CHAPTER 1. INTRODUCTION

Despite significant advances in injectable, transdermal, nasal, inhalable and other routes of administration, oral drug delivery remains the preferred delivery route. Oral dosage form mainly comprised of tablets, capsules, and solutions. Tablet is the most popular dosage form amongst all other oral dosage form due to its unit dosage form, ease of manufacture, and also has a high patient compliance compared to other dosage forms. However, there are some disadvantages associated with the tablet dosage form like, condition in the gastro intestinal tract are unfavorable for some drugs. Some drugs shows extensive first pass metabolism. Most common disadvantage of tablet dosage form is difficulty in swallowing (Dysphagia). In one of the studies, it has been estimated that nearly about 50% of the population is affected by the problem of dysphagia, which results in high incidence of non-compliance and ineffective therapy [1]. In some cases such as motion sickness, unavailability of water, and sudden episode of allergic attack. Mainly the pediatric and geriatric patients are prone to experience these difficulties.

These problems can be resolved by means of fast dissolving tablet (FDT) formulation. These are the dosage form, which when placed on tongue, dissolve or disintegrate in the mouth, from a hard solid to smaller granules or gel like structure allowing easy swallowing by the patients. The disintegration time of fast dissolving tablets varies from a few seconds to a minute. Fast dissolving tablet disintegrates and instantaneously release the drug in saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva possesses down into stomach. Time required for this process is about 5-10 minutes [2]. In such cases, drugs bioavailability and on set of action can be greatly enhanced than compare to conventional dosage form [1].

During the last decade, fast dissolving tablet technologies that makes tablet disintegrate in the mouth without additional water intake have drawn a great deal of attention. This novel technology of fast-dissolving tablets is also known as fast dispersing, rapid dissolve, rapid melt or quick disintegrating tablets.
1.1 Desired characteristic and development challenges of fast dissolving tablets

As the administration of FDTs is different from conventional tablets, the FDTs should have several unique properties to accommodate. Some properties essential to good FDTs are listed below.

1.1.1 Ease of administration

For better patient compliance, fast dissolving dosage form should be easy to administer and handle.

1.1.2 Fast disintegration

Fast dissolving tablets should disintegrate in mouth without taking water or with a very small amount (1 or 2 ml) of water. When placed on tongue, the disintegrated tablet should become a soft paste or liquid suspension which can provide good mouth feel and ease of swallowing. The disintegration time should be less than a minute.

1.1.3 Tablet strength and porosity

As the fast dissolving dosage form designed to have quick dissolution/ disintegration time, tablet porosity was maximized to ensure the water absorption in to tablets. Porosity is inversely proportional to compression force. In some FDT technology, tablets are compressed at a very low compression force, this cause fast dissolving dosage form to be soft, friable and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet hardness without sacrificing tablet porosity should be provided.

1.1.4 Taste of the active ingredient

Because fast dissolving tablets dissolve or disintegrate in patient’s mouth, the drug will be partially dissolved in close proximity of the taste buds. So, a pleasant taste inside the mouth becomes critical for patient acceptance. When the drug is not tasteless or does not have an desirable taste, taste masking technique should be used. The amount of taste masking material should be kept low to avoid excessive increase in tablet size. If the drug particles are coated to minimize the bad taste, the coating should not be broken during compression and should not dissolve during wet granulation.
1.1.5 Drug property

For the ideal FDT technology, the drug properties such as, solubility, crystal morphology, particle size and bulk density should not affect the performance and final tablet characteristic, such as tablet strength and disintegration.

1.1.6 Moister sensitivity

Fast dissolving should have low sensitivity to humidity. This problem can be challenging because many highly soluble excipients are used in formulation to enhance fast dissolving properties as well as good mouth feel. Those highly soluble excipients are susceptible to moister. Therefore a good package design or other strategy should be made to protect FDTs from various environmental conditions [3].

1.1.7 Cost

Fast dissolving tablets need to be manufactured at low cost.

1.2 Major theories in FDT technologies

Fast dissolving tablets are formulated in such a way that they disperse, dissolve or disintergrate rapidly in the mouth, which enables medication to be swallowed without water. Fast dissolving tablet may avoid first-pass hepatic metabolism because of absorption of drug across the oral mucosa. This may potentially increase the rate and extent of uptake and reduce the undesirable metabolites. The potential for such pre-gastric absorption rest largely in the physiochemical properties of the drug molecule [4].

