Domperidone: A literature based review on pharmacokinetic control using different drug delivery strategies

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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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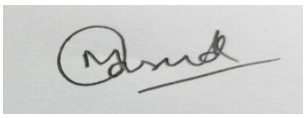

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Approval

The thesis titled "Domperidone: A literature based review on Pharmacokinetic Control using Different Drug Delivery Strategies" submitted by Md. Masudur Rahman (16346007) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human and animal trial.

Abstract

Domperidone (DMP), a potent gastroprokinetic and antiemetic drug, exhibits poor aqueous solubility and extensive first-pass metabolism. Therefore, to develop its oral preparations with optimized absorption and bioavailability, the pharmacokinetic parameters of this drug need to be controlled. This study aims to discuss the physicochemical characteristics of DMP causing its unfavorable oral delivery, explore the viable oral formulation approaches such as direct compression, amorphization, micronization, thin film preparation, pelletization etc. based on their pharmacokinetic parameters for determining the most valuable strategies and to provide adequate information in developing novel alternatives to the current commercial products. In this study, some effective strategies in this regard have comparatively discussed. It has been found that the amorphous solid dispersion approach could be more convincing from the scalability perspective along with its significant improvement in dissolution behavior and oral bioavailability. Finally, some future perspectives of these strategies have been addressed to facilitate efficient formulation development.

Keywords: Domperidone; solubility; drug delivery strategy; pharmacokinetic parameters; amorphization; drug-drug interactions.

Dedication

I want to dedicate this project to my parents who are the constant support of my life.

Acknowledgement

I would like to proceed by thanking the Almighty who is the source of our strength and knowledge which have enabled me to complete this project with full diligence.

I would like to express my deepest gratitude and appreciation to my project supervisor, Dr. Eva Rahman Kabir (Professor and Chairperson, Department of Pharmacy, Brac University) and Dr. Md. Abul Kalam Azad (Assistant Professor, Department of Pharmacy, Brac University), whose expertise, ample time spent and consistent guidance in every step have helped me to accomplish this project efficiently. I would like to thank them for their great advice and patient behavior throughout this phase whenever I encountered difficulty.

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List of Abbreviations

BA	Bioavailability
DDI	Drug-drug interaction
DDS	Drug Delivery Strategy
DMP	Domperidone
HPMC	Hydroxypropyl methylcellulose
PD	Parkinson disease
PEG	Polyethylene Glycol
PVP	Polyvinyl pyrolidone
SSG	Sodium Starch Glycolate

Chapter 1

Introduction

Domperidone (DMP), a selective dopamine D_2 antagonist, is a gastroprokinetic and antiemetic agent which was first marketed in 1978 under the brand name 'Motilium' and was developed by Janssen Pharmaceutical (Vetrivel et al., 2018). The chemical formula of DMP is 5-chloro-1-[1-[3-(2,-3-dihydro-2-oxo-1H-benzimidazol-1-yl)-propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one where the 4-position of the piperidine ring is substituted by a 5-chloro-1,3-dihydro-2H-benzimidazol-2-on-1-yl group (Vardanyan, 2017). After its first chemical synthesis in 1974, it has been used both as a research method for assessing the molecular functions of dopamine and dopamine receptors and as a potential therapeutic agent with varying clinical applications in gastroenterology (Reddymasu et al., 2007). Clinically, it is used to treat upper gastrointestinal motility disorders by controlling the motility of the gastric and small intestinal smooth muscles (Ahmad et al., 2006). Additionally, certain effects on the motor activity of esophagus have been shown to suppress nausea and vomiting as well as bile reflux without affecting gastric secretion. It also exhibits anti-emetic behavior by creating resistance of dopamine receptors in the Chemoreceptor trigger zone (CTZ) (Osinski et al., 2005). It commonly eases many complications including nausea, vomiting, abdominal pain, early satiety, bloating, anorexia and distension in patients of diabetic gastropathy. Moreover, it offers short-term relief in patients with dyspepsia and also prevents nausea and vomiting associated with emetogenic chemotherapy or in patients with Parkinson's disease (Brogden et al., 1982). Additionally, DMP is also often suggested by physicians to promote lactation (breast milk production) through the release of prolactin (Grzeskowiak et al., 2018). It can be taken orally or rectally and is available in the market in the form of tablets, oral disintegrating tablets, suspensions, and suppositories. The oral formulations of DMP have

shown limited bioavailability (BA) (13%–17%) due to its low solubility and higher first pass metabolism characteristics even after having higher permeability rate whereas intravenous or intramuscular preparations have shown reportedly better BA that is about 90% as no first pass metabolism is taken place in these routes (Brogden et al., 1982).

Solubility and dissolution rate are one of the key parameters for every drug to attain its optimum systemic circular concentration to show its effective pharmacological activity. The Biopharmaceutics Classification System (BCS) is an experimental tool based on the measures of permeability and solubility rate of any drugs under the specified conditions as well as facilitates all the pathways for drug developers and generic companies to access a waiver of clinical bioequivalence studies (Amidon et al., 1995). Conversely, Biopharmaceutics drug disposition classification system (BDDCS) performs as a complementary method by predicting transporters' role in drug disposition and drug-drug interactions (Chen et al., 2011). The four classes of BCS and BDDCS (***Table 1***: BCS and BDDCS classification of drugs) have been designed based on aqueous solubility and intestinal permeability rates of drugs that signify four distinct expectations of *in vitro-in vivo correlations* (IVIVC) (Benet, 2013). Among the BCS categories of drugs, BCS class-II drugs have been categorized as poor aqueous low solubility and high permeability which demonstrates higher absorption but poor dissolution (Kumar et al., 2013). The rate-limiting step on BA for these drugs is therefore dissolution limited because a little increase in dissolution results a significant increase in its BA (Löbenberg & Amidon, 2000). These drugs demonstrate that their dissolution time is longer than the time of residence in the GI tract, resulting in poor BA of these drugs (Charalabidis et al., 2019). Studies have been shown that drugs with aqueous solubility of less than 100 µg/mL commonly have BA problems (Hörter & Dressman, 1997).

Table 1: BCS and BDDCS classification of drugs

Class I High solubility **BCS** High permeability **BDDCS** Extensive metabolism	**Class II** Low solubility **BCS** High permeability **BDDCS** Extensive metabolism
Class III High solubility **BCS** Low permeability **BDDCS** Low metabolism	**Class IV** Low solubility **BCS** Low permeability **BDDCS** Low metabolism

The key factors affecting the kinetic model of drug dissolution has been made easy to describe from the Nerst-Brunner and Levich modification of the Noyes-Whitney equation given as below (***Equation 1***) (Noyes & Whitney, 1897; Levich & Tobias, 1963).

Equation 1: Noyes-Whitney equation of dissolution rate

$$DR = \frac{dX_d}{dt} = \frac{A.D}{\delta}\left(C_s - \frac{X_d}{V}\right)$$

Here, "DR" represents the dissolution rate, "A" is effective surface area of the solid drug, "D" is the diffusion coefficient of the drug, "δ" is the effective diffusion boundary layer thickness adjacent to the dissolving surface, "C_s" is the saturation solubility of the drug under lumenal conditions, "X_d" is the amount of drug already in solution and V is the volume of the dissolution medium. BCS class II drugs have possible scope in biowaiver extension Due to its limitation of oral absorption by in vivo dissolution. In the case of Class II drugs, the role of medicinal chemists and pharmaceutical scientists come into play by increasing the surface area and solubility saturation which ultimately can lead to an immense increase in dissolution rate and hence BA of the drug (Pinnamaneni et al., 2002). Among them, one of the two common approaches that have been used widely for enhancing solubility of drugs include chemical modifications of the drug compound and bringing modifications in formulation

design. However, drug developers have preferred formulation approaches over chemical modification as it is usually less time consuming and less resource intensive (Pinnamaneni et al., 2002). Nevertheless, it has been found that designing a new drug delivery system for these drugs is always challenging as various complications have been raised in the formulation strategies. In the complex and dynamic environment, the solid-state properties of the drug and the transitions between different states in the gastrointestinal tract are not easily evaluated. Moreover, the response of excipients to this complex digestive environment is mainly individual-dependent, and the resultant interaction of the dissolving drug with these components is not yet fully predictable (Ladas et al., 1984). Additionally, others common challenges such as undefined crystallization of the drugs, the unpredictable intraluminal behavior of advanced formulations, the food-drug interactions, drug-excipient interactions, self-assembled colloid formations for lipid based formulations etc. are often observed in developing new formulation techniques (Boyd et al., 2019). Hence, every effort that has been taken for designing new delivery systems for these drugs is considered in such a way so that it can improve the patient's compliance.

