# Formulation and Contemporary Approach to Mini Tablets: A Review

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**ABSTRACT**

As a new approach to solid dosage forms, mini-tablets (MTs) are designed to subjugate some kind of therapeutic disincentives, like poor swallowing properties and polypharmacy therapy, as well as to provide therapeutic advantages like dose flexibility and release patterns. These pills are a viable method of delivering medication to patients. It has smaller tablets than typical, with a diameter of between 2 and 3 mm, compared to conventional tablets. Other advantages of tiny tablets include their uniform shape and size, which reduces unit-to-unit fluctuation in the medicine and allows for precise weighing of the substance. Since they have a very smooth surface area, it is possible to cover them with a drug-delaying coating in order to prolong their shelf life. It can also be used in the same way as other multiple-dose forms, such as capsules. MTs are good substitute to pellets and granules. Lower potential drugs can be encapsulated as mini tablets in different sizes of gelatin capsule shells, if the qualities are adequately regulated. This review article depicts various aspects of mini-tablets, such as their marketed product, types, formulation prospects, current trends of manufacturing, novelties in research work, patent related works that will be beneficial for those who are conducting research on the formulation and development of this mini tablet dosage form.

**Keywords**: Encapsulation, gastro retentive, mini tablets, pulsatile, oral drug delivery, pediatrics

## Introduction

In terms of systemic effects, delivery of the medicament through oral route is the most appealing and preferred technique of giving therapeutic medicines.[1] Furthermore, oral medication is considered to be the first step in discovering and developing new pharmacological entities and pharmaceutical formulations.[2] Patient compliance, ease of administration, and low production costs are the key reasons. Patients can tolerate conventional immediate-release formulations of numerous medications while still achieving clinically effective treatment with balanced pharmacokinetic and therapeutic characteristics.[3]

In this context, mini-tablets brings a new trend in tablet manufacturing in order to overcome difficulties in swallowing and multiple-drug regimens.[4] One of the most promising drug delivery systems for improving patient compliance is the mini-tablet.[5] Mini-tablets(MTs), as the name implies, are much smaller tablets than standard tablets, ranging in diameter from 2 mm to 3 mm. As a further advantage, there is a very little unit-to-unit variance in the amount of medicine required and an exact amount can be placed into mini-tablets.[6] Manufacturing them is simple and they can even be coated to postpone the release of the medication due of their good smooth surface area.[7] Other multiple unit dose forms can also be encapsulated in hard gelatine capsule shells. So that it seems like a good substitute for pellets and granules.[8]

Oral route of medication is the most convenient for patients in which tablets are the popular solid oral dosage form.[9] MUDFs(Multiple unit dosage forms) divide a single dose into multiple smaller doses, each of which contains a different amount of medication.[10] Certain factors that influence the overall dosage of a medicine, comprising how well each of the subunits performs.[11] When the selected components demonstrate synergistic effects or the dosage can be adjusted; in that cases both SUDFs(Single unit dosage forms) and MUDFs are appropriate.[12] The dosage are dispersed throughout the areas of stomach and intestines, reducing the risk of local discomfort as a result of an equal distribution of medicine.[13] In terms of bioavailability and absorption, a MUDFs has a more dependable dissolving profile than a single unit.[14] Figure 1 showing a pictorial difference of mini tablets with conventional solid dosages forms.

