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# Recent developments in orally disintegrating mini tablets

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Abstract

Solid oral dosage forms are most suitable dosage forms; preferably tablets are widely accepted by people of different age groups. Mini tablets are tablets with a diameter equal to or smaller than 2–3 mm. Mini tablets are multiple unit dosage forms and are advantageous than pellets or any other oral dosage forms as they are easy to manufacture and stability problems are less. Many types of mini tablets are there like bio adhesive mini tablets, pH responsive mini tablets, gastro retentive mini tablets, paediatric mini tablets, oral disintegrating mini tablets. Current ODT developments meet multiple pharmaceutical and patient needs, including better life-cycle management to easy treatment for paediatric, geriatric and psychiatric dysphagic patients. Orally disintegrating dosage forms are X suitable for patients, especially who find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water for one reason or another. These essentially reduce the variation between subjects. Mini tablets which disintegrate orally can be evaluated by testing for dissolution, disintegrating testing and hardness. The need for non-invasive delivery systems continues due to the poor acceptance and enforcement by patients of current delivery schemes, limited market space for drug companies and product usage, coupled with high disease management costs. The review emphasizes on advantages of mini tablets, types, methods of manufacturing and modes of administration and evaluation of mini tablets.

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## INTRODUCTION

Solid dosage forms (tablets) are widely used forms of dosage forms. There are many inventions which have taken place in delivery of drugs, but ingestion is identified as best site for administering because of its best properties like ease of administration, therapy is low, dose is accurate and is also intensive of patient conformity, particularly for geriatrics patients as well as paediatrics. The most common form of dosage used in pediatrics is liquid dosage form because it is safe and easy form of administration for children. But in some cases liquid dosage forms have difficulties in formulation in conditions like taste maskin, bitter drugs. Mini tablets and pellets (oral dosage form) are said to be novel method for pediatric delivery. The diameter size of mini tablets are between 2 and 5 mm (Lennartz and Mielck, 1998). Orally disintegrating mini tablets are new type of dosage forms which disintegrate in mouth (1 to 3 min) devoid of the requirement of water distinct different forms of oral-solid dose forms (Abdelbary *et al.*, 2005). Orally Disintegrating Mini Tablets (ODMTs) are known as "quickly disintegrating", "quickdissolve", "crunchmelt", "bitedis-

persible", "mouthdissolve", of API that breakdown rapidly generally within 1 minute once located on tongue." ODTs disintegration and "oro-dispersible" tablets (Habib *et al.*, 2000). USFDA outlined ODTs as "A solid dosage form comprising time usually varies from seconds to about a minute. United States Pharmacopoeia (USP) approves the terminology of these dosage forms as ODTs. In recent times, EP has been made use of the word oro-dispersible tablet which dissolves immediately and inside 3 minutes in buccal cavity prior to swallowing (Fu *et al.*, 2004). These also emphasizes on classification, advantages, disadvantages, categories, characterstics, and method of preparation of mini tablets.

## CLASSIFICATION OF ODT'S

ODTs are classified into three categories such as first, second and third generation ODTs (Reddy *et al.*, 2009). Table 1 depicts the methodology involved in preparation of ODTs along with its advantages and disadvantages (Bangale *et al.*, 2011; Ghosh *et al.*, 2011).

### Advantages

Advantages of mini tablets are as follows

a) Helps in maintaining steady plasma levels

b) Required strengths and required sizes can be prepared (Pich and Moest, 1989)

c) Helps in masking the bitter taste which is useful for infants (Munday and Fassihi, 1989)

d) Mini tablets have quick dissolving time of drug and absorption generate faster onset

f) Mini tablets gives high drug loading and lesser risk of dose dumping (Mastoi, 2018)

### Disadvantages

a) The drugs with high dose can not be administered through mini tablets.

b) Flow gets affected due to the smaller size of powders and it may even get stuck to the die or punches (Preis, 2015)

### Different categories of Mini-tablets

Table 2 depicts the types of mini tablets along with the advantages and disadvantages.