Like other BCS class-II drugs, oral DMP preparations have similar characteristics of poor aqueous solubility (0.986 mg/L) and shows extensive metabolism due to its high permeability rate and also for its excessive 'first-pass' hepatic and gut-wall metabolism by CYP3A4 enzyme which results in overall low oral BA (13%–17%) of DMP (Brogden et al.1982). The problems associated with DMP formulations are also significantly similar to that of BCS class II drugs. The oral preparations of DMP are available in form of immediate release, sustained release, delayed release, controlled release etc. different formulation systems (Khan et al., 2018). But most of these formulation systems have not been seen to meet patient compliance satisfactorily due to their inappropriate dose maintenance, site targeting, risk of dose dumping, less flexible dosage regimen (Khan et al., 2018). Additionally, various factors

such as unpredictable crystallization, drug precipitation, the complex intraluminal behavior, the food-drug interaction, unpredictable excipient response as well as other external factors associated with formulation design are also responsible for impotent drug delivery system (Boyd et al., 2019). In view of such multifaceted issues, these problems related to formulation design needs to be resolved from an individual's perspective. For years after years, researchers have tried heart and soul to overcome these issues by developing new drug delivery systems while only limited progress has been made in specific areas. Besides, no globally coherent approach has been taken to bringing together these findings of this drug in a comprehensive manner (Boyd et al., 2019). Hence, there have been many future scopes to identify such multiple barriers of formulation techniques as well as to develop worldwide accepted new delivery strategies. Despite of enormous challenges in formulation development, there have been also many established drug delivery strategies available which are quite successful to ensure improved solubility and therefore increased oral BA of DMP. Some of the drug delivery strategies for oral DMP include melt granulation technique (Patel et al., 2011), solid dispersion technique (Tyagi & Dhillon, 2012), wet gelation technique (Majekodunmi & Uzoaganobi, 2017), self-micro emulsifying system (Deepa Patel & Sawant, 2009), wet granulation (Prajapati & Patel, 2010), solvent evaporation technique (Khan Sadozai et al., 2013) etc.

There is not enough study available for this drug that combines all the potential formulation approaches and can contribute it to develop novel formulation in a practical manner. Therefore, considering these gaps, different potential drug delivery methods are identified which can be used to deliver DMP in a way that can improve its pharmacokinetic characteristics and hence oral BA. The current study discusses different pharmacokinetic parameters of various drug delivery systems including combination strategies and compares their main features in improving solubility of oral DMP. The objectives of this current study

are to provide a better insight of different oral formulation techniques of DMP based on their pharmacokinetics and BA control as well as to give facile access of gaining information about these formulation strategies in order to encourage researchers to develop new strategies for this drug.

Chapter 2

Considerations/factors for oral administration of DMP

2.1 Physiochemical Characteristics of DMP

DMP, chemically a benzimidazole derivative, has a similar structure closed to haloperidol and other tranquilizers in butyrophenone (***Figure 1***) (Valenzuela & Dooley, 1984). It is weakly basic drug (pKa value of 7.89) in nature having a molecular weight of 246 g/mol (Champion et al., 1986; Michiels et al., 1981). Moreover, it shows poor water solubility

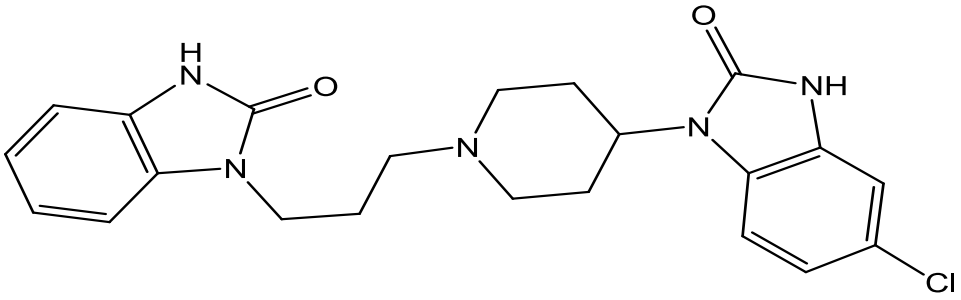

Figure 1: Chemical Structure of DMP

which is reported 0.986 mg/L. When any oral controlled release weak base drugs are exposed to pH-increasing environments then the insoluble free base become precipitated in the intestinal fluid. Hence, drugs content is unable to release from the formulation and resulting in overall low BA (Naonori et al., 1991; Thoma & Zimmer, 1990). It is nearly insoluble in water (1 part in 50,000 part of water) with a ratio of lipid to water (log P) of 3.90 (Michiels et al., 1981). Moreover, it is sparingly soluble in dimethylformamide, slightly soluble in methanol and very slightly soluble in alcohol. The characteristic peak of DMP has shown an endothermic peak at 251.9℃ (Zhang et al., 2011) corresponding to its melting point which indicates that it has been present in crystalline form (***Figure 2***). The melting point of this material is also identified within a range from 236-239℃ (Rathod et al., 2018).

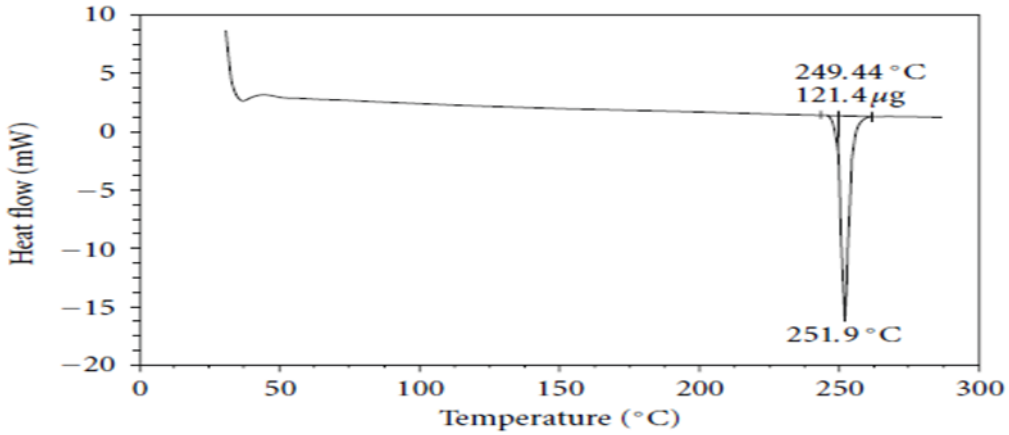

Figure 2: DSC thermogram of DMP (Zhang et al., 2011)

2.2 Pharmacologic considerations

2.2.1 Mechanism of action

DMP usually affects gastric neurotransmitters to a precise extent (Reynolds, 1989; Valenzuela & Dooley, 1984; Kohli et al., 1983). Dopamine has been observed as a modulator of GI tract motility to facilitate gastric relaxation (Valenzuela, 1976) as well as to reduce muscle tension in the esophageal sphincter (De Carle & Christensen, 1976). However, DMP counteracts such effects of dopamine receptor through effective and selective peripheral dopamine antagonist activity (***Figure 3***) (McCallum, 1985; Kohli et al., 1983; Washabau, 2012). From in vitro studies, it has been shown that DMP binds selectively to the respective dopaminergic regions of the brain but not to the frontal cortex or cerebellum. Moreover, from ex vivo receptor binding studies, it has been evidenced that the intravenous DMP does not enter the CNS to occupy striatum neuroleptic receptor sites (Laduron & Leysen, 1979). Having higher molecular weight and lower lipid solubility are considered to be one of the crucial factor for its limited permeation to the blood brain barrier. Decreased levels of DMP in the brain have been found in animal studies after following oral and intravenous administration (Brogden et al., 1982). In comparison, a dose-dependent increment was observed following administration of metoclopramide (Laduron & Leysen, 1979).The antiemetic properties of DMP include both blockade of dopamine receptors (D2 and D3) at CTZ and at the gastric level where these receptors are found responsible for inducing nausea and vomiting (Osinski et al., 2005; Freedman et al., 1994). Since the CTZ is located outside the blood-brain barrier, DMP can block the CTZ modulated dopamine activation, hence it prevents stimulation of the vomiting within the medulla center (Barone, 1999). This indicates that in cases where the concern about side effects has constrained for using metoclopramide, there, DMP has offered beneficial effects without any extrapyramidal side effects (Brogden et al., 1982).

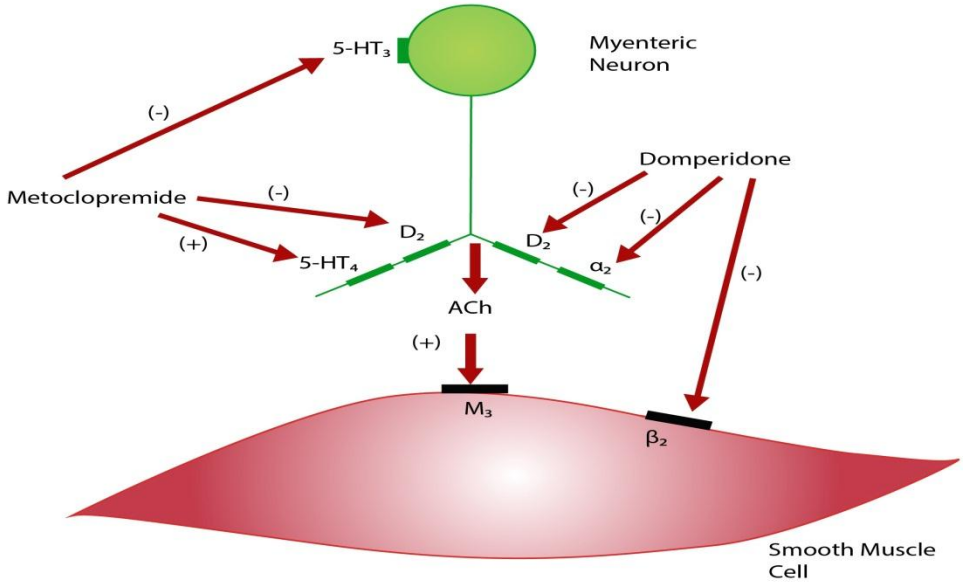

Figure 3: Dopaminergic regulation of gastrointestinal motility and mechanism of action of metoclopramide and DMP (Washabau, 2012)

2.2.2 Pharmacodynamic considerations

The pharmacodynamic assessment of prokinetic drugs in humans have been focused on the administration of tests measuring esophageal, gastric, and intestinal motor functions, including esophageal sphincter pressures, gastric emptying rates, contractile activity and gastric tone (Horowitz and Fraser 1994; Tack et al. 2006). Based on different conducted test results, the pharmacodynamic effects of DMP are summarized below.