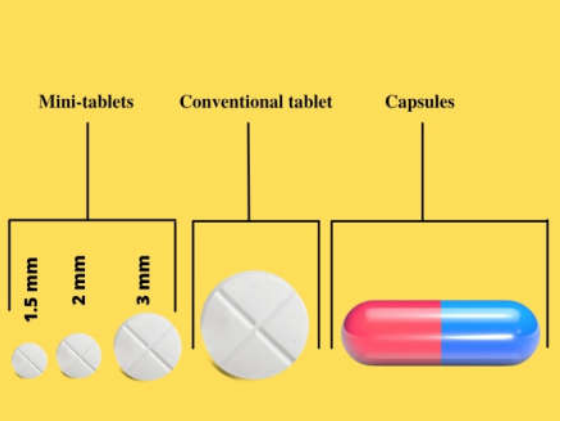


**Figure 1: Comparison of the MTs with conventional solid dosage form**

**Supremacy related to mini tablets**

- As a result, the creation of MTs is an excellent alternative to granules and pellets, which are difficult in its production consistently.[15]
- Delivers a more consistent release kinetics throughout the course of treatment. A abrupt rise in blood concentration so becomes less likely.
- Furthermore, it's easy to create new products.
- The homogeneity of its shape and size makes it easy to coat.[15-17]
- Because it can go through the digestive tract, there is less chance of local irritation.
- The amount of drugs that can be loaded into the body is relatively high.
- The process of creating a release profile is quite simple.
- Compared to pellets and granules, MTs have a flat surface, a steady surface area, and a high mechanical resistance.
- Sophisticated manufacturing techniques such as extrusion spheronization or fluid bed granulation or procedures are used for the preparation of pellets, whereas MTs are created using straightforward tablet production techniques. This is a time and money saver, as well.[18-19]

**Formulation approach to Mini Tablets**

- Compressed MTs
- Encapsulated MTs
- Biphasic drug delivery system prepared as MTs

***Compressed MTs***

The basic difference between creating regular-sized tablets and MTs is the type of tooling set required. Making MTs using rotary tablet press with multi-tip tooling, a tablet press is often needed.[20] It's possible, though, that the press and tooling will need to be modified. There may be a substantial difference in tablet density between deep concave-tooled mini-tablets and straight forward or shallow concave designs.[21] Tablet attrition can occur during packaging, coating, or other handling processes because of the wide range of gradients.[22] Reducing residual stresses through tapered die designs could result in more durable MTs. Punch tips can also be protected by concave dies.[23] Figure 2 showing the tooling sets for MTs manufacturing.

**Figure 2: MTs tooling set**

***Encapsulated MTs***

Granules, pellets, mini-tablets, and powder can all be filled using encapsulation machines, which use various types of direct and indirect filling systems.[24] MTs are used in the direct filling operation and are fed into the body until they compressed. The direct filling operating mechanism of the Qualifill TM encapsulator fills pellets.[25] A 40E Zanasi Encapsulator, for example, has a modified osator that may be used for either suction or pushing through the material bed, depending on the application. However, the Bosch GKF 2500 is the most current advancement in encapsulating technology. Capsules of MTs can be filled with a certain quantity of mini-tablets per capsule using these equipment.[26] Table 1 shows quantities of 1mm to 2 mm sized MTs can be packed into various sizes capsules. Table 2 presents common available encapsulated MTs available in market. Dosing discs having cavities that can be filled with mini-tablets are utilized in this process. Dosing discs have been designed to fit the correct size and number of mini-tablets and capsules. Only one mini-tablet per cavity can be held by an uneven

thickness of dosing disc that slides under the machine.[26] An electronic webcam sensor is used to monitor a vacuum unit that places the mini-tablets on the wheel and then examines the disc for mini-tablets. An automatic rejection system in the finished product discharge unit rejects any capsules that are not properly filled with the required dosage. Dosing discs are required to precisely fill MTs across a large varieties of target sizes for the purpose of counting.[27] Figure 3 shows encapsulated MTs in different size hard gelatin capsule shells.

**Figure 3: MTs encapsulated in hard gelatin capsule shell**

**Table 1: Approximate quantity of MTs to be filled in HGCs**

| Capsule Size | Number of Mini-tablets filled(approx.) |
|---|---|
| 000 | 106 |
| 00 | 74 |
| 0 | 52 |
| 1 | 34 |
| 2 | 22 |
| 3 | 18 |
| 4 | 12 |

**Table 2: Encapsulated MTs available in the market**

| Brand Name | Therapeutic Indications | API | Manufacturer's Name |
|---|---|---|---|
| Ultresa | Enzyme product | Pancrelipase | Aptalis Pharma |
| Razadyne ER | Alzheimer's disease | GalantamineHBr | Janssen |
| Trilipix | Lowering Cholesterol | Fenofibric Acid Capsules | Abbvie |