### Pediatric mini tablets

Pediatric mini tablet is administered mainly to small children. As when compared with regular tablets which are larger in size and has problems to swallow.

To overcome these problems preparation of mini tablets helps in patient receiving.

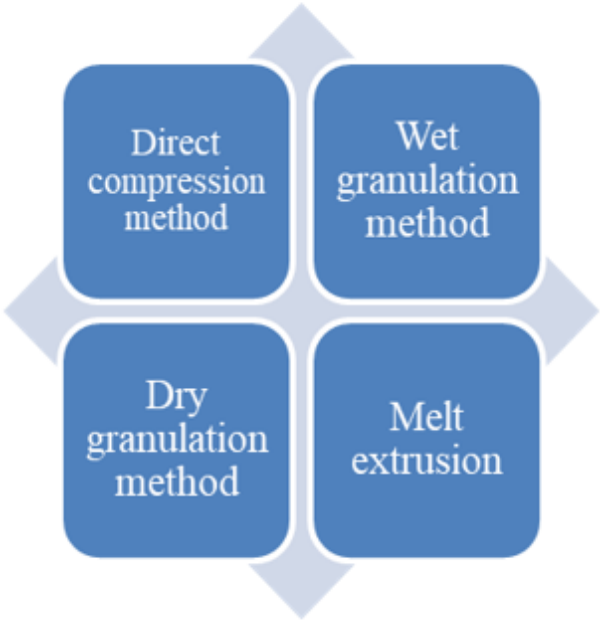


**Figure 1: Methods involved in manufacturing mini tablets**

### Floating-mini tablets or Gastro-retentive mini tablets

GRMT are administered to discharge the drug in GIT for longer duration. Gas generating agents helps tablet to float on gastro intestinal fluid content. To increase the drug loading gas generating agents like sodium bicarbonate are used for coating purpose. Mini tablet coating is mainly done by fluid bed processor technique (Thomson *et al.*, 2009).

### Bioadhesive Vaginal Mini orally disintegrating Tablets

These dosage forms lead to less retention time, leakage, and less patient compliance. To avoid these type of problems the use of bio-adhesive polymers is better. Bio adhesive polymers are easily soluble and helps in overcoming these type of problems (but in larger size tablet loss is reported) (Biradar and Bhagavati, 2005).

### pH responsive orally disintegrating mini tablets

PH of GIT varies (small intestine 4-5),(stomach 1-3), (colon5.7-6.8),(ileum6.6-7.6). Mainly used polymers are Eudragit L100and Eudragit S 100

### Oral dispersable mini tablets

These are suitable for infants because of their characters like smaller size and faster disintegration but the condition is that they have to disintegrate in mouth without the use of water. Soft paste or suspensions helps in providing smooth swallowing and

**Table 1: ODT's Classification.**

| | 1st generation ODTs | 2nd generation ODTs | 3rd generation ODTs |
|---|---|---|---|
| Methodology | By freeze drying process | wet granulation method | Dry granulation technique |
| Advantages | Rapid disintegration of ODTs | Rapid disintegration of ODTs | 1. Rapid disintegration of ODTs<br>2. Less friable then first generation |
| Disadvantages | 1. Handling was difficult<br>2. moisture senstive<br>3. No taste masking<br>4. Low density and hardness | 1. low hardness of tablets<br>2. High porosity<br>Low density | 1. High porosity<br>2. Low density<br>3. low hardness |

**Table 2: Type of OTDs**

| Sl/No | Type | Advantages | Dis-Advantages |
|---|---|---|---|
| 1 | Pediatric mini tablets | Simpler to administer | Microbial instability |
| 2 | Gastro retentive mini tablets | Can generate gas when administered | Patient compliance is an issue |
| 3 | Bio adhesive mini tablets | High dose accuracy | Vaginal disintegration is low |
| 4 | Bi-phase mini tablets | Simpler to administer | Patient compliance is an issue |
| 5 | Oral disintegrating mini tablets | Rapidly disintegrates | Taste masking is an issue |