Effects on gastric emptying

Single-dose intravenous administration and acute oral administration has been involved for preliminary tests of the effects of DMP on gastric emptying by using radioactivity (Del Genio et al., 1984; Baeyens et al., 1979). It has been reported that DMP considerably has enhanced delayed gastric emptying in adult patients with delayed motility disorder due to dyspepsia ($p < 0.01$ solid phase; $p < 0.05$ liquid phase) (Corinaldesi et al., 1983) and gastroesophageal disease ($p < 0.001$) (Del Genio et al., 1984). To calculate gastric emptying time after acute

dosing in patients with diabetic gastroparesis by using scintigraphic techniques, DMP has been reported in improving the rate of both solid and liquid emptying (Horowitz et al., 1985). It has not been found any noticeable impact on solid emptying after 35–51 days however the emptying of liquids has been increased drastically ($p<0.025$) (Horowitz et al., 1985). In these findings, the intensity and frequency of gastroparesis symptoms has been evidenced less for using DMP compared with other drugs in this category($p<0.001$ (Horowitz et al., 1985), $p<0.01$ (Koch et al., 1989)).

Effects on gastric motility

The gastric slow-wave behavior is an important physiological phenomenon linked to gastric motility (Koch et al., 1989). Gastric slow waves usually regulate gastric contractions at three cycles per minute and dysrhythmias of this contractility are considered in association of symptoms of nausea (Barone, 1999). A study conducting on six patients with serious diabetic gastroparesis has been found that long-term (6 months) administration of DMP therapy has improved both the gastroparesis symptom and gastric dysrhythmias through the assessment of electrogastrography (Koch et al., 1989). It has also been recorded that DMP boosts antroduodenal synchronization that can contribute to stabilize contraction (Baeyens et al., 1978; Johnson et al., 1983).

Effects on esophagus

In patients with diabetic gastroparesis, the acute and chronic oral administration of DMP has no substantial impact on esophageal emptying levels which has been measured by using scintigraphic technique (Maddern et al., 1985). After acute intramuscular administration to infants with GERD symptoms, it has been reported that the percentage of peristaltic contractions in the esophagus' body has been increased drastically without altering lower esophageal sphincter pressure (Grill et al., 1985). Additionally, in another study of healthy

volunteers (Weihrauch et al., 1979) and in pregnant patients (Brock-Utne et al., 1980), it has been found that the intravenous administration of DMP has increased lower esophageal sphincter pressure (LESP).

Effects on prolactin release

Like with other antagonists of dopamine receptors, DMP induces the production of pituitary prolactin in both men and women but peak prolactin concentrations has been found higher in women than men (Sowers et al., 1982; BROUWERS et al., 1980). Comparative studies on metoclopramide and DMP have shown an increase in serum prolactin concentrations with their equivalent oral and intravenous concentrations however their release patterns have been seen to vary from each other (Barone, 1999). Studies in healthy volunteers and in patients with hypothyroidism, DMP 0.2 mg to 10 mg intravenously or 20 mg orally in single doses has been resulted in a substantial increase in plasma prolactin concentrations up to the peak level after 15 to 30 minutes of intravenous injection (Camanni et al., 1982; Fujino et al., 1980; Hilland et al., 1981; POURMAND et al., 1980) and 30 to 120 minutes of oral intake (Kaufman et al., 1981). Additionally, as a result of its action, DMP can also increase the thyroid-stimulating hormone at the pituitary level including in patients with hypothyroid (Massara et al., 1981).

Antiemetic effect

In dogs, DMP has been found to prevent emesis of apomorphine 0.31 mg/kg, hydergine 0.1 mg/kg, morphine 5mg/kg and levodopa 80 mg/kg (Niemegeers et al., 1980) where all of these have caused vomiting by stimulating the CTZ (Brogden et al., 1982). The ED_{50} has been reported as 0.026 mg/kg to 0.056 mg/kg (Niemegeers et al., 1980) for DMP against levodopa induced vomiting in dogs. However, DMP has not exhibited any beneficial activity in

inhibiting emesis induced by copper sulphate that acts centrally at dosages up to 2.5 mg/kg (Brogden et al., 1982).

Effect on Aldosterone and Renin

Unlike metoclopramide (Sowers et al., 1982), in healthy individuals with a continual dietary intake of sodium and potassium, it has been found that intravenous DMP of 10mg has not induced any potential changes in aldosterone (Degli Uberti et al., 1981) or renin (Sowers et al., 1982) plasma concentrations. Moreover, after administrating DMP, there no significant changes have been observed from standard plasma cortisol (Sowers et al., 1982; Staessen et al., 1985), plasma catecholamines (Staessen et al., 1985), serum electrolytes (Staessen et al., 1985), mean blood pressure (MacDonald, 1991), heart rate (Worth et al., 1986), or renal hemodynamics (MacDonald, 1991).

2.3 Pharmacokinetic behavior of orally dosed DMP

2.3.1 Absorption and bioavailability

Absorption of drugs refers to the amount of drug that enters into the systemic circulation in the unchanged from using different drug administration routes. All the drugs which are administered through oral routes are mainly absorbed by gastrointestinal tract (Ashford, 2017). When drugs are released in oral dosage form into the GIT, it will be ready to absorb following by molecular dispersion or solution. For most dosage forms, once the drug is in solution form, it can cross the GIT through passive transport or active transport system and hence can absorb using different pathways (***Figure 4***) (Devadasu et al. 2018; Salama et al., 2006; Wagner et al., 2018). It is the similar way for any drug to be absorbed like the absorption of nutrients have been occurred through GIT (Keogh et al., 2016). Passive transport is the passage of drugs through the membrane of cells without demanding any energy and it is also the major mechanism through which most of the drugs are absorbed (Smith et al., 2014).

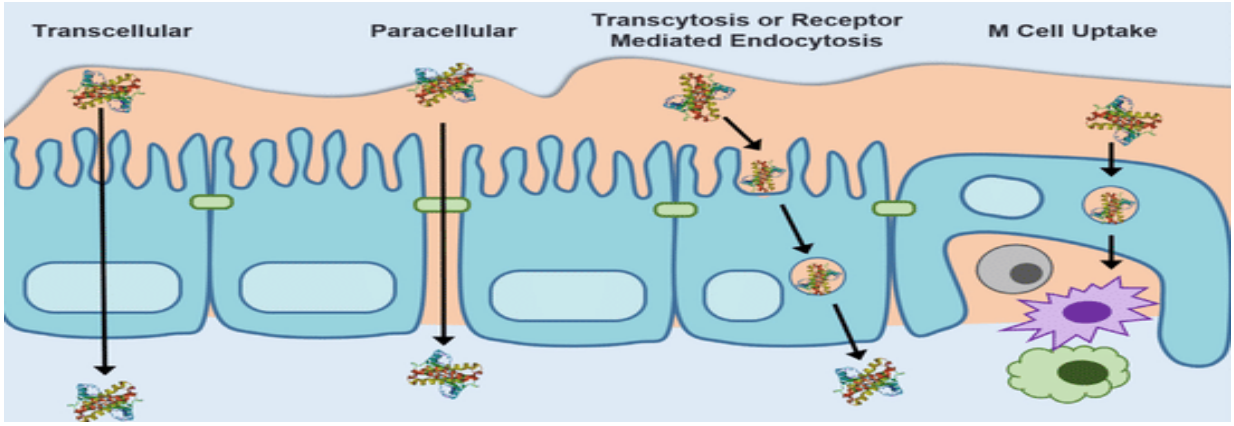

Figure 4: Schematic representation of oral absorption pathways (Wagner et al., 2018)

Being a BCS class II drug, DMP is readily absorbed when it is given as oral dosage form as well as in intramuscular and rectal administration (Heykants et al., 1981; Huang et al., 1986; Brogden et al., 1982; Barone, 1999). Even though absorption from the GI tract is almost sufficient however due to extensive first-pass and gut-wall metabolism oral BA is only about 13-17% (Heykants et al., 1981). However, it is evident that the oral BA increases from 13 to 24% when the tablets are taken after a meal compared to being taken under fasting state as meals help to slow down its gut-wall metabolism (Heykants et al., 1981). When DMP is taken orally 90 minutes after a meal, the mean time to peak concentration (t_{max}) is slowed down compared with fasting conditions but nevertheless BA has been increased dramatically (Heykants et al., 1981). DMP BA has been decreased by prior administration of cimetidine 300 mg or sodium bicarbonate solution (100 mL 0.5N) (Brogden et al., 1982) which confirms that in case of nonfasting condition (Heykants et al., 1981) the acidic environment boosts its oral BA. Additionally, for oral tablets or solutions of 60mg dose, the overall t_{max} and BA have been found within similar range (Heykants et al. 1981; Huang et al. 1986). Besides, it is evidenced that the plasma level concentration has been found maximum within 30 minutes though the oral solution (102 ng/mL) has showed higher level than oral tablets (80 ng/mL) (Heykants et al., 1981). It has seemed that DMP exhibits linear pharmacokinetics across the clinically used dosage range (almost 80mg/d) (Huang et al. 1986; BROUWERS et al. 1980; Raia et al. 1990). The proportionality of doses has been examined in 12 healthy individuals where the mean peak concentration (C_{max}) and AUC has been resulted a linear increase with single doses of 10mg, 20mg and 40 mg (Huang et al., 1986). The mean plasma concentrations in eight healthy subjects have been recorded 21 ng/mL after 14 days of therapy with 30 mg/d of DMP which is close to the mean plasma concentration (18 ng/mL) that has been observed after the first dose (BROUWERS et al., 1980). However, a significant rise in AUC at doses of 160 mg/d has been observed (Raia et al., 1990). From the above

study, it is clear that the pharmacokinetic activities of DMP can be explained better by correlating with tissue concentration than plasma concentration although it demands further comprehensive study on this drug (Barone, 1999).