1.2.1 Disintegration

The disintegration defined by U. S. Pharmacopoeia XX is “state in which any residue of the unit, except fragments of insoluble coating or capsule shell remaining on the screen of the test apparatus is a soft mass having no probably firm core”. Disintegrants are excipients that have the capability to efficiently break bonding created by compression and binder. The material used as disintegrants include starches, agar, amyllose, cellulose and its derivatives, gum and its derivatives, gelatin, resin etc. The following several mechanism of action of disintegrants have been proposed [5, 6].

1.2.1.1 Evolution of gas

The basis of effervescent tablets is the reaction of sodium bicarbonate with citric acid or tartaric acid to yield carbon dioxide upon contact with water. The release of gas generates enough pressure to disintegrate a tablet.
1.2.1.2 Adsorption

The heat of wetting of the ingredient that occurs when the tablet is immersed in a fluid cause the entrapped air in the tablet to expand and disintegrate. It is not clear whether the amount of heat generated can cause sufficient increase in the volume of air cause pressure builds up thus, breaking the tablet apart. This mechanism provides partial explanation.

1.2.1.3 Effect of water absorption (wicking)

Disintegrants introduce water in to tablet and form large system of capillaries inside the tablet to cause tablet disintegration.

1.2.1.4 Swelling

Disintegrants such as Cross carmelllose sodium are reported to swell when moisturized. Swelling of these will produce enough pressure to disintegrate whole tablet. Tablet compressed at low pressure have high porosity. When disintegrant swell, it will not generate enough pressure due to high porosity. Medium pressure create just enough space that allow water to come in and exert high pressure when disintegrant swell. High pressure is tought to squeeze most porosity away and the water cannot flow in to a tablet. Swelling theory cannot explain all experimental result. For e. g. many substance swell to a large degree than starch, but still show poor disintegration property. On the other hand, amylose does not swell as much but is a good disintegrant.

The maximum disintegration force developed related to the quality and quantity of the disintegrating agent and the amount of water absorbed by the tablet. Water penetration rate had more impact on the disintegration time than the amount of water absorbed [7]. In many formulations, there exist a critical concentration of disintegrant. Below this critical concentration, the disintegration is very slow. The disintegration time dramatically decreased at the critical concentration. Beyond, the critical concentration, depending on the type of disintegrant, the disintegration time may decrease slowly, or remain at its lowest level or even increase again [8]. In an attempt to improve the dissolution of a practically insoluble drug, a super-disintegrant was used to physically mix with drug. It was found that solubility of the fillers and/or binders affects the minimum amount of disintegarnt necessary. The required amount of disintehrant was reduced when soluble diluents were used [9].
1.3 **Factors involved in disintegration**

1.3.1 **Disintegrating agent**

In many cases, the disintegrants have a major role in the disintegration and dissolution process of fast dissolution dosage forms. The choice of suitable type and an optimal amount of disintegrant is critical for ensuring a fast disintegration. The understanding of disintegrant properties and their effect on formulation has significantly advanced during the last few years, particularly regarding so-called superdisintegrants [10]. The purpose of disintegrant is to counteract the action of the tablet binder and the compression force used [11].

1.3.1.1 **Hydrophilic disintegrants**

High hydrophilicity is important for a fast liquid uptake in to tablet [12]. Ingram and Lowenthal stated that water absorption is a qualitative measure of many disintegrants, but it does not give any quantitative information about their effectiveness [13].

Starch was the first disintegrant used, but when the demand of faster disintegration and drug dissolution increased, more efficient agents were searched. At first, swelling properties of native starch were improved by carboxymethylation, and the integrity was kept by a cross linkage. The main product of this group are Primogel® and Explotab®.

Crosopovidone is a cross-linked polyvinylpyrrolidone, which is insoluble but highly hydrophilic due to its high molecular weight and cross-linked structure. Cellulose and derivatives are derived by various physiochemical manipulation from the pulp of woody plants. Carboxymethylated cellulose sodium (Caremellose sodium) is soluble in water and highly hydrophilic. Further, sodium substitution causes higher hydrophilicity on the material. Cross-linked sodium carboxymethyl cellulose (Ac-Di-Sol®), is nearly insoluble. It is highly hydrophilic in nature and cause fast fluid uptake in to tablet structure. Because of their high effectiveness, carboxymethyl starches, Ac-Di-Sol®, etc. is listed as superdisintegrants.