**Table 3: Examples of Coloring agent.**

| FD & C Aproved Color | Common Name |
|---|---|
| YELLOW5 | Tartrazine |
| YELLOW6 | Sunset Yellow |
| RED3 | Erythrosine |

Glidants: Talc, PEG 400, Paraffin, Mg-stearate, Zn-stearate, etc

**Table 4: Weight Variation (IP)**

| Avg.wt | % variation |
|---|---|
| $\leq$80 miligrams | $\pm$10 percentage |
| $\geq$ 80 miligrams to $\leq$ 250 miligrams | $\pm$7.5percentage |
| $\geq$250 miligrams | $\pm$5percentage |

also good feel to the mouth (Singh *et al.*, 2018).

ODTs are categorised into Pediatric mini tablets, Gastro retentive mini tablets and Bio adhesive mini tablets etc and its advantages and disadvantages are listed in Table 2.

## EXCIPEINT USED IN THE PREPARATION OF MINI-TABLET

The below excipients were required in development of ODTs (Pahwa *et al.*, 2010; Nagar *et al.*, 2011).

### Super disintegrants

Microcrystalline cellulose, Sodium starch glycolate, Crospovidone, Cross Carmellose Sodium, Pregelatinized starch, Calcium CMC and Modified corn starch.

### Bulking agents

$CaCo_3$, $MgCaCo_3$, Mannitol, $CaSO_4$etc

### Emulsifying Agents

PEG-Ester, Alkyl sulfates, Sucrose ester etc.

 

**Table 5: List of mini tablets available in market**

| Sl/No | Generic Name | Brand Name |
|---|---|---|
| i. | Zafirlukast | Accolate |
| ii. | Pancrelipase | Ultresa |
| iii. | Donepezil Hydrochloride | Aricept |
| iv. | GalantamineHBr ER | Razadyne ER |
| v. | Fenofibric Acid( Capsules) | Trilipix |
| vi. | Levonorgestrel and Ethinyl Estradiol | Alesse |
| vii. | Prasugrel( Tablets) | Effient |
| viii. | Olanzapine | Zyprexa, ZyprexaZydis |
| ix. | Sumatriptan and Naproxen SodiumTablets | Treximet |
| x. | Warfarin Sodium tabs | Coumadin |
| xi. | Vorapaxar Tablets | Zontivity |
| xii. | Hydromorphone HCLExtended Release Tablets | Exalgo |

**Table 6: Encapsulated mini tablets available in the market**

| Sl/No | Generic- Name | Brand Name |
|---|---|---|
| 1 | Pancrelipase | Ultresa |
| 2 | GalantamineHBr ER | Razadyne ER |
| 3 | Fenofibric Acid Capsules | Trilipix |

### Sweetening agent

Natural-Dextrose, Sucrose, Mannitol, Lactose.

Artificial-Cyclamate, Aspartame, saccharin.

### Flavoring agent

Strawberry, Vanilla, Fruit essence, Peppermint oil, menthol etc.

### Surface Active agents

SLS, Polyoxyethylene sorbitol fatty acid esters etc.

### Binders

HPMC, PVP, PVA.

### Colorings Agents

FD and C approved colors include tartrazine, sunset yellow, erythrosine as described in Table 3.

### Methods to Manufacturing Mini Tablets

Mini tablets can be prepared by Direct compression, wet granulation, dry granulation and melt extrusion techniques as shown in Figure 1 based on the excipients used and class of drug.

### Direct- compression method

The method involves pressing the tablets directly from powder blend comprising Active pharmaceutical ingredient and adjuvants into biconvex mini tablet (Rao *et al.*, 2011).

