INTRODUCTION

Solid medicinal preparations have been used since antiquity. The earliest reference to a dosage form resembling a tablet can be found in Arabic medical literature, in which drug particles were compressed between ebony rods, the force applied by a hammer. Details of the tabletting process were first published in 1843 when Thomas Brockendon was granted a patent for "manufacturing pills and medicinal lozenges by causing materials when in a state of granulation, dust or powder, to be made into form and solidified by pressure in dies."

In 1895, an editorial in the Pharmaceutical Journal predicted, "tablets have had their day and will pass away to make room for something else." After a century, tablets are still the most popular dosage form because they have significant advantages.

The tablet is the most widely used dosage form existing today because of its convenience in terms of self administration, compactness and ease in manufacturing. To make more effective dosage forms of tablets with addition of removing the basic drawback such as gastric irritation, taste problem etc which leads to poor patient compliance, scientists have developed innovative drug delivery system know as mouth dissolving tablets (MDTs), Oral dispersible tablets. These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem. The benefits of MDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular.1,2,3

Advantages of the tablet as a dosage form.4,5

- Simple administration
- Rapid drug therapy intervention
- Taste Masking, Improved Taste
- Accurate dosage
- Easy to transport in bulk
- Easy for the patient to carry
- Inexpensive to manufacture
Uniform product

More stable than liquid preparations.

Improved Patient compliance

An alternative to the traditional swallow tablet is a special formulation, which will quickly disintegrate in water to form a suspension that can be drunk. It combines the Ease of swallowing and the potentially improved bioavailability of a liquid formulation, with the accurate dosing. Stability and ease of transportation of a tablet. Active ingredients unstable in aqueous Solution may be stable as a dispersible tablet. ⁶

The dispersible tablet provides a utility dosage form, reducing the need for multiple Formulations of the same drug. In the current world health economy, this reduces Development costs significantly. Today the pharmaceutical industry operates in an Environment where containment cost and optimization of drug delivery must be considered along with efficacy and safety before a new drug product will be licensed. It is for this reason that the German Registration Authorities (BGA) has advocated the formulation of dispersible tablets. Germany is not alone, however. The trend towards the formulation of dispersible tablets is evident across Europe. For example, all tablets marketed in the Netherlands must form an adequate dispersion when placed in water.⁷

**Problems Associated with Conventional Oral Dosage Forms**

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients.

The advantages offered by solid dosage forms mean that most drugs are initially marketed as a tablet or capsule. Furthermore, there are certain drugs where different dosage forms are used to overcome local irritation of the gastro-intestinal tract after solid oral administration.
The absence of a liquid formulation is a particular problem when large doses must be administered orally, resulting in a very large tablet or capsule, especially when doses are taken frequently and chronically. This may result in considerable physical and psychological discomfort for the patient.

Problems in swallowing may only be detected in the oropharyngeal phase; the distal esophagus has no somatic sensation. Consequently, patients are not aware of tablets or capsules lodged within the esophagus and below the pharynx. Hard gelatins, when moistened, becomes sticky and firmly adheres to the esophageal mucosa. It has been suggested that capsule formulations are thus more prone to delayed esophageal transit. Lodged solid dosage forms can cause obstruction, esophageal ulceration, stricture, hematoma, and in some cases hemorrhage. The incidence of lodged tablets is a particular problem in the elderly, where esophageal lesions are common and peristaltic activity may be impaired, delaying esophageal transit. Dry mouth is also prevalent among older people and this may cause tablets to adhere to the esophageal mucosa.

Solid dosage forms also pose problems for children. In addition to swallowing difficulties, clinical studies and case reports suggest highly variable absorption patterns in neonates and infants and there have been reports of incomplete absorption. Therefore it is desirable to select a more readily bioavailable dosage form, such as a chewable tablet or liquid. It is standard practice in British hospitals for pediatric formulations, when not available commercially, to be extemporaneously prepared in the pharmacy. In addition to the extra work this creates, the lack of data available regarding the stability of products in suspension or solution may mean that storage conditions or shelf life may not provide optimal activity at the time of administration. Adult patients may receive treatment with an extemporaneously prepared liquid formulation or by nurses crushing tablets. The medication and persons carrying out the procedure may be contaminated, and loss of medication will result in under dosing. When a controlled release preparation is crushed, the rate at which the drug is released and absorbed into the bloodstream may be too high and cause overdosing.
Approaches to formulating a solid dosage form which rapidly disintegrates

**Effervescent tablets**
Effervescent tablets depend on the reaction of bicarbonate or carbonate with an acid or other excipients with the capacity to evolve a gas after contact with water. The tablet rapidly disintegrates to produce a solution or suspension. However, production is expensive and demanding and requires manufacturing at low relative humidity. Many drugs are incompatible with bicarbonate and acids, which render them unsuitable.