***Biphasic drug delivery system prepared as MTs***

If a formulator choose biphasic delivery method, the medicine will be released at either a rapid or a gradual rate, depending on its preference. Initially, drugs are released slowly over time. The reverse is true for slow release systems, that produce release which is followed by a steady rate of release over time.[28] Fast-acting therapeutic efficacy is achieved by using biphasic release systems, which are followed by sustained release phases to overcome this type of delivery. NSAIDs, antihistaminics, antiallergens, and antihypertensive, antihistaminic medicines are good medication candidates for this sort of delivery.[29] Traditional controlled dose forms typically decreases the unleash of therapeutic systemic levels and usually do not provide an immediate start of action. Fast-acting instant granules, on the other hand, are unable to maintain their effect over a longer period of time.[29] For the maintenance of the drug concentration within the therapeutic window, a steady level of plasma concentration of the drug is desirable. When taking a once-daily dosage form, it's especially important to keep this in mind because the gastrointestinal (GI) tract's environment affects medication diffusion and absorption differently depending on where you are.[30]

**Categorization of MTs**

Classification of MTs is possible based on the criteria's like place of application, patient requirements, and manufacturing method

- Paediatric MTs
- pH Responsive MTs
- Oral disintegrating MTs
- Gastro retentive MTs
- Bio-adhesive MTs

***Pediatric MTs***

MTs are convenient & safe alternative to liquid medications for children of all ages and stages of development. Combination therapy, which is quiet difficult to achieve with capsules or ordinary pills, is another advantage. It may be more difficult to create a dosage form based on mini-tablets because they are more likely than bigger tablets to be dropped or lost, however these risks can be overcome by the proper selection of package configurations. Unit activities such as wet or dry

granulation, compression utilizing multi-tip tooling, Würster coating, pan coating, encapsulation are all part of the manufacturing process. To make mini-tablets, these production methods face a variety of problems, but a careful review of each single unit operations can result in a more robust MT dosage form. In this regard, mini-tablets appear to be best suited to high-value products with a low volume and a high price point, particularly for pediatric populations.[31]

Some Marketed Paediatrics MTs are given in the Table 3.

**Table 3: Pediatric MTs available in market.**

| Brand Name | Therapeutic Indications | API | Manufacturer's Name |
|---|---|---|---|
| Elepsia | Epilepsy | Levetiracetam | Mayo Pharmaceuticals |
| Kalideco | Cystic fibrosis | Ivacaftor | PCD Pharma |
| Lamisil® | Antifungal treatment | Terbinafine HCl | Novartis |

***pH responsive MTs***

Polymers like Eudragits, which are pH responsive release polymers, may can be used to enhance the absorption of a medicine at a specific spot. As an alternative to pellets, coating can be applied on granules and then put inside capsule shells to achieve the desired release timing. Eudragit S100 and Eudragit L100, pH-responsive polymers were employed to achieve the desired release pattern.[32]

Hadi MA[33] formulated and evaluated a novel pH-responsive MTs for with target towards ileo-colonic delivery of naproxen in chronotherapeutic for the treatment of rheumatoid arthritis.

Kishore M[34] studied colon targeted drug delivery system for Atenolol which is a Anti-Hypertensive drug and also used for treatment of chronic cardiac diseases like increase in blood pressure and Heart failure. MTs of Atenolol which are prepared by wet granulation method taking matrix making natural polymers like Guar gum, pectin and Xanthum gum in combination and also with different percentage.

***Oral disintegrating MT***

Because to their mini size, good mouth feel, and rapid breakdown, oral dispersible mini tablets (ODMTs) are preferred by pediatric patients.[35] The ODT should also have some notable

characteristics, such as the ability to dissolve completely in the mouth without the use of extra water. There should be a liquid suspension or soft paste, which may generate pleasant tongue sensations and easy swallowing with oral disintegrating tablet products.[36] Patients' taste buds will be in close contact to dissolved drugs since ODTs dissolve or disintegrate in their mouths. For patients, a pleasant taste in the mouth becomes increasingly important. The employment of taste-masking procedures is common unless the medicine is flavourless or does not have an unpleasant flavour.[37] K. M. El-Say et al[38] study was aimed formulation and development of risperidone ODMTs as age-appropriate formulations and accessed their suitability for pediatric use.