### Wet granulation method

The technique involves granulation attained in a fluid media utilizing polyvinyl pyrrolidone k-30 (PVP K30) as a primary binder in a blend (Bandelin, 1989). The granular part produced are pulverized in an Erweka FGS oscillator mill (sieve 0.6 mm).

### Dry granulation method

This method involves the use of instrument called roller compactor. The compacted sub0stance is decreased to the appropriate size to obtain granules that are blended with inert adjuvant and ultimately compressed on a rotary compression equipment (Lopes *et al.*, 2006).

### Melt-Extrusion technique

In melt-extruder device variables such as screw speed, feeding rate and temp are maintained in melting point range of substance. The obtained granules are then packed together to mini tablets using compression machine (Karthikeyan *et al.*, 2013). As a result, tablets with different content, doses and release properties can be manufactured (Shaikh *et al.*, 2018).

### Coating of mini tablets

Polymers are used in coating of mini tablets for modifying the release of the drug in a sustained manner enterically. Some of the polymers used in enteric

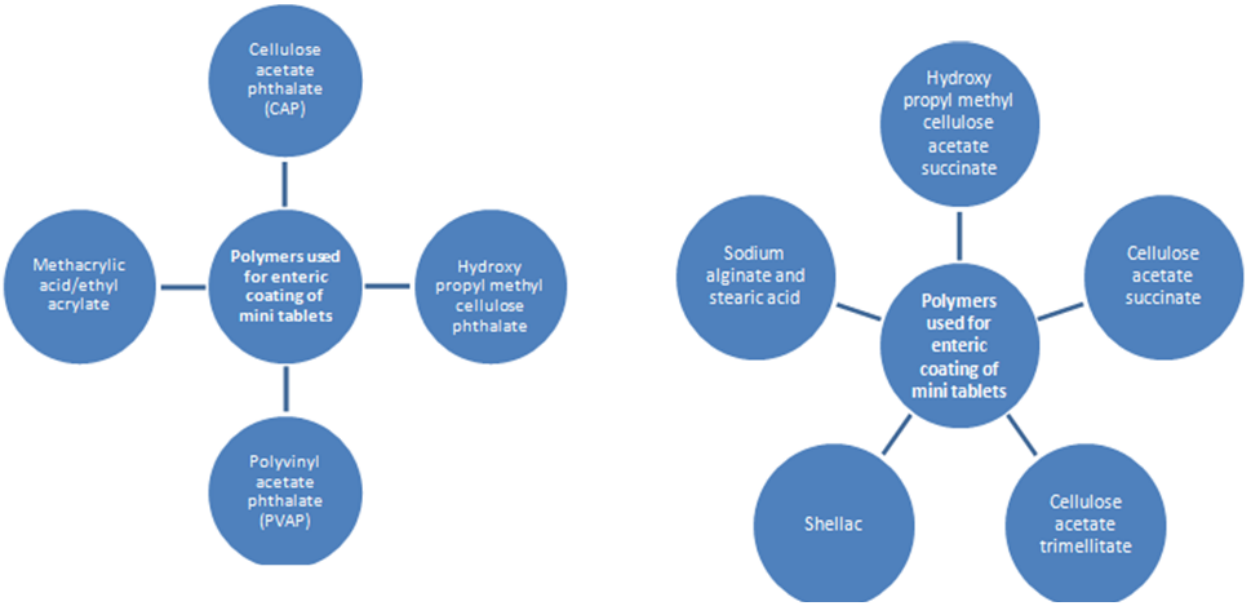


**Figure 2: Polymers used to prepare ODMTs**

coating include cellulose derivatives, acrylate polymers and phthalates (Keerthi *et al.*, 2014).

Polymers control the release of the drug from the dosage form by acting as a reservoir of the drug. Commonly used polymers in the fabrication of ODTs have been picturised in Figure 2. Mini tablets can be administered by direct administration, filling in hard gelatin capsules or automatic dose dispensing device (Chauhan, 2017).