1.3.1.2 **Insoluble disintegrant**

If the solubility of disinterant is high, the viscosity of the penetrating fluid increases. This slow down the fluid uptake and also the disintegration. Insolubility of disintegrants may be increased by three methods. They are cross linkage, salting the material by an insoluble cation and increase the degree of polymerization.
1.3.2 Effect of diluents

The solubility of diluents in tablet affects both mechanism and rate of tablet disintegration and dissolution. Water soluble diluents tend to dissolve rather than disintegrate, while insoluble diluents produce rapid disintegration. With soluble compound the viscosity of penetrating fluid increases, which reduce the effectiveness of strongly swelling disintegrating agents [14-16]. The soluble disintegrant will also compete for the locally available water thus inhibiting the action of disintegrants [17].

1.3.3 Effect of binder

Besides tablet disintegration, tablets should have adequate tensile strength. Binders may counteract rapid disintegration. Binders can have significant effect on tablet disintegration. If the binder concentration is high, delayed release of drug may obtained [5].

1.3.4 Effect of lubricants

Lubricating agents are added to tablets to prevent sticking of the powder mass or the finished tablets to the machinery. Most of the lubricants are very hydrophobic and act by particle coating. Lubricant particles are generally smaller than other particle in mixture. When the mixture is mixed, lubricant particle may adhere to the surface of particles, thus inhibit the wetting and consequently tablet disintegration.

1.3.5 Effect of disintegrating fluid

Superdisintegrants can behave differently in acidic and neutral dissolution media. Botzolakis and Augsburger reported that when fluid is changed from acidic to water, the efficiency and liquid uptake of superdisintegrat is altered [18]. Visavarunjroj and Remon reported that superdisintegrant promote faster dissolution in a neutral fluid than in an acidic fluid [11].

1.4 Rational for the selection of anti-emetic drugs (Domperidone and Ondansetron HCl)

- Domperidone is a potent anti-dopaminergic drug used orally and intravenously for suppressing nausea and vomiting without extrapyramidal side effects as it crosses blood brain barrier poorly.
- Ondansetron HCl is a potent selective serotonin 5HT3 receptor antagonist which has a role in prophylaxis of postoperative chemotherapy/ radiotherapy induced emesis.
• Domperidone is practically insoluble in water; Fast dissolving tablet is a better alternative for administration of domperidone to obtain rapid dissolution.

• Ondansetron HCl is very bitter in nature, by using taste masking approach in fast dissolving tablet provides good mouth feel to nauseated patients.

• In general, emesis is preceded with nausea; in such condition administration of drug with a glass of water is very difficult. Hence, fast dissolving tablets are beneficial to administer the drug.

• Rapid onset of action is required in case of emesis and fast dissolving tablets provides rapid onset of effect.

• In case of motion sickness, fast dissolving tablets provides better patient compliance, as no need of water during travelling, which makes FDTs, traveler-friendly dosage form.

• FDT of antiemetic drugs would be the best alternative to conventional tablets or injectables formulation for cancer patients as they suffer from nausea and vomiting compounded with difficulty in swallowing.

**Table 1.1 Currently available market products of domperidone**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Type</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Domperi DT</td>
<td>Dispersible Tablet</td>
<td>IPCA LABS</td>
</tr>
<tr>
<td>Domstal MT</td>
<td>Mouth dissolving Tablet</td>
<td>TORRENT PHARMA</td>
</tr>
<tr>
<td>Domel MT</td>
<td>Mouth dissolving Tablet</td>
<td>INTAS LAB</td>
</tr>
<tr>
<td>Dom DT</td>
<td>Dispersible Tablet</td>
<td>MOREPEN</td>
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<tr>
<td>Dometric DT</td>
<td>Dispersible Tablet</td>
<td>ELITE DT</td>
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**Table 1.2 Currently available market products of ondansetron HCl**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Type</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>Ondanz DT</td>
<td>Dispersible Tablet</td>
<td>ELDER PHARMA</td>
</tr>
<tr>
<td>Ondem MD</td>
<td>Mouth dissolving Tablet</td>
<td>ALKEM LAB</td>
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<tr>
<td>Onstar MD</td>
<td>Mouth dissolving Tablet</td>
<td>CELON LAB</td>
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All above listed products are suffer from drawbacks such as, low mechanical strength (2-2.5 kg/cm²) and slow disintegration. So in the present study, an attempt has been made to develop fast dissolving tablet of domperidone and ondansetron HCl as model drugs with improved mechanical strength and rapid disintegration. The optimized batches of both the drugs were further selected for pharmacokinetic and pharmacodynamic study. Wistar rat and swiss albino mice were used as animal models.