Some Marketed Oral disintegrating MTs are given in the Table 4.

**Table 4: Oral disintegrating MTs available in market**

| Brand Name | Therapeutic Indications | API | Manufacturer's Name |
|---|---|---|---|
| Olanex | Nausea & Vomiting | Ondansetron | Eris Life Science |
| Maxalt | Acute Migrane | Rizatriptan | Merck Labs |
| Torrox MT | Osteoarthritis | Rofecoxib | Torrent |
| Imodium (Encapsulated Mini Tablets) | Diarrhoea | Lopermaide HCl | Janssen Pharmaceuticals |

***Gastro retentive MTs***

To stay the drug in the region stomach for a specific period of time, gastro retentive micro pills are employed. Gas producing agents are commonly used in formulas to make tablets float in GI fluids.[39] When these tablets come into contact with food, they release $CO_2$ and the resulting gas is embedded in a swellable hydrocolloid, causing the tablet to float and retain in the stomach for the intended duration of time. Since the polymer utilised for floating is so high in conventional single-unit tablets, the medication loading is modest.[40] A film coating of sodium bicarbonate or calcium carbonate might be used in the formulation of MTs, but eudragits coating in situ of swellable polymers is also an option.[41] Fluid bed processors might be helpful for coating purposes. Mina M[42] research findings aimed towards antispasmodic drug i.e Drotaverine hydrochloride(DRH) having a short time in the intestine during diarrhea that promotes poor

bioavailability and frequent dosing. Their research study was aimed to enhance the gastric residence time and controlling the release of DRH so that increasing patient compliance using gastro retentive MTs. Their preparations are made by taking specified amounts of sodium bicarbonate and sodium alginate using wet granulation technique.

***Bio-adhesive MTs***

Use of bio-adhesive MTs in vaginal drug delivery ensures that the drug is delivered precisely and for a long retention of time. There are numerous dose units in each tiny tablet, allowing it to be dispersed more evenly in the cavities of vagina and can reach a greater area of the vaginal epithelium.[43] By creating and expanding micro gels and releasing the medicine in a regulated manner, bio-adhesive mini tablets may achieve the highest bioavailability.[44]

Similarly biosdhesive MTs for ocular drug delivery also having significant role in the current research trends. Ahmed B[45] study aimed towards the enhancement of levofloxacin's ocular residence time and formulated into sustained release mucoadhesive MTs for once daily administration using a hydrophilic-hydrophobic matrices of polymer. Table 5 represents popular brands of MTs available in the market.

**Table 5 : MT brands available in Market**

| Brand Name | Indication | API | Manufacturer's Name |
|---|---|---|---|
| Orfiril | Epilepsy | Sodium Valproate | Desitin |
| Enzym Lefax | Indigestion | Pancreatin | Bayer |
| Rythmol SR | Antiarrhythmic | Propafenac HCl | GlaxoSmithKline |
| Trilipix | Cholesterol | Fenofibric Acid | Abott |
| Kalydeco | Cystic Fibrosis | Ivacafter | Vertex |
| Pankreatan | Pancreatic Insuffciency | Pancreatin | Novartis |

**Methods of manufacturing of mini tablets**

Manufacturing of MTs can be done by some conventional methods which includes;

Direct compression

Wet granulation

Dry granulation

Extrusion by means of melting

***Direct compression technique***

Powder mixes including API and excipients are crushed directly into tablets using this approach. Direct compression into a biconvex or flat small tablet shape is possible. Direct compression grade excipients are employed to achieve the desired hardness and friability. Tablets made by dry granulation have more stability issues.[46]