**Lyophilization**
Lyophilization (freeze drying) has been used to produce tablets with an open matrix which rapidly disintegrate in water or saliva. This type of dosage form is a matrix of water soluble / dispersible material impregnated with a unit dose of drug. A suspension of drug and excipients is dosed by weight into pre-formed blisters before freeze-drying. Although this type of product has good stability and can be easily dispersed in aqueous solution, the porous "open matrix network" produced by the sublimation process renders the tablet very fragile and handling is severely compromised. Peel able blister packaging has been developed to allow removal of dosage units from the pack without damage, as it is not possible to push them through aluminum sealing foil typically used in blister packs without rupturing the product.

**Vacuum drying**
Vacuum drying has been used as an alternative method of removing liquid to produce a rapidly dispersing tablet. It is claimed to have a lower porosity, Greater density and greater mechanical strength, while still disintegrating in normal amounts of saliva / aqueous solution. However, there is a possible explosive release of liquid from the material being dried, which may disrupt the structure of the material. For this reason, the process has previously been considered unsuitable for commercial production of well-formed shapes such as dispersible tablets. However, in the process described by Pebley, it is claimed that maintaining the temperature of the matrix during primary drying between the collapse temperature and the equilibrium freezing point, gave a satisfactory product.
Wet compression
Rapidly disintegrating tablets have been developed using wet powders containing drugs. Drug and excipients are blended and the powder mixture is moistened with a solvent containing a binding agent. The wet mass is either molded or compressed under low force and dried in ambient air or an oven. Bi et al describe the mechanism and optimization of a wet compression method to produce rapidly disintegrating lactose tablets. Low compression force gives high porosity, and solid bridge formation, which occurs due to drug recrystallisation, confers tensile strength.²

Conventional tabletting
Conventional tabletting is the most widely used method of producing dispersible tablets. It is simple and the least dependent on the use of specialized equipment. A review of the literature has revealed little work relating to the research and development of dispersible tablets using conventional tabletting technology. Patents describing processes for the manufacture of specific products are the main source of published material. The aim of the present research is to develop generic technology for the formulation of dispersible tablets using conventional tabletting.

Dispersible tablets using conventional technology
STANDARDS
Dispersible tablets BP are "uncoated tablets that produce a uniform dispersion in water." They are characterized by:
(i) High speed of disintegration in water «3 minutes when examined by the BP disintegration test for tablets and capsules, using water at 19-20°C).
(ii) Dispersion of the particles below 710-μm.

Method of manufacture
The manufacturing process is critical to the design of a dispersible tablet formulation. The excipients used will depend to a large extent upon the process selected. This is influenced by the physicochemical properties of the drug and the dose. Dispersible tablets are very sensitive to moisture and their stability is compromised by granulation. Direct compression (DC) is therefore the preferred technique. The most significant advantage is that tablets normally disintegrate more
rapidly than those made by wet granulation which reduces the effective surface and requires the addition of binding agents which slow the disintegration rate.

Dry granulation, or compression granulation, is useful where the dose is too high for direct compression and the drug is unstable when exposed to moisture or heat. For example, it has been employed in the manufacture of dispersible amoxicillin tablets.

A review of the patent literature reveals that wet granulation is the most commonly used method for the manufacture of dispersible tablets. This is logical since most drugs formulated into a dispersible tablet are high dose drugs where patients commonly experiences difficulties swallowing large tablets.

The theory of wet granulation
Wet granulation produces size enlargement when small primary particles are aggregated to form larger, physically strong agglomerates where the original particles are identifiable. Bonds are formed between powder particles which adhere to form granules. The use of soluble adhesives, called binders, causes particle agglomeration and granules are influenced by binder type and its distribution within the aggregates.

Bonding mechanisms for agglomeration in wet massing
Rumpf identified five mechanisms responsible for agglomeration, and stated that more than one applied to any particular system.

[a] Adhesion and cohesion caused by immobile liquid films.
Sufficient moisture must produce a thin, immobile adsorption layer to contribute to the bonding of fine particles, by decreasing the distance between particles and increasing the inter particulate contact area. Thin, immobile films of highly viscous solutions of adhesives can form exceptionally strong bonds.