2.3.2 Distribution and protein binding

Since there has no available data regarding on the tissue distribution of DMP in humans however based on animal studies, it is found that DMP distributes quickly throughout the body following oral administration with the highest concentrations occurring in the stomach, small and large intestines, liver, urinary bladder, kidney, and some glandular tissue (Michiels et al., 1981). Although DMP shows poor oral BA however, the therapeutic activity has been seen to remain present during its absorption process which is because of its affinity towards GI tissue as well as for the possible direct and local interaction with dopamine receptors in this area (Heykants et al. 1981; Huang et al. 1986). Additionally, it has been reported that large apparent volume of distribution (440 L) is consistent with extensive distribution to tissues (Heykants et al., 1981). By using equilibrium dialysis, plasma protein binding values of titrated oral DMP preparation has been found 91.8% and 93% at plasma concentrations of 10 ng/mL and 100 ng/mL respectively (Heykants et al., 1981).

2.3.3 Metabolism and elimination half-life

Hydroxylation and oxidative N-dealkylation are the main metabolic pathways of DMP which yields hydroxydomperidone and 2,3-dihydro-2-oxo-l H-benzimidazole-l-propionic acid respectively (Meuldermans et al. 1981; Brogden et al. 1982). Like other BCS class II drugs, DMP undergoes extensive metabolism both by GI and hepatic enzymes. Additionally, upon administration of a single oral dose of DMP to healthy male volunteers, the characteristics of the metabolites in urine and feces have been determined by using enzymatic hydrolysis, reverse phase high performance liquid chromatography and mass spectrometry

(Meuldermans et al., 1981). Moreover, after oral administration of the tablet formulations, it has been reported that the half-life of the dose has been ranged between 12.6 to 16 hours (Huang et al., 1986). The proportion of the remaining unchanged drug is limited which demonstrates only 1.4% of the total urinary and 10% of the faecal radioactivity (Meuldermans et al., 1981). From another study, it has been evidenced that the plasma concentrations of unchanged DMP (53 ng/mL) are about 8 times lower than the concentration of total radioactivity (395 ng/mL) at 30 minutes after oral administration which confirms its rapid metabolism (Heykants et al., 1981).

2.3.4 Excretion

Upon oral administration of DMP in healthy volunteers, it has found that 31% of radioactivity excretes in urine and 66% in feces during that 4-day period (Meuldermans et al., 1981). Almost the entire urinary radioactivity is been recovered within the first 24 hours; however, it is present only in 1.4% as an unchanged drug. Besides, Approximately 10% of the faecal radioactivity (6% of the dose) is due to its unchanged drug formation. The 0.4% of the dose that is been recovered in the urine is in the form of conjugates of 2, 3-dihydro-2-oxo-1H-benzimidazole-1-propionic acid and the 7% of the dose which is been recovered in the feces is in the form of conjugates of hydroxydomperidone (Meuldermans et al., 1981). The total plasma clearance of DMP that is measured is 700 mL/minute and renal clearance of unchanged drug is amounted to only 2.4% of the dose (Heykants et al., 1981).

2.4 Factors influencing pharmacokinetics of DMP in human

2.4.1 Interactions with co-administered drugs

DMP is mostly metabolized by CYP3A4 in the liver and also with limited contributions of CYP1A2, CYP2D6 and CYP2C8 (Simard et al., 2004;Ward & Azzarano, 2004). The major metabolic pathway that can trigger potential drug-drug interaction of DMP is when the metabolism of other drugs is also mediated by the CYP3A4 enzyme (Youssef et al., 2015). With the inhibition of DMP hepatic metabolism, it can potentially lead to elevated systemic DMP concentrations resulting in an increased blockage of the delayed rectifier potassium current and consequently the risk of drug-induced long QT syndrome, which is usually detected via electrocardiogram (Drolet et al., 2000). DMP has been often suggested to use in combination with erythromycin for gastroparesis treatment (Reddymasu et al., 2007). However, erythromycin, which is a known mechanism-based CYP3A4 inhibitor (Zhou et al., 2005) can result in elevated systemic concentration of DMP and subsequently can trigger cardiac side effects (**Error! Reference source not found.** (Ung et al., 2009). For the study, n *in vitro-in vivo correlations* (IVIVC) model has been used to estimate the intensity of in vivo interaction between DMP–erythromycin based on the in vitro data where a significant inhibition of DMP metabolism has been found by erythromycin (Ung et al., 2009). Besides, systemic in vivo exposure (measured as AUC) has been reported to increase 2.5-fold in the presence of erythromycin compared to its absence (AUCi/AUC ratio) which confirms greater DMP exposure when used with erythromycin (Ung et al., 2009).

Pioglitazone, an another mechanism-based inhibitor of CYP3A4 (Lim et al., 2005), has been reported to inhibit DMP metabolism largely which has been measured in Human liver microsomes (HLM) (Youssef et al., 2014). In this study, the in vivo systemic exposure of

DMP has been reported to increase two fold in presence of pioglitazone which indicates a significant *in vivo* DDI (**Error! Reference source not found.** (Youssef et al., 2014).

In a randomized placebo-controlled, double-blind, crossover study in healthy subjects, antifungal ketoconazole has been reported to increase the steady state plasma concentration of DMP threefold (Boyce et al., 2012). In this study, it has been recorded to have considerably higher mean QTcF (15.90 ms; $p < 0.001$) in men on both drugs than on placebo (**Error! Reference source not found.** (Youssef et al., 2015). The increase in plasma oncentration and subsequent cardiac side effect of DMP was due to the potent inhibitory action of ketoconazole on DMP's CYP3A- mediated metabolism (Boyce et al., 2012).

2.4.2 Interactions with food

Numerous drugs display major clinical variations in pharmacokinetics when delivered with food compared to when administered under fasted conditions (Harris et al., 2003). Metabolic interactions between food and drugs are similar to metabolic drug-drug interactions. All forms of interactions arise when an inducer or inhibitor modulates the metabolism and pharmacokinetics of another xenobiotic (the substrate drug) (Harris et al., 2003).

A study has reported that the concurrent use of piperine (black pepper) with DMP significantly increases the area under the plasma-concentration curve (AUC), the maximum plasma concentration (C_{max}) as well as the elimination half-life ($t_{1/2}$) (Alhumayyd, Bukhari, & Almotrefi, 2014). The increase in pharmacokinetic activities of DMP is occurred due to the active inhibition of hepatic CYP3A4 enzymes by piperine (**Error! Reference source not ound.** (Alhumayyd et al., 2014).

The consumption of grapefruit juice involves in inhibition of CYP3A4 which can lead to trigger potential food-drug interaction of DMP by increasing its plasma concentrations (Bamburowicz-Klimkowska et al., 2007). The main mechanism of interaction with DMP has

been predicted that it involves both inhibition and inactivation of CYP3A4 by dihydroxybergamottin (Harris et al., 2003). Study has been reported that the concurrent use of grapefruit juice with DMP significantly increases the area under the plasma-concentration curve (AUC) by 29%, the maximum plasma concentration (C_{max}) by 19% (**Error! Reference ource not found.** (Bamburowicz-Klimkowska et al., 2007).