***Wet granulation***

Granules are formed using binder solution and squeezed in tablet press to produce micro tablets in the wet process. Polyvinyl pyrrolidone (PVP) is commonly employed as a binding agent.[47]

***Dry granulation***

Tablets containing heat and moisture-sensitive medications can benefit from dry granulation because it is a well-balanced method. The roller compactor is a piece of processing equipment used in this system.[48] Under intense pressure, two counter-rotating rollers in this machine compress pre-mixed powders. It can produce a sheet or brittle ribbon or a fragment depending on the roller setup. The granules formed from the compressed substance are then combined with additional inactive excipients and further compressed using a rotary compression machine to achieve the desired final compression ratio.[49]

***Extrusion by means of melting***

As a part of the melt-extrusion process, the powders are mixed together and then fed into the melt-extruder.[50] Speed, feed rate, and temperature can all be adjusted to match the melting point of the material being processed in a melt-extruder.[51] A milling and sieving process follows the extrusion step. The resulting granules are compressed using a compression machine to create small tablets.[52]Coating of MTs can be done using various polymers which are depicted in Figure 4

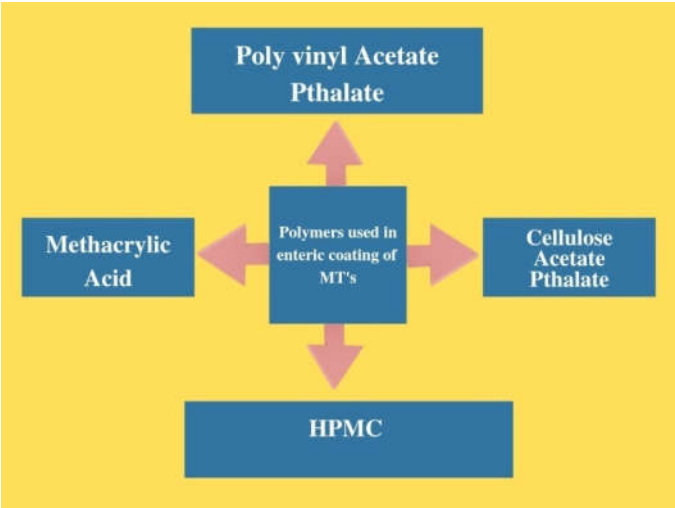


**Figure 4: Various Polymers used to prepare MTs**

**Patents**

Although MTs having a history of nearly one decades, the number of papers and patents is increasing every year, which is a good indicative of the continuous progress of their applications in academic research, formulation and industrial processes . In Table 6, some recent examples of patents for MTs as drug-delivery systems are mentioned below.

**Table 6 : Patents related to MTs**

| Pharmaceutical Applications | Drug Used | Summary | Reference No. |
|---|---|---|---|
| To prevent and treat abnormally fast heart rates. | Flecainide | Flecainide minitablets are prepared with different sustained profile using pH dependent release polymers and excipients. | 53 |
| To regulates night and day cycles or sleep-wake cycles. | Melatonin | Minitablets of Melatonin prepared with acceptable polymers and compressed into controlled release profile tablets. | 54 |
| Antibiotic | Amoxicillin | The present invention relates to a composition comprising a first | 55 |

| | | | |
|---|---|---|---|
| | | granule with an antibiotic and a second granule with a β-lactamase inhibitor wherein at least one of the granules is a mini-tablet. | |
| To treat Obesity | Phentermine HCl with Topiramate | Multilayer minitablets for oral administration of a combination of active pharmaceutical ingredients which release the active pharmaceutical ingredient at different release rates are described | 56 |
| To treat heartburn in patients with gastroesophageal reflux disease | Cisapride | Prepared sustained release cisapride oral dosage formulation which is effective for once-daily administration and comprises a plurality of MTs containing cisapride or a salt thereof with an organic acid and capable of releasing cisapride at various sites of GIT. | 57 |
| To reduce pain, swelling, and joint stiffness from arthritis | Piroxicam | The invention aimed towards bioadhesive compounds of multilayers MTs where the bioadhesive layer is directly compressible into MTs | 58 |
| To treat the symptoms of schizophrenia | Paliperidone | The present invention is related to an extended release pharmaceutical composition for oral administration of a MT core comprising one or more water-soluble polymers, an inner layer | 59 |

| | | | |
|---|---|---|---|
| | | comprising paliperidone. | |

**Novelties of Mini tablet formulation and research**

Planning formulation and research on MTs having many promising opportunities for the researchers and formulation scientists. Some of the important aspects of research area are given in the Figure 5.

