INTRODUCTION

Conventional solid oral dosage forms like tablets, capsules, powder, lozenges are generally administered to the patients through oral route and are expected to deliver the drug at the target site in a shortest possible time. The onset and duration of any drugs administered depends on its route of administration, site of action, therapeutic index and half-life. Among several problems involved with the formulation and use of conventional solid dosage forms, interval for dosing was found far shorter than the drugs half-life, resulting in numeral limitations. Some of other issues related to a conventional dosage form are like this kind of dosage form leads to poor medical adherence of patient which leads to increase the risk of losing a dosage of short-lived medication that requires frequent administration. Such dosage forms were found tough to achieve a stable state from the previously obtained plasma concentration time profile. Sometime fluctuation in the drug level will result improper medication which may lead to adverse effects [1]. Though conventional unit dosage forms were being used effectively since decades, its wide range of variations in blood stream concentration and its consequences signposted the need for improvement and innovation in solid unit dosage form [2].

Solid dosage forms used for controlled release can be considered as, Forms of single unit dosages (SUDFs) like capsules, coated or uncoated tablets and other forms are Mini tablets, pellets, granules are the (MUDFs) multiple forms of unit dosage [3, 4]. Since last decade, mini tablets which are one of multiple unit dosage forms considered as more convenient because they aided the ease of administration. Mini tablets found commonly encapsulated in capsules, sometimes in sachets. They can also be compressed into bigger tablets. These tablets were found ranging from 1.0 to 3.0 mm in diameter. They are intended to deliver and maintain desired concentration of medicament at particular site [4].

Mini tablets have various applications based on target sites and patient requirements [5]. They are used for/as pediatrics, gastro retentive, bio adhesive, pH responsive, orally disintegrating and biphasic mini tablets.

Pediatric mini tablets

Since syrups and tablets can be easily administered, they are the widely used for children. These kind of dosage forms exhibit various issues related to organoleptic characters, physicochemical properties, drug release pattern during formulation. Also it was found that it is difficult to adjust the dose since many parents are practiced to break tablet half and use for their children. This practice sometimes may lead to improper dosage and function of respective drug. Patient compliance is also one of the issues with conventional dosage form [6]. Viviane klinmann along with coworkers conducted clinical trials on newborns and preschoolers to assess mini tablets’ acceptance in comparison with syrup. Results indicated the superior acceptance of uncoated mini tablets in comparison to syrup in total patient population of 306 children (with different proportions 14.8%, 95%, CI 10.2-19.4; P<0.0001). The level of swallowing capability for uncoated mini tablets was also found higher among children of 6 mo to 6 y of age and found more suitable than liquid formulations [7]. Natalie spomer and team conducted clinical trials in young children to check that uncoated mini tablets are accepted in very young age group. The finding of a prospective cross-over study concluded that uncoated mini tablets are very promising substitute to fluid formulation and can be used in pediatrics drug therapy. Mini tablets were absolutely swallowed by specimens (6-12 mo of age) and they were able to handle them much better than the fluid formulation. Tablets were chewed by children between 2 and 4 y of age, but still handled quite well. Overall, acceptance rate of mini tablets was found superior than expected [8]. Therefore usage of mini tablets for pediatrics was found more useful.

Gastro retentive/ floating mini tablets

These kind of dosage forms are designed for extended release of the medication in the stomach and formulated by using agents which produce gas in the tablets so that they float on gastro intestine fluid. Sodium bicarbonate (NaHCO₃) or calcium carbonate (CaCO₃) (gas generating agents) coating, eudragits coating instead of swelling polymers were used in mini tablets to improve drug loading in the formulation. Mini tablets coating was done by using Fluid bed processor [9]. Sally A. El-Zahhaad others designed gastro retentive levofloxacin as tablet-in-capsule in floating form and evaluated conducted method for the development and evaluation of the mini tablets in capsule floating and evaluated antibacterial action against Helicobacter pylori. Study results have shown better physicochemical properties and floating parameters. Optimized formulation exhibited floating time lag less than 1s and maximum floating time was more than 24 h. Volunteers held floating mini tablets of levofloxacin having polymer HPMC KL04 M in the stomach for over 4 h was proved as better alternate for the eradication of H pylori[10].