[b] Interfacial forces and capillary pressure at mobile liquid surfaces
When the liquid level on the surface increases beyond a thin film, mobile liquid forms bridges where capillary pressure and interfacial forces create strong bonds. This is reversible after
drying. However, mobile liquid films are required to form solid bridges from binders dissolved in the granulating fluid.

\[c\] **Solid bridges**

Solid bridges form by the crystallization of dissolved substances. A hardening binder is a common bonding mechanism in pharmaceutical wet granulations. Liquid and the adhesive will harden or crystallize on drying to form solid bridges. Equally, the solvent may dissolve one of the powdered ingredients. When the granules are dried, crystallization will take place and the dissolved substance then acts as a hardening binder. The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules.

\[d\] **Attractive forces between solid particles**

Electrostatic forces are of importance in causing powder cohesion and the formation of agglomerates during mixing. However, they do not contribute significantly to the final strength of the granule.

\[e\] **J Form-closed bonds or interlocking bonds**

Fibers or particles can interlock or fold about each other resulting in "form-closed" bonds. Although mechanical interlocking of particles influences agglomerate strength, its contribution is generally considered small in comparison with other mechanisms. With increasing liquid addition, granulation moves from an immobile liquid to a mobile liquid film state. Newitt & Conway-Jones defined the theory of granulation in terms of three states, and Barlow added a fourth. These four states are termed: pendular, funicular, capillary and droplet (or suspension).

**Dispersible tablet formulation**

**Drug**

High dose drugs which are highly water soluble, poorly compressible and hygroscopic pose the greatest difficulty in a dispersible tablet formulation. Excipients must be carefully selected to produce a tablet matrix with high compressibility and low aqueous solubility and hygroscopicity. However, there is a limiting tablet size (= 750mg) and where the dose of drug is high, the mass of excipients which can be used to modify the physical properties of the tablet is severely restricted.
**Disintegrants**

A Disintegrants accelerates the rate at which a tablet breaks up in water. The current research will use so-called super disintegrants, so-called because of high disintegrant efficiency attributed to their remarkable ability to absorb water and swell. Many of these combine wicking and swelling action which allows a high and fast movement of water into the tablet structure at a low concentration. Super disintegrants can be used in smaller concentrations and therefore the negative effects on flow and compression, exhibited by most of the starches, are minimised. Different grade specifications for a super disintegrant will cause differences in disintegrant activity. Using calcium diphosphate tablets, showed significant differences in the disintegrant force generated by Polyplasdone-XL and Kollidon-CL. They attributed the difference to the different particle size of the two commercial brands, since similar results were obtained when samples having the same particle size range were compared.

**Super disintegrants**

- Sodium Starch Glycollate
- Cross-linked polyvinylpyrrolidone,
  - (Crospovidone)
- Cross-linked sodium carboxymethyl cellulose (Croscarmellose)
- Low substituted carboxymethyl cellulose
- Polacrin Potassium

**Commercial variants**

- Primojel
- Explotab
- Polyplasdone- XL
- Kollidon-CL
- AC-Di-Sol
- Nymcel-ZDIO
- Nymcel-ZD16
- Amberlite IRP88

The choice of disintegrants depends on the physicochemical properties of the base formulation. In hydrophobic and water-insoluble base formulations, the disintegrants are capable of developing maximum swelling force and capillarity. Highly hydrophilic and strongly swelling
Disintegrants are preferable. In hydrophilic and water soluble formulae, the disintegrant assists in drawing water inside the compact but is not always able to develop maximum swelling force.

Many workers support the idea that for a formulation there is a critical disintegrants concentration and below this concentration, disintegration is slow. At this critical concentration, disintegration time decreases, often dramatically. A critical amount of disintegrants corresponds to the setting up of a continuous hydrophilic network, which allows for fast movement of water throughout the tablet.

**Binder**

The binder and solvent in wet granulation have a profound effect on the disintegration properties of the tablet. The aqueous solubility of the binder will affect tablet disintegration properties, and this is well documented. Holstius & Dekay evaluated the disintegration of tablets containing different binders and disintegrants, and found that binders were more important.

**Water soluble binders**

- Hydroxyethylcellulose
- Hydroxypropylmethylcellulose
- Methyl Cellulose
- Polyvinylpyrrolidone
- Sucrose