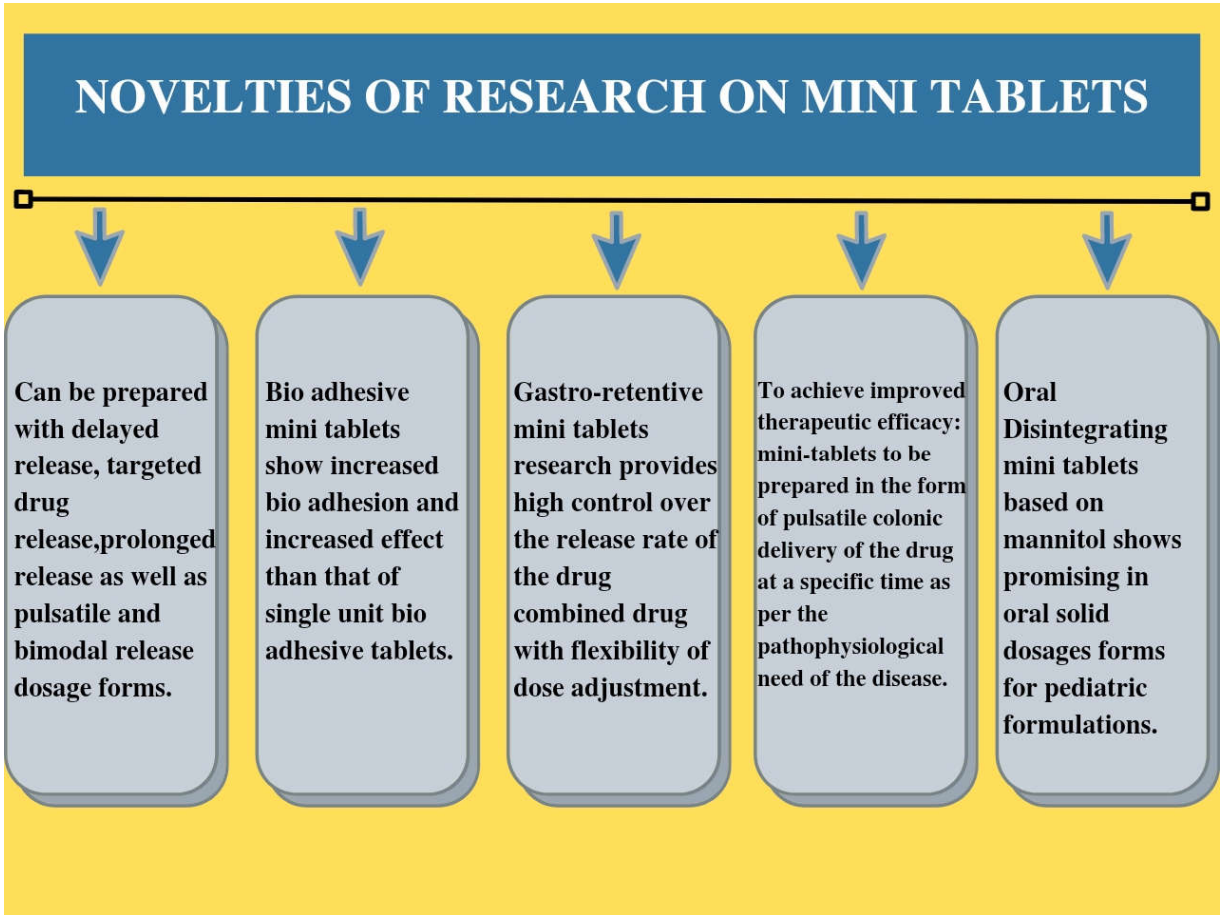


**Figure 5: Novelties of research on MTs**

**Current Trends in manufacturing of Mini Tablets**

MTs which are manufactured by recent techniques such as embedded 3D, fused deposition, hot melt extrusion etc., and their specific features are depicted in the Table 7**.**