2.4.3 Patho-physiological Conditions of the Patients

Levodopa is one the most commonly used drugs in the treatment of Parkinson disease. However, the excessive side effects of this drug including increased risk of neuroleptic malignant syndrome (NMS) due to its dose reduction or withdrawal hinders the optimum therapeutic activity of the drug (Leenders et al., 1986). Nevertheless, studies have been found that the pharmacokinetics of levodopa can improve significantly by concomitant use with a usual dose of DMP during the course of regular PD (**Error! Reference source not found.** ADDIN CSL_CITATION {"citationItems":[{"id":"ITEM-1","itemData":{"DOI":"10.1097/WNF.0b013e3182575cdb","ISSN":"03625664","PMID":"22751085","abstract":"OBJECTIVES: The aim of this study was to examine the effects of the peripheral dopamine D2-receptor antagonist, domperidone, on the plasma kinetics of levodopa in patients with Parkinson disease (PD). METHODS: In a randomized crossover design, 18 hospitalized patients with PD received a single dose of levodopa/benserazide, 100/25 mg, with or without domperidone, 10 mg, under fasting conditions. Plasma levodopa concentrations were determined up to 3 hours after dose administration. RESULTS: Mean ± SEM levodopa maximum plasma concentration (Cmax) (14.1 ± 2.9 vs 9.7 ± 1.6 μmol/L; $P < 0.01$), plasma concentration at 30 min (C30 min) (13.7 ± 3.0 vs 8.1 ± 2.0 μmol/L; $P < 0.01$), and area under the plasma concentration-time curve from 0 to 3 hours (AUC0-3 hr) (15.9 ± 3.1 vs 12.1 ± 2.4 μmol/L • hour; $P < 0.05$) were significantly higher after coadministration of levodopa with domperidone compared to levodopa alone. Thus, domperidone increased

levodopa Cmax and AUC0-3 hr by 1.5- and 1.3-fold, respectively. There were no exacerbations of PD by concomitant domperidone administration. CONCLUSIONS: The results demonstrate that coadministration of domperidone increased the bioavailability of levodopa. This may be the reason for no exacerbation of PD in concomitant administration of domperidone, a dopamine D2-receptor blocker. Copyright © 2012 by Lippincott Williams & Wilkins.","author":[{"dropping-particle":"","family":"Nishikawa","given":"Noriko","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Nagai","given":"Masahiro","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Tsujii","given":"Tomoaki","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Iwaki","given":"Hirotaka","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Yabe","given":"Hayato","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Nomoto","given":"Masahiro","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Clinical Neuropharmacology","id":"ITEM-1","issued":{"date-parts":[["2012"]]},"title":"Coadministration of domperidone increases plasma levodopa concentration in patients with Parkinson disease","type":"article-journal"},"uris":["http://www.mendeley.com/documents/?uuid=248c2e61-5d90-4e01-aa10-6c082754adb2"]}],"mendeley":{"formattedCitation":"(Nishikawa et al., 2012)","plainTextFormattedCitation":"(Nishikawa et al., 2012)","previouslyFormattedCitation":"(Nishikawa et al., 2012)"},"properties":{"noteIndex":0},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}(Nishikawa et al., 2012). The study has been suggested that the BA of levodopa increased as a result of increased absorption of levodopa in the intestine rather than the promotion of gastric motility (Shindler et al. 1984; Nishikawa

et al. 2012). In another study, the pharmacokinetics of DMP in patients with severe renal dysfunction (serum creatinine >530 ~mol/L) have been reported significantly lower than in healthy subjects as well as the elimination half-life was prolonged to 20.8 hours (Brogden et al., 1982). Due to the renal dysfunction, since the renal clearance is small hence plasma protein binding may be decreased and consequently the volume of distribution is also increased resulting in an increase in the relative therapeutic activity of the drug (Brogden et al., 1982).

Table 2: Factors influencing pharmacokinetics of DMP in human

Factors	Mechanisms for the pharmacokinetic change	Effects on the pharmacokinetic behavior	References
Diet			
Piperine (black pepper)	Inhibition of hepatic CYP3A4 enzymes	Increase of AUC, C_{max} and $t_{1/2}$ in rats.	(Alhumayyd et al., 2014)
Grapefruit juice	Inhibition and inactivation of CYP3A4	Increase of C_{max} and AUC by 150% and 186%, respectively, in rats.	(Bamburowicz-Klimkowska et al., 2007)
Patient conditions			
Parkinson disease	Stimulation of gastric dopamine receptor and increased absorption of levodopa	Mean 12% increases in peak plasma levodopa concentration.	(Shindler et al., 1984),(Nishikawa et al., 2012)
Renal dysfunction	Decreased plasma protein binding with small renal clearance	Lower plasma concentrations and prolong elimination half-life to 20.8 hours.	(Brogden et al., 1982)
Concomitant drugs			
Erythromycin	Mechanism-based inhibition of CYP3A4	2.5-fold increase in systemic plasma level.	(Ung et al., 2009)
Pioglitazone	Mechanism-based inhibition of CYP3A4	2-fold increase in systemic plasma level.	(Youssef et al., 2014),
Ketoconazole	Inhibition of hepatic CYP3A4 enzymes	Increase in mean QTcF value of 15.90 ms and C_{ss} value.	(Youssef et al., 2014), (Boyce et al., 2012)

Chapter 3

Formulation strategies applied to improve the biopharmaceutical behavior of DMP

Depending on poor solubility and BA of DMP, numerous formulation approaches have been taken in order to improve its oral delivery as well as to ensure patient compliance. Herein, the formulation approaches will be discussed and compared, highlighting their main features based on their pharmacokinetic behavior in the literature (***Table 3***).

3.1 Amorphous Solid Dispersion

Amorphization refers to the process in which structurally amorphous drugs are formed. Amorphous state of the drugs is more favorable for improving dissolution rate than crystalline state which can lead to a significant improvement of BA (Mallick, 2004). To form stable amorphous state of the drugs via solid dispersion, the drug content in the solid state disperses into inert hydrophilic carrier and results in improvement of the drug's wettability and surface area and eventual enhancement of solubility, dissolution rate, absorption and BA (Dhirendra et al., 2009; Y. Huang & Dai, 2014; Singh et al., 2011).

In the study of Aboutaleb et al. 2016, oral DMP was formulated with several hydrophilic carriers including sorbitol, mannitol, PEG 4000, PEG 6000, pluronic F-68 and pluronic F-127 by solid dispersion technique. However, Pluronic F-68 and pluronic F-127 showed the best results and were selected as carriers for drug in the solid dispersions. The ratio of DMP-pluronic 1:7 (w/w) solid dispersions showed higher dissolution rate (182.59±2.71μg/mL) within 1 hour which was about 27 times greater and drug release was found about 10-fold increase than the conventional DMP.

In another study of NAGPAL et al., 2016, poorly water soluble DMP was developed using modified locust bean gum (MLBG) by solvent evaporation in solid dispersion technique. It was assumed that mixing of drug with MLBG in solid dispersions leads to increase in solubility of drug which may be due to wetting characteristics of MLBG. Besides, the in vitro release from tablet batch revealed better dissolution characteristics (95% in 30 min) in comparison to marketed tablet (50% in 60 min). It was recorded that prepared batch (T2) showed 100% drug release in 45 min which showed almost 65% increase in overall drug release than the marketed preparation Vomistop® (T3) only 45% in 60 minutes.

In the study of Patel et al. 2014, fast dissolving DMP tablet was developed by ternary solid dispersion technique where gelucire 50/13 and poloxamer 188 were used as formulation carrier. Here, ternary dispersion containing the ratio 1:2:1.5 of drug: Gelucire 50/13: Poloxamer 188 was successfully formulated by the fusion method. It was found that intermolecular interactions between drug and carriers result in improved dispersion of drug in the polymer matrix, reduced size of drug particles, increased amorphous existence, increased wettability and decreased surface tension consequently results in an increased dissolution of the drug from the ternary dispersion systems. It was reported that the fast dissolving tablets containing superdisintegrants crospovidone (4%) showed greater disintegration time of 19 seconds and at 30 minutes the percentage of drug content release in vitro was reported near to 100% in 0.1N HCL which showed 15% increase than marketed preparation (85% in 0.1N HCL).

In the study of Palem et al., 2013, the DMP hot-melt extruded (HME) buccal films were prepared using PEO N10 and/or its combination with HPMC E5 LV or Eudragit RL100 as polymeric carriers and PEG3350 as a plasticizer by both in vitro and in vivo techniques. It was found that the selected HME film formulation (DMP2) demonstrated higher Cmax (129.7 ± 24.5) with about 36% increase than marketed preparation (94.22 ± 12.9) and in vitro

drug release of 84.8% in 2 hours. Additionally, total AUC concentration and BA of the optimized HME buccal film formulation was found 1.5 times higher than the oral dosage form and the results showed statistically significant ($p < 0.05$) difference.

3.2 Inclusion Complex

Complexation method, an effective technique for improving the solubility of poorly soluble drugs, refers to interactions of two or more molecules to form a non-bonded entity with a well- defined stoichiometry. Complexation depends on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Inclusion complexes are formed by introducing the non-polar molecule or the non-polar region of one molecule (called guest) into the compartment of another molecule or group of molecules (called host) (Hetal et al., 2010).

In the study of Thapa et al., 2014, the enhancement of the solubility of DMP was done by inclusion complexation with Hydroxypropyl-β-Cyclodextrin (HP-β-CD) using kneading technique and formulation of fast disintegrating tablets were prepared by using SSG as superdisintegrants. The optimum concentration of HP-β-CD was found to be in 1:2 molar ratios and SSG of 7%. Moreover, the concentration dependent increment in the solubility indicates that HP-β-CD is the major factor to enhance dissolution of drug and higher disintegration rate was due to SSG. It was reported that the fast dissolving tablets containing optimum formulation showed greater disintegration time of 19 seconds and at 30 minutes the percentage of drug content release in vitro was reported near to 100.12%.in 0.1N HCL which showed about 7% increase than the marketed drug (93.06%).

3.3 Granulation

Granulation, the agglomeration method of particle enlargement, is one of the most important unit operations in the manufacture of pharmaceutical dosage types, mainly tablets and

capsules (Jannat et al., 2016). The granulation method converts fine powders into free-flowing, dust-free, easily compressed granules.

Wet granulation

In wet granulation, the granules are formed by wet excipient massing with or without binder granulation liquid and API (Shanmugam, 2015) where the granulating fluid contains of a volatile solvent so that it can be removed by drying during the process (Jannat et al., 2016).