**Filling in hard gelatin capsules**

Mini tablets handling is difficult as they are smaller in size so they are filling in hard capsule (gelatin) and administered (Bechgaard and Nielsen, 1978).

**Dose dispensing device (Automatic)**

Helps in dispensing tablets of required dose (Rs, 2006).

## EVALUTION STUDY OF FAST DISSOLVING MINI TABLET

**Preformulation studies mini-tablets**

Preformulation study is seen by techniques such as angle of repose, bulk density and tapped density, Carr's index and Hauser's ratio (Priyanka *et al.*, 2018).

**Compatibility studies of drug excipients**

By DSC and FT-IR studies (Abdelmaqsoud *et al.*, 2019).

**POST-COMPRESSION STUDIES**

**1. Tablet thickness**

y using Vernier Callipers

**2. Weight variation**

From the prepared batch twenty tablets were taken randomly for weighing to check for variation of weight as shown in Table 4. (Patil *et al.*, 2010).

**3. Friability**

The test for friability is done using Roche friabilator (Sachin *et al.*, 2010).

$$\%Friability = 1 - (Final\ weight\ /\ Initial\ weight)\ X\ 100$$

**4. Hardness**

The limit for hardness of uncoated tablet is 3-5 kg/cm2 (Songa *et al.*, 2013).

**5. Drug content (uniformity)**

Absorbance of drug is calculated at their respective wavelength by using Ultra violetvisible spectrophotometer (Morita *et al.*, 2002).

**6. Disintegration time**

Disintegration time is observed at 25 rpm, 37°C. (Bajaj and Singla, 2012)

**7.In vivo disintegration time**

A panel of healthy human volunteers is used to perform this test. The time taken by volunteers to disintegrate by retaining the tablet in mouth is noted.

**8. In-vitro Dissolution Studies**

This study was done using USP type 2 apparatus at particular temperature and RPM for exact point in time in appropriate buffer solution.

**9. Stability Studies**

Storage conditions

$40°C \pm 2°C/75\%$; $RH \pm 5\%RH$, $25°C \pm 2°C/60\%RH \pm 5\%RH$ (Tehseen and Rao, 2013)

The generic and brand names of the mini tablets available in the market is depicted in Table 5.

The generic and brand names of encapsulated mini tablets availbale in the market are shown in Table 6.

## CONCLUSIONS

The overview of mini tablet formulation has resolved number of the issues encountered in administration of medication to the paediatric and aged patients, who constitute a larger proportion of the world's population. Nowadays, ODTs are available in market has OTC products to treat flu symptoms, cold and allergies. These ODTs were formulated as full porous in structure of the tablet for rapid dissolution of tablet matrix with pleasant taste and with appropriate mechanical strength. Therefore for rapid disintegration of tablets, super disintegrating agents were used in different concentration depending on the drugs. The research work is still going on and more number of manufactures are formulating fast dissolving tablets. More number of ODTs products was marketed and which are formulated by utilizing advanced innovative technologies. Therefore, ODTS were formulating for more number of drugs and for various treatment of disease in the future.

Mini Tablets offer great advantage over single unit dosage forms. Accurate dose of drug can be given to patients to increase the efficiency. Inter and intra subject variability can be decreased by using mini tablets. The toxic effects of potent drug overdose while using conventional dosage forms can be reduced by mini tablets. Dose dumping and local irritation can be avoided by the use of mini tablets. For those drugs whose absorption is more in small intestine mini tablet dosage form is beneficial as they can easily pass through the duodenum independent of gastric emptying and intestinal motility.

Bio adhesive mini tablets show increased bio adhesion and increased effect than that of single unit bio adhesive tablets. Mini tablets are more acceptable in children and elderly people as they are easy to swallow. Mini tablets can be used as a solution for the shortcomings of single unit dosage forms. Although manufacturing cost is more and problems like sticking, handling may arise during manufacturing of mini tablets, they are effective alternative solution for single unit dosage forms.

### Conflict of Interest

None.

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