Bio adhesive mini tablets

These mini tablets are used to administer medication through vaginal route reliably for longer duration. Division of mini tablets
were done into several units so that they get spread uniformly in vaginal cavity covering maximum vaginal epithelium. These tablets released the drug by swelling and forming micro-gels in a steady manner with optimal bioavailability. This type of mini tablets have been developed by Hiorth M and colleagues and found that mini tablets with either HPMC or HPC matrix possessed adequate mechanical strength, greater bio adhesive actions along with pH independent release of prototype drug. Results indicated that both formulations can be considered for women’s treatment. Therefore these mini tablets can be used to have better interaction with mucosal tissue and sustained drug release [11].

pH responsive mini tablets

Human GIT pH differs considerably. If drug absorption is more at any one site, selected drug dissolution can be easily accomplished by coating with polymer like Euadningits which is a form of pH responsive release [12]. H. N. Shuvakumar and coworkers designed and developed a pH sensitive mini tablet formulation and carried out estimation of chronotherapeutic theophylline delivery and concluded that the 10% of coating weight gain was found enough to convey gastro-resistant property to release drug at higher pH value. pH sensitive polymer can be used to establish a colon-specific drug delivery system successfully. Pulsed release observation in most of the cases was found highly desirable for targeting a multi-unit systems nocturnal peak symptoms of asthma at night [13].

Biphasic mini tablets

These kind of tablets includes a quick release component and a slow release portion for two parts. First part of the drug releases immediately with the administration of the drug and other part of the drug gets released slowly in a controlled mode. This form was found useful in anti-hypertensive drugs where repeated dosing could be avoided. Specific medications can be packed into mini tablets to treat various diseases in the same capsules. Carla M. Lopes et al., conducted an experiment where mini tablets were compressed into biphasic drug delivery system using different composition of (HPMC or EC) at in order to achieve different drug release. 10 or 21 mini tablets were used to study release profile of drug and to analyze whether it depends on the number and composition of the subunits. Hydroxypropyl methyl cellulose mini-tablets disintegrated at a constant rate within a fraction of a second showing dissolution profile for a continuous time of eight hours. Mini-tablets powder release biphasic formulation causes some improvements in the process such as separation of the powder, Hydroxypropyl methyl cellulose mini-tablets disintegrated at a constant rate within a fraction of a second showing dissolution profile for a continuous time of eight hours. Mini-tablets powder release biphasic formulation causes some improvements in the process such as separation of the powder. Secondly, by increasing the number of tips, the force applied to a pair of opposing punch tips is multiplied by the number of tips, resulting in a greater overall compression force that can be controlled more accurately. Multiple-tip punches tools offers multi-part assemblies and monoblock from tablet devices sellers. Monoblock punches provide quicker tool installation and easier cleaning, can be made with tighter tolerances and are more resistant to tip breakage than multi part tooling installed. Multi-tip tool must meet more stringent requirements for machining and mechanical stability compared to larger tablet tools and are more labor-intensive to manufacture, resulting in higher production costs [19]. Showing various multi tip punches used for compression in fig. 1, 2, 3 and mini tablets in fig. 4 below:

Processing of pellets involves technically challenging process such as fluid bed granulation, extrusion or spheronization, on the other hand simple tableting procedure can be employed for the development of mini tablets [14]. With low porosity and high strength these tablets were found to retain more reproducible structure and shape than other multi particulate dosage forms [17]. Thus multi particulates, mini tablets showing potential applications as a flexible drug delivery system for various particulates.

Pre formulation studies for mini tablets

These studies deals with physicochemical and various pharmaceutical properties related to drugs and excipients and will provide an idea of any modification in the properties affecting the nature of drug product to get better results.

Drug polymers compatibility studies [3]

Studies of compatibility with drug polymers were conducted using FTIR. Drug compatibility with the excipients can be tested by using spectral analysis. Also this study help to carry out drug polymers study on individual pure drugs and physical mixture of the drug and additive.

Precompression parameters like, Angle of repose, Bulk density and tapped density, Compressibility index and Hausner's ratio were performed for the powder blend to ensure the best powder flow property and achieve good end product.