In the study of Khan et al., 2018, DMP matrix tablets were developed using Hydroxypropyl methylcellulose (HPMC) K100M, 5CPS and combination with Acrypol 974P as release retarding polymers by wet granulation method. The prepared tablets were evaluated for number of parameters like thickness, diameter, weight variation, swelling index and in vitro release studies where every parameters were found in the normal range. From the study, the data clearly showed that the formulations containing HPMC K100M and Acrypol 974P, HPMC-5CPS and the marketed sample Vomistop® 30mg SR follows first-order drug release with non-fickian diffusion. Moreover, the maximum drug release was found to be 99.2±2.1% over a period of 10 hours in HPMC K100M and Acrypol 974P based tablets which showed overall 6% increase than marketed formulation (92.42%). On the other hand, in HPMC-5CPS based tablets, it was found to be 98.3±2.8%. Additionally, drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 96.33 ±0.41 to 99.75 ± 0.34.

Melt granulation

Melt granulation or thermoplastic granulation is a technique that promotes powder particle agglomeration using meltable polymers and surfactants which melt or soften at relatively low temperatures (50–90°C) (Haramiishi et al., 1991). The granulation process is completed by cooling the agglomerated powder and the consequent solidification of the molten or soft

binder (Maejima et al., 1998) (Jannat et al., 2016). More precisely, the melt-in method of the melt granulation process involves heating up a mixture of drug, binder and other excipients to a temperature below or above the binder's melting level (Abberger, 2001;Aleksić et al., 2014).

In the study of Patel et al., 2011, DMP Granules were prepared using hydrophilic PEG-6000, 4000 and Myrj-52 which acts as a melting binder by melt granulation technique. The ratio within the melt granules of DMP: Myrj-52, DMP: PEG 4000 and DMP: PEG6000 were found relatively rough surface and spherical shape which enhanced drug dissolution rate. Moreover, formulation having the ratio 1:3:1 of DMP: Myrj-52: PEG6000 gave fast dissolution rate 85.77% of drug as compared to others formulation and marketed product in 1h. Additionally, the drug release was found about 88.52% in the prepared melt granules which showed about 20% increase compared to marketed preparation (about 68%).

3.4 Microcrystal formulation

To improve oral BA, micronization and nanonization methods are used to increase the dissolution rates of drugs into the biological environment. Drug micronization is conducted using jet milling techniques, rotor stator, colloid mills etc. (Rasenack & Müller, 2002). This approach is called in situ micronization technique because the micron size particles are produced directly during the process without any reduction in size (*Error! Reference source ot found.*) (Vandana et al., 2014; Rasenack et al., 2004). In this method, the molecularly dissolved drug is converted into the desired particle size by solvent change or pH change method, and a stabilizer is used to stabilize and cover the particles (Varshosaz et al., 2008).

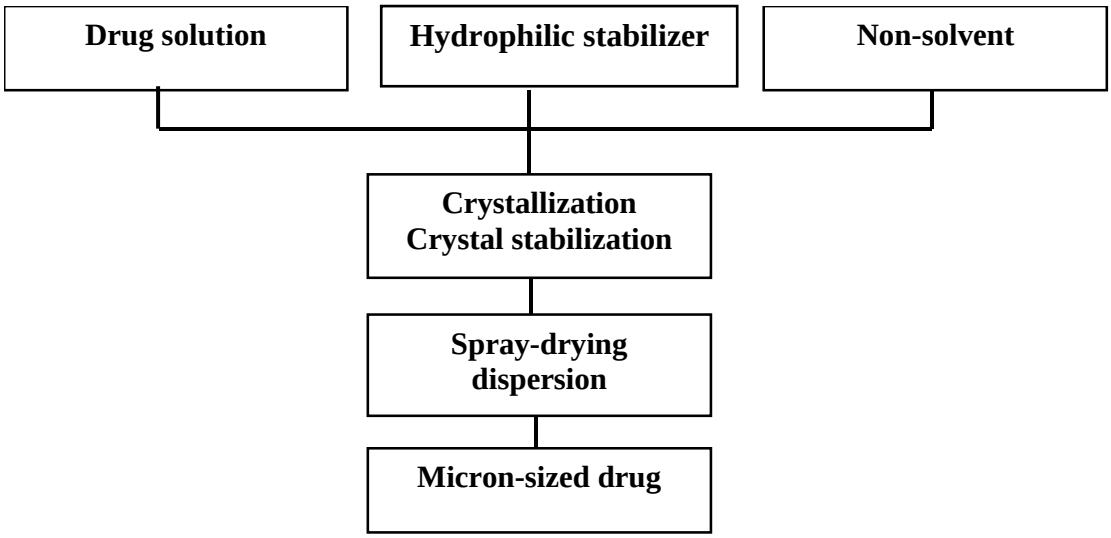

Figure 5: Schematic diagram of micronization process (Rasenack et al., 2004)

In the study of Enteshari & Varshosaz, 2018, the solubility of DMP was enhanced by the preparation of micron-sized particles where the process was carried out using solvent change method in the presence of Soluplus® or PEG6000 as stabilizing agents. It was found that DMP was dissolved in appropriate solvent (acetone and methanol 1:1 v/v) and the stabilizing agent was dissolved in water (as non-solvent). The formulated sample of in situ micronization technique formed microcrystals with uniform size and dissolution rates was found higher than conventional drugs. Moreover, the size of the microcrystals obtained in this study was between 3 to 6.9μm compared to the initial size of pure DMP that was 13.4μm. Additionally, the formulation containing the ratio of 1:5 of DMP: PEG6000 showed 95.95% of dissolution efficiency (DE60%) which was 1.84 times higher than the DE60% of the pure drug (52.18%).

3.5 Thin film preparation

Thin films have been recognized as an interim approach to the traditional ways of dosage forms where it offers convenience for swallowing, self-administering, and rapid dissolving dosage type, all of which render it a dynamic drug delivery platform (Karki et al., 2016). Among other various film manufacturing techniques, solvent casting method is more achievable, preferred and certainly widely used because of its simple production steps and low processing cost (Karki et al., 2016). In this technique, the rheological properties of the polymer mixture should be taken into serious consideration as they influence the drying rate, film thickness, morphology and also the film material uniformity (Russo et al., 2016). The mixing process may accidentally introduce the air bubbles into the liquid; hence, de-aeration is a necessary for acquiring a homogeneous product (Dixit & Puthli, 2009). On the final stage, they are left for drying after casting the solution into a suitable substrate to permit the solvent to evaporate where it contains only a polymeric film with a drug on it (***Figure 6***) (Patel et al., 2011;Amin et al., 2015).

In the study of Zayed et al., 2020, fast dissolving muco-adhesive buccal films of DMP were prepared using varying amount of polyvinylpyrrolidone (PVP K-90) through the solvent casting method. Here, in this study ethyl alcohol was used as casting solvent and PVP as film forming material which acted both as film forming matrix and also converted the drug from the low water solubility form to more water soluble form. Moreover, the maximum plasma concentration C_{max} (223.8ng/mL) was obtained after only 30 min of film administration which showed about 42ng/mL of overall increase than the marketed sample C_{max} (181.74 ng/mL in 2 hours). Additionally, it was found that the sample oral film had a higher area under the curve (AUC) of 38,875.75±1168 $ng.hr^{-1}mL$ and consequently higher relative oral BA of 131.89% than the commercial tablets.

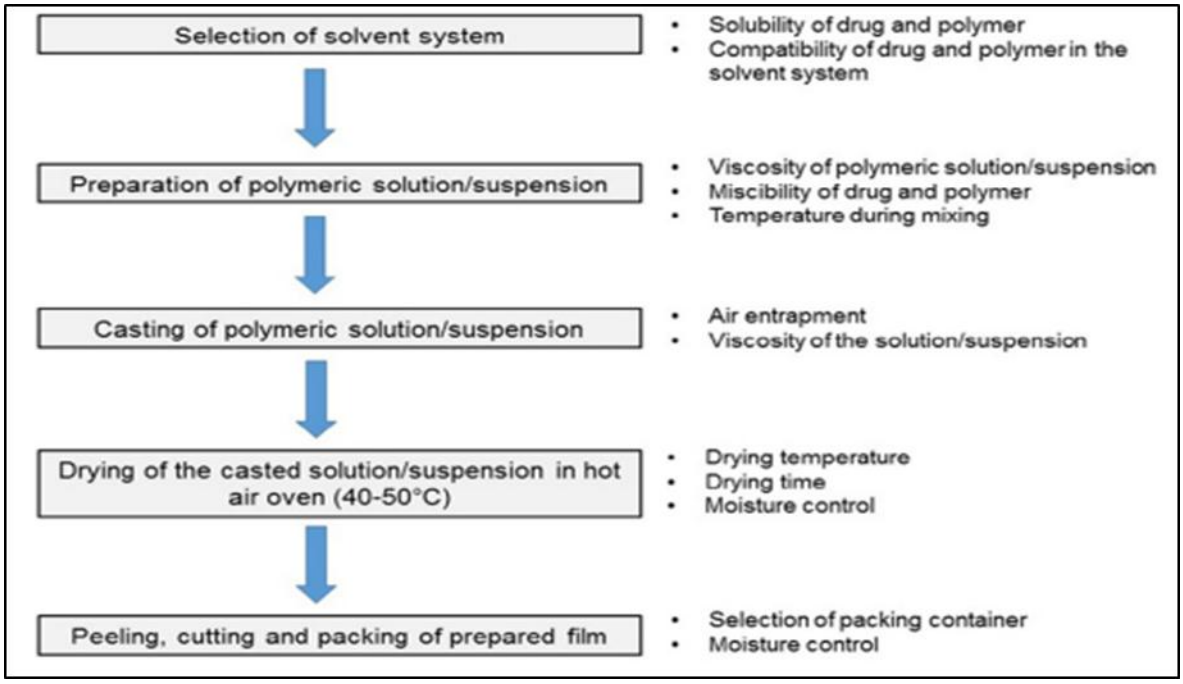

Figure 6: Solvent casting method for film preparation with quality control parameters (Karki et al., 2016)

3.6 Pelletization

One of the earliest techniques for manufacturing spherical pellets is agglomeration granulation in coating pans that requires a layering operation. Layering method includes the deposition of the active compound in subsequent layers onto inert core particles or crystals/granules of the active compound (Vuppala et al., 1997). There are various other processing steps also required for completing this technique which includes wet massing, extrusion, spheronization and drying followed by coating etc. (***Figure 7***) (Ghebre-Sellassie, 1989).