**Table 7: Advanced techniques used for manufacturing of MTs**

| Method Manufacturing used | Key Features | Formulation | References |
|---|---|---|---|
| Hot melt extrusion | Coated Tablet Diameter 5 mm, Friability less than 1%, Mean Drug content 94–110% Dissolution completed within 20 minutes | Ketoprofen 40% & Eudragit | 60 |
| Compression using electrospun nanofibers | Uncoated MTs Diameter 2 mm, Friability is less than1%, Mean Drug Content 96% Dissolution completed within 20 min | Prednisolone 10%, Poly Vinyl Pyrrolidone 90% | 61 |
| Embedded 3D printing | Chewable mini tablets , 99% drug released in 2 hours (pH 7.2) | Paracetamol/Ibuprofen glycerol, gelatin Locust bean gum | 62 |
| Fused Deposition Modelling printing via passive diffusion drug loading | Uncoated Tablet diameter 6 mm, Friability is less than 1% Mean Drug Content 4% Sustained drug release upto 6 hours | Nifedipine 4%, Poly Vinyal Acrylate –Poly Ethylene Glycol 96% | 63 |
| Granulation using High shear + Dry API added to the powder blend | Mean diameter 1.2–1.5 mm, 0.66% w/w Active ingredient loading and & 75% drug released in 20 min | Ibuprofen 0.67%, MCC 10% Mannitol 81.3% Croscarmellose Sodium 2%, HPMC 2% Croscarmellose Sodium 2% Sodium stearyl fumarate 2% | 64 |
| Cocrystallization of the active ingredients plus direct compression | Uncoated Oro-dispersible tablet having Mean diameter 4 mm, Friability less than1% Disintegration time within 1 min, 80% drug released in 6 minutes | Piroxicam 41%, Mannitol 19.5%, CMC 10% Croscarmellose Na 5%, Mg stearate 0.5% | 65 |

| | | | |
|---|---|---|---|
| Nano Suspension of active ingredient added in the granulation fluid leads to High shear wet Granulation using Ultra RMG | Ibersartam Uncoated Tablet Mean diameter 2 mm, Friability less than1% Disintegration time within 1 min, 90% drug released in 6 minutes | 0.1% to 0.5% Ibersartam MCC 9.5%, Crospovidone 4%, HPMC 2% Extragranular: Silicone Dioxide 0.5%, Sodium stearyl fumarate 3% | 66 |
| Direct compression with an interactive mixture | Oro-dispersible tablet Mean diameter 1mm to 2 mm, Disintegration time within 1 min, 85% drug released in 6 minutes | Sodium salicylate 1%, Mannitol , Magnesium stearate | 67 |

**Conclusion & future approach**

From this review article, it has been inferred that pharmaceutical MTs have a number of advantages. Patients are frequently given a predetermined dosage of medication in an effort to increase efficacy. MTs are a better choice than granules and pellets when it comes to dosage forms. However, in order to ensure a proper flow, correct and complete filling of the die, and damage to the tooling equipment, production parameters must be rigorously evaluated. Recent manufacturing of MTs using current techniques like cocrystallization, granulation with high shear, fused deposition modeling are some promising techniquies which results better than the conventional methods. For the researchers and formulators this dosages form offers one excellent area for the continuous development and patents filing. This review article provides a clear and verified datas regarding the manufacturing, novelties, and current trends in the formulation and development of MTs for its advanced study. Attentive evaluation of every single unit operation can yield a more suitable and sturdy MTs formulation which will ultimately help pharmaceutical industries as well as researchers for their growth and blooming.

**Ethical Issues**

Not Applicable

**Conflict of Interest**

Authors have no conflict of interest.

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