingredients were added to obtain the blend for compression using compression force between 22-34 KN. [20]

4. Melt-Extrusion technique:

Remon *et al.,* prepared minitablet's of ibuprofen that actively binds with the microcrystalline wax and the optimum concentration of starch which act as a disintegrating agent as well as binding agent. The API and in-active excipients were mixed in a planetary mixer. The melt extrusion was performed using MP19TC-25 laboratory scale co-rotating twin screw extruder of APV Baker (Newcastle-under-Lyme, UK). The machine was equipped with a control panel (allowing control of barrel temperatures, screw speed and powder feed rate) and twin screw shaving 2 mixing sections, a 3 mm cylindrical dies and a twin screw powder feeder. The extrusion parameters were set at a screw speed of 100 rpm and a powder feed rate of about 700 g/h. The temperature profile of the extrusion barrel depended on the melting range of the micro crystalline wax used. The extrudates (diameter 3 mm) were milled using a Kenwood® mill (KenwoodChef, Hampshire, UK), followed by sieving on a Retsch VE 1000 shaker (Retsch, Haan, Germany) using 250, 500 and 710 mm sieves. The granules (250–500 mm) were compressed using an eccentric tabletting machine (Korsch, EK 0, Frankfurt, Germany) equipped with a standard filling shoe. Punch holders were equipped with flat punches 2 mm in diameter. The mean compaction pressure was 156916 MPa for each mini-tablet. Each mini-tablet weighed approximately 7.5 mg [21].

Conclusion

ODMTs represent the advancement in the formulation technology and dosage form development. These dosage forms display several advantages like accurate dose, dose flexibility, require fewer or less problematic excipients and improve drug stability. These are easy to manufacture and are well accepted by pediatric and geriatric patients. Pharmaceutical industries have carried out a great deal of developmental studies to develop various technologies for the manufacturing of ODMT's. Still there is much scope in exploration of candidate drugs for their possible conversion into ODMT's as an alternative to conventional tablets.

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