In the study of Kibria et al., 2010, DMP pellets were prepared by powder layering technology using sugar-based cores that continuously treated with micronized drug powder and binding solution. This procedure resulted in the formation of several layers of drug particles around an inert core, leading to the development of pellets that can be further coated to achieve

modified release formulations by different polymers. The color and shape of the pellets were found to be unchanged even at the end of 3 months' stability study in all conditions except 40°C/75%RH. From the study, it was revealed that about 100% drug was released in 0.1N HCl media within 30 minutes in dissolution testing due to the usage of PVP. For the study, it was found that about 93.21% pellets of the optimized formulation were within 18/24 mesh size which reflects the uniform powder loading on the NPS. Additionally, there no major change in potency of the products was seen (>97%) from the storage conditions which indicates that the formulated pellets have more stable properties than other formulated preparations in this study.

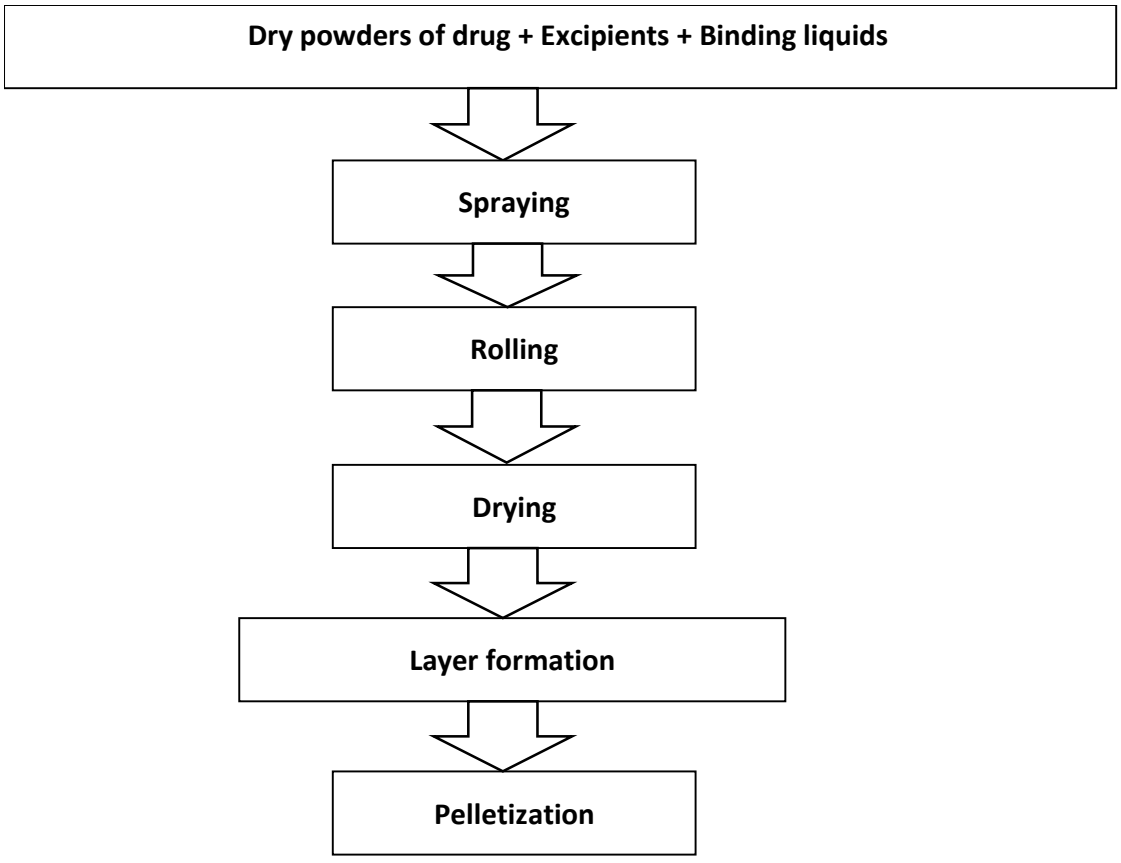

Figure 7: Steps of pellet formation by powder layering process

3.7 Tablet preparation

Porous matrix tablets

The rapid disintegration of the matrix tablets can be accomplished in the sublimation process by forming pores in the tablets prior to the sublimation of volatile components applied to the tablets. The saliva fills those pores and allows the tablets to disintegrate rapidly into the oral cavity. It also offers greater absorption and therefore greater therapeutic value than other ordinary formulation techniques. The porous structure is responsible for the faster absorption of water, thereby promoting wetting action to lead to faster disintegration (Shirsand et al., 2009).

In the study of Sutradhar et al., 2012, taste masked oral dispersible DMP tablets were prepared by sublimation method using Kollidon 30, Ispaghula husk and Guar Gum as excipients. It was found that high porosity of the formulation was achieved using the camphor as a volatilizing agent that enabled fast penetration of dissolution media resulting in the rapid release of drug (***Figure 8***). Moreover, the wetting time for all the formulated tablets

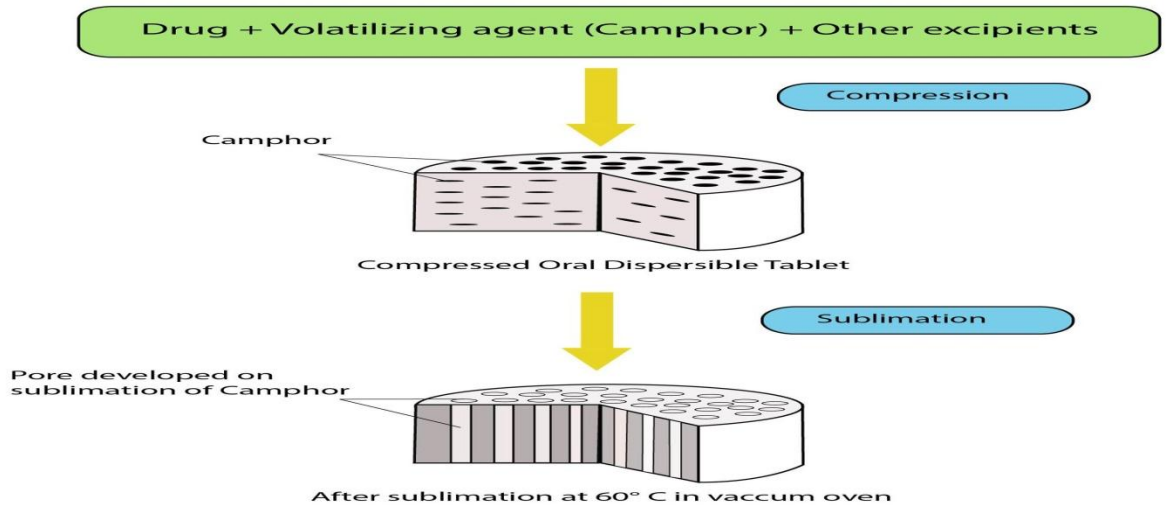

Figure 8: Schematic illustration of the preparation of a high porosity compressed tablet using sublimating/volatilizing agent (Camphor) (Sutradhar et al., 2012)

was found in the range of 29 to 48 sec. Additionally, optimized formulation containing Kollidon 30 against Kollidon CL showed the dissolution time of 24 seconds which was almost 2-fold increase than other formulations. Besides, it also showed an adequate drug release of more than 84% whereas the other formation having Ispaghula husk against Kollidon CL showed dissolution time of 25 seconds with an immediate drug release of more than 88% within ten minutes.

Fast dissolving tablets

To manufacture fast dissolving tablets easily, direct compression method is mostly preferred where conventional equipment, commonly available excipients and limited number of processing step are involved. The characteristics of disintegration and solubilization of the tablet greatly rely on the single or combined action of disintegrates, water soluble excipients and effervescent agents (Halakatti, 2005).

In the study of Parmar et al. 2009, fast dissolving DMP tablets were prepared with Avicel PH 102 (Microcrystalline cellulose) and SSG as superdisintegrants by direct compression method. Prepared fast-dissolving tablet was reported to get dispersed in the mouth quickly and releases the drug early as compared to its formulated conventional tablet. After formulation, disintegration time and wetting time of the tablets were measured 27 seconds and 29 seconds respectively where it showed 2-fold increase in disintegration than the conventional pure drug. Moreover, in vitro drug release was found not less than 95% within 30 minutes whereas the conventional drug was less than 80%.