Tooling used in compression of mini tablets

Normal tablet compression is performed using single tip tools that can be interchanged as needed. Mini tablets can be generally manufactured by compression using a rotary tablet press [18]. A special tools can be used for the mini tablets called multi-tip tooling. This can be mostly used for two reasons. First, this increases the output efficiency and reduces the powder dwelling time in the feed frame, which contributes to over-lubrication or separation of the powder. Secondly, by increasing the number of tips, the force applied to a pair of opposing punch tips is multiplied by the number of tips, resulting in a greater overall compression force that can be controlled more accurately. Multiple-tip punches tools offers multi-part assemblies and monoblock from tablet devices sellers. Monoblock punches provide quicker tool installation and easier cleaning, can be made with tighter tolerances and are more resistant to tip breakage than multi part tooling installed. Multi-tip tool must meet more stringent requirements for machining and mechanical stability compared to larger tablet tools and are more labor-intensive to manufacture, resulting in higher production costs [19]. Showing various multi tip punches used for compression in fig. 1, 2, 3 and mini tablets in fig. 4 below:

**Fig. 1:** It shows upper and lower multi-tip punches and die (with 3 and 5) tooling.
Fig. 2: It shows tip sizes of the multi tip punches/compression

Fig. 3: It shows multi tip tablet punches

Fig. 4: It shows mini tablets

Fig. 5: It shows mini tablets in capsule
Methods of manufacturing mini tablets [20]
Different methods will be employed for the manufacturing of mini tablets given below:

Direct compression technique
This is a process where the powder mixture holding API and excipients which can be compressed directly into biconvex mini tablets. Direct compression grades have been used to achieve the required hardness. Problems of stability were found lower than those of tablets with wet granulation.

Dry granulation technique
This technique is used to develop thermo-labile, moisture-sensitive tablets. A roller compactor or chilsonar processing equipment can be used for this technique. This machine compresses under extreme pressure as premixed powders have been found in the shape of a brittle ribbon, board, or fragment between two counter spinning rollers. By employing ‘slugging’ techniques granules can be produced, where slug are screened or milled and granules are mixed and finally compressed with other excipients.

Wet granulation
This technique involves using binder solution to form granules which are further compressed into mini tablets.

Melt-extrusion technique
The premixed powder API and excipients is allowed to move towards melt-extruder. In the melt extruder material range, a speed of the screw, feed rate and temperature parameters can be set. Then the extrudates are milled and sieved. Using a compression tool, the granules collected are then compressed into mini tablets.

Coating of compressed mini tablets
Principles involved in coating for mini tablets are based on some objectives like: such tablets help to mask the drugs taste and odor also monitor the release of the drug form the tablet. To protect the drug product with an acid resistant enteric coating from the stomach environment. Providing concurrent release of medication. Use different color and contrasting printing to enhance medicinal appearance of the drug.

Coating procedures for mini tablets
Mini tablets are coated by using different techniques as sugar, film compression and enteric coating processes.
Several polymers will be used for enteric coating of mini tablets such as Methacrylic acid or ethyl acrylate, Sodium alginate and stearic acid, Cellulose acetate succinate, Cellulose acetate trimellitate, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose phthalate, Hydroxy propyl methyl cellulose acetate succinate [21].
Polymers used for the film coating of mini tablets like Polyox WSR 1105, microcrystalline cellulose 200, Cellidial silicon dioxide, Magnesium stearate [22]. Polymers used for the compression coating mini tablets such as Eudragits RS/RL 30D, Trietilcitrate, Talc, Titanium dioxide, Yellow quinoline, Pigment dispersion WAS, Water [23].

With different coating procedures suitable polymers can be used for the mini tablets coating.

Mini tablets are usually coated by using fluidized bed coaters or using modified coating pans with enteric coating polymers. Enteric coating is a polymer membrane that protect it against the acidic pH of the stomach when added to a drug and releases the medication in the small intestines alkaline environment. They cannot dissolved in the stomach acidic juices, but they break down in the small intestines alkaline setting. Drug which leads to mucosa inflammation or are inactivated in stomach can be covered with material that dissolves in the small intestine alone [24, 25]. Film coating is considered to produce an elegant product appearance. High stability against heat, light, moisture, air. High compatibility with other coating solution additives. Resistance to non-toxic pharmacological activity. Compatible to printing procedure [26, 27].