Another study of Patil et al. 2016, orodispersible sustained release (ODT-SR) of DMP were developed by comprising microspheres of DMP followed by direct compression method. Here, ethyl cellulose was used in three different concentrations (1.5, 2 and 2.5% w/v) as the polymer for the preparation of sustained released microspheres. It was found that the ODT-

SR of DMP dispersed rapidly within 21 seconds which maintained the disintegration time specification guidelines of US FDA. Moreover, it was recorded that the mean AUC of the ODT-SR was 415.3µg.h/ml which was about three times greater than the commercial DMP. Besides, the highest percentage of drug content was found 98.95%. Additionally, the in-vivo pharmacokinetic study in wistar rats was showed that the ODT-SR maintained plasma drug concentration up to 24 hours with three times greater BA.

Table 3: Literature-based oral formulations of DMP

Formulation systems	Main features	Pharmacokinetic parameters	References
Direct compression			
Dry binder based direct compression	Blending of excipients and API, followed by compression.	DT: 2-fold ↑; Drug release: up to 15%↑ (vs. pure DMP)	Parmar et al., 2009
Polymeric based microspheres	Dry blending of microspheres with excipients and API, followed by compression.	C_{max}: 3-fold ↑; AUC: 3-fold ↑ (vs. pure DMP) BA: 3-fold ↑ up to 24 hours (vs. pure DMP) in wistar rats	Patil et al. 2016
Kollidon based matrix tablet by sublimation method	Formulation of highly porous drug results faster dissolution. Dissolution media penetrating property of camphor.	DT: 2-fold ↑(vs. other DMP preparations)	Sutradhar et al., 2012
Amorphization			
Pluronic F-68 based hydrophilic carriers	Conversion of drugs from crystalline state to the amorphous state.	Drug release: up to 10-fold ↑; DR: 27 fold ↑ (vs. pure DMP)	Aboutaleb et al. 2016
Modified locust bean gum (MLBG) based carrier	Mixing of drug with MLBG in solid dispersions lead to increase in solubility.	Drug release: up to 65% ↑ in 45 min (vs. Vomistop®)	NAGPAL et al. 2016
Gelucire, Poloxamer based polymer in fusion method	Intermolecular interactions between drug and carriers results in improved dispersion in the polymer matrix.	Drug release: up to 65% ↑ in 30 min (vs. marketed DMP)	Patel et al. 2014
PEO N10, HPMC E5 LV based polymeric carriers in hot melt extrusion(HME)	Dispersion of drug into polymer carriers prevents the films from crystallizing.	C_{max}: 65% ↑; AUC and BA: 1.5-fold ↑ (vs. marketed DMP)	Palem et al., 2013

Hydroxypropyl-β-Cyclodextrin (HP-β-CD) based inclusion complex	Encapsulation of drug into the interior cavity of CD leads to enhance solubility.	Drug release: about 7% ↑ in 30 min (vs. marketed DMP)	Thapa et al., 2014
Granulation			
HPMC K100M and Acrypol 974P based polymer in wet granulation	Enlargement of drug particles using effective matrix forming polymer results in extended drug release.	Drug release: about 6% ↑ up to 10 hours (vs. Vomistop® 30mg SR)	Khan et al., 2018
PEG6000, Myrj-52 based hydrophilic polymer in Melt granulation	Agglomerations of drug powder with meltable hydrophilic polymer lead to enhance drug dissolution rate.	Drug release: about 20% ↑ in 60 min (vs. marketed DMP)	K. Patel et al., 2011
Soluplus®, PEG6000 based polymeric carriers in micronization	Formation of uniform sized microcrystals lead to enhance dissolution**.**	DE: 1.84 fold ↑ (vs. pure DMP)	Enteshari & Varshosaz, 2018
PVP K-90 containing thin film by solvent casting method	Conversion of the drug from the low to high water soluble form. Film forming property of PVP.	C_{max}: 42ng/mL ↑; BA: 131.89% ↑ (vs. marketed DMP)	Zayed et al., 2020
Pelletization by powder layering technology	Formation of multiple layers of drug particles around sugar-based cores.	Drug release: about 100% within 30 min (vs. other DMP preparations).	Kibria et al., 2010

DT= Disintegration time; DR= Dissolution rate; DE= Dissolution efficiency.

Chapter 4

Conclusion and future perspectives

Knowing the pharmacokinetic drawbacks of oral DMP, several formulation approaches have been discussed in this study in order to provide desirable insight for improving its pharmacokinetic profile. From this study, it is evident that all the formulation techniques are quite promising in increasing the solubility or dissolution rate and hence in improving the overall oral BA of DMP. Like other BCS class II drugs, DMP also has similar downfall to achieve its optimum therapeutic activity which is due to the structural differences of the gastrointestinal tract and physicochemical characteristics of the drug. In this review, most prominent formulation strategies including direct compression, solid state amorphization, inclusion complexation, granulation techniques, hot melt extrusion, micronization, sublimation, solvent casting and power layering technology have been discussed and compared from their pharmacokinetic perspectives.

At the preformulation stage, drug particles having thermodynamically stable crystalline form is mostly preferred over metastable forms to prevent polymorphic transformation during manufacturing and storage. One of the common approaches to facilitate the formation of metastable drug is amorphization which results in improvement of the drug's wettability and surface area and eventual enhancement of solubility, dissolution rate, absorption and BA. In this study, it has been mentioned that the use of Pluronic F-68 based hydrophilic carriers by solid dispersion method has showed significant improvement in converting drugs from crystalline state to the amorphous state which results up to 10-fold increase in drug release and 27-fold increase in dissolution rate than the pure DMP preparation. In addition to solid dispersions, formulations containing cyclodextrin, microcrystal formulations have been identified as one of the effective options for formulating in the final market as they have the

potentials to trap hydrophobic drugs into their hydrophobic cavity, leads to improved water solubility and BA. Moreover, formulating DMP with direct compaction method is another easier way through which improved solubility and dissolution property of the drug has been achieved by skipping longer manufacturing steps. Similarly, it is worth noting that some novel formulation approaches like porous matrix formulation, thin film preparation, pelletization can offer additional benefits in meeting patient compliance especially for children and bedridden patients along with its improved pharmacokinetic parameters. Despite different favorable formulation strategies, the use of each delivery options can be hindered by multiple factors. Precisely, direct compression approach at low dose may exhibit non-uniform blending. The amorphous approach sometimes possesses innate thermodynamic instability since amorphous solid reverts to its stable crystalline form during storage. Moreover, for wet and melt granulation method, they both have stability issues with moisture and heat sensitive drug substances during storage. Additionally, the microcrystal method using wet-milling techniques may be unviable for drug substances having low melting points because the emergence of heat friction during the wet milling process results in partial amorphization. It also converts high energy polymorph to low energy crystalline form which is therapeutically inactive. Thereby, the physicochemical property of the drug product as well as the selected excipients may influence the choice of suitable delivery options. Usually, direct compression, micronization, wet and melt granulation are classified into conventional methods whereas other formulation strategies such as thin film preparation, amorphization, and pelletization can be defined as non-conventional methods. Most of these non-conventional methods are suitable for low scale preparation or in laboratory-scale experiments as scale-up manufacturing will require extensive investment and specialized equipment including spray dryer, hot melt extruder, bead milling equipment, and high-pressure homogenizer. However, based on the current state of technological advancement for DMP, the amorphous solid

dispersion approach could be convincing from the scalability perspective along with its significant improvement in dissolution behavior and oral BA as it eases the formulation through using melting, solvent evaporation and solvent-wetting method.

Although great progress has been achieved over the past few decades, there are still many questions and challenges for different oral formulations techniques of DMP. So, before developing a delivery system, it is necessary to recognize the reason behind the poor BA. To overcome such issues further comprehensive study is necessary. Moreover, to evaluate and monitor the drug-release process effectively, real time biomedical imaging techniques such as position-emission tomography, photo acoustic imaging, magnetic resonance imaging etc. are necessary for better understanding and to know of how drug delivery systems are handled in the GI tract. Furthermore, ample research is required to mitigate the potential drug-drug interactions in case of concomitant usage of DMP and also to develop improved formulation techniques. Additionally, for commercial development of the product, special research is required to mitigate some challenges like scale up, cost effectiveness and instability of the formulations. Finally, animal studies are also required for the moment to verify the drug's intraluminal actions from these mentioned drug delivery systems.

There is also another approach available for this drug to deliver it as a personalized medicine. Through incorporating 3D printing (3DP) technology, DMP will broaden the opportunity of customization in the era of advanced drug delivery system for an individual’s perspective by enhancing the solubility and drug release. Moreover, it is also possible to combine traditional technologies with the advancement of 3DP technology to establish patient-oriented cost effective oral drug delivery systems. However, some considerations such as stability, quality, and applicability of 3DP drug delivery devices for this drug is required for developing safe and effective pharmaceutical formulation (Pandey et al., 2020).

In conclusion, several delivery options have been developed in academic and industrial fields to improve the physicochemical and pharmacokinetic behaviors of DMP. However, by knowing the physiochemical properties of the drug candidates and drawbacks of each approach, it can be said that the amorphous solid dispersion approach would be more promising than other formulation approaches which have been discussed in this study from the scalability perspective along with its significant improvement in dissolution behavior and oral bioavailability.

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