Different formulations of mini tablets
The three steps in the formulation process (mini-tablet-in-capsule systems) where first step is the Mini tablet formulation/manufacture, second step is coating of mini-tablets by using sufficient polymer coating, encapsulation of mini tablets were filled with hard gelatin or Hydroxypropymethyl cellulose capsules of coated mini tablets. Third step is the preparation of mini tablets or granules into capsules systems; by using formula to calculate the immediate-release dose, DL = Cmax/Vd
Cmax = the maximum plasma concentration, and Vd is the distribution volume.

Preparation of immediate release component (Granules) or immediate release coated mini tablets IRCTM
Due to its strong compaction and disintegration properties, the measured amount of medication and other appropriate excipients released immediately like (Microcrystalline cellulose [avikel PH 102]). Appropriate super disintegrants were used to get the medication release immediately. Wet granulation method will be used to prepare the granules. Also wet granulation techniques will be employed for the preparation of IRCTM.

Preparation of sustained-release coated mini-tablet (SRCM1T)
These tablets were developed by using same process which was employed for the immediate release coated mini tablets. Hydroxypropyl methyl cellulose 5cps/15cps. dieethyl cellulose, magnesium stearate, ethyl alcohol, and water have been used to prepare coating suspension. In the coating preparation, magnesium stearate were used to reduce the friction between the mini tablet surfaces, the filling device and the capsules of HPMC.

Preparation of coated mini-tablet-in-capsule system
Two IRCTM and three Sustained release mini tablets were placed in each HPMC capsule of size 1 in order to prepare the IRCTMs. A similar or different SRCMT ratio is put in each HPMC capsule in order to obtain different sustained release profile of the CMTEs [28, 29].

Evaluation of mini tablets [30, 31]
Mini tablet evaluation is like regular tablet evaluation, general tests are evaluated given below:
Weight variation test
Randomly 20 tablets were selected and weight of the individual tablets is noted. It calculates the average weight. Note: individual tablet weight should not be less than 90% and more than 110 percent of the average weight, as per USP.

Hardness
It is calculated and expressed in kg/cm² using Pfizer hardness tester. Six tablets were picked randomly for hardness testing. From the each formulation mean and the standard deviation values will be determined.

Thickness
A digital caliper and screw gauge (Mitutoyodigmatic caliper) can be used for measuring mini tablets. This is expressed in the terms of mm.

Percentage friability
Mini tablets are performed with the aid of Roche friabilator or veego friabilator. Normally twenty mini tablets of each lot are selected at random and the initial weight (W₀) is noted and transferred to friabilator. Allow the drum to rotate for 4 min at 25 rpm. With aid of a soft brush, any loose dust was collected and mini tablets were weighed again (W₁).

Drug content uniformity
Using UV visible spectrophotometer, 5 mini tablets were weighed and they are grounded into a mortar and then accurately weighed
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All authors have contributed equally

AUTHORS CONTRIBUTION
supporting us in the literature review and drafting of manuscripts.

Stability studies [32]
It is an essential part of the process of drug development and plays vital role in pharmaceutical product registering. This study were conducted in compliance with ICH guidelines and also it will help to track changes in product material consistency over time by taking into account temperature, humidity and light effects. Implementing storage conditions: 40 °C±2 °C/75% RH±5%RH, 25 °C±2 °C/60% RH±5% RH for the period: 1, 2, 3 mo.

CONCLUSION
The review focused on few applications of mini tablets along with various aspects of mini tablets manufacturing. Production of these tablets was found to be identical to standard normal tablets, but due to small dose it requires good powder flow property and precise control of process parameters and special care. Mini tablets were found to be more advantageous over single unit dosage forms and attained alternative when compared to granules and pellets. They are patient friendly drug delivery system and hence evolved into a transformed release system (extended-release, delayed release of color, pulsatile and bi-modal release and gastro-retaining systems) which shows better bioavailability compared to unit single dosage form.

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