FORMULATION DEVELOPMENT AND EVALUATION OF LOPERAMIDE SOLID DISPERSIONS.

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DECLARATION OF ORIGINALITY

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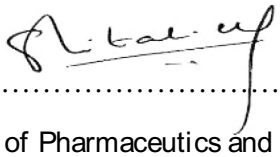

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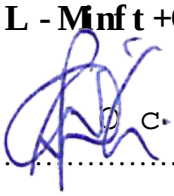

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ACKNOWLEDGEMENTS

Psalm 40:1-5

I waited patiently for the Lord; And He inclined to me, and heard my cry. He also brought me up out of a horrible pit, out of the miry clay, and set my feet upon a rock, and established my steps. He has put a new song in my mouth- Praise to our God; Many will see it and fear, and will trust in the Lord. Blessed is that man who makes the Lord his trust, and does not respect the proud, nor such as turn aside to lies. Many, O Lord my God, are Your wonderful works Which You have done; And Your thoughts toward us Cannot be recounted to You in order; If I would declare and speak of them, they are more than can be numbered.

I would like to first and foremost thank God almighty for giving me strength and standing with me throughout life and in all my endeavors.

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DEDICATION

I would like to dedicate this project to my wife Babrah for standing with me during the many moments of school work and to my parents for all the facilitation provided.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS AND ACRONYMS

API	Active pharmaceutical ingredient.
ATR FTIR	Attenuated total reflectance Fourier transform infrared.
AUC	Area under curve.
BCS	Biopharmaceutics classification system.
BP	British pharmacopeia.
CI	Crystallinity index.
CMA	Critical material attributes.
CMC	Critical micelle concentration.
CPP	Critical process parameter.
CQA	Critical quality attributes.
CRS	Chemical reference standard.
DE	Dissolution efficiency.
DoE	Design of experiments.
FTIR	Fourier transform infrared.
GI	Gastrointestinal.
HME	Hot melt extrusion.
HPMC	Hydroxypropyl methylcellulose.
IUPAC	International Union of Applied and Pure Chemistry.
IV	Intravenous.
LPM	Loperamide hydrochloride.
MDT	Mean dissolution time.
MRT	Mean residence time.
Mw	Molecular weight.
PDA	Photodiode array
PEG	Polyethylene glycol.
Pgp	P- glycoprotein.

pKa	Dissociation constant.
PM	Physical mixture.
PVA	Poly vinyl alcohol.
PVP	Polyvinyl pyrrolidone.
QbD	Quality by design.
QbT	Quality by testing.
QTTP	Quality target product profile.
SDs	Solid dispersions.
SLN	Solid lipid nanoparticles.
SLS	Sodium lauryl sulfate.
T_g	Glass transition temperature.
T_m	Melting temperature.
USP	United states pharmacopeia.
UV	Ultraviolet.
WHO	World Health Organization.

ABSTRACT

Background

Loperamide is classified as an essential drug in both the 2019 World Health Organization and Kenya essential medicines lists. It is an opioid mu receptor agonist used in the control and relief of acute non-specific diarrhea, traveler's diarrhea and chronic diarrhea. Unfortunately, its clinical use is hampered by its poor water solubility that affects its dissolution, negatively impacting its oral bioavailability. The objective of this study is to enhance the solubility and consequently dissolution of Loperamide hydrochloride through the use of hydrophilic polymer blends to prepare solid dispersions through a melt mixing technique.

Methods

A laboratory comparative design was employed in the study. With quality by design principles used in preformulation studies, with critical material attributes taken into account to design the experimental studies. Drug excipient interactions and miscibility studies using mathematical models were applied to guide excipient selection. Binary solid dispersions of loperamide in polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) were prepared through fusion/melt method. With ternary solid dispersions incorporating the surfactant sodium lauryl sulphate into the formulations with highest polymer concentration (1:5). The crystallinity of the prepared solid dispersions was ascertained through Fourier Transform infrared spectroscopy. Dissolution studies were undertaken to illustrate the effect of hydrophilic polymers and the surfactant sodium lauryl sulfate (SLS) on the solubility of loperamide hydrochloride.

Results

The dissolution profiles of loperamide from the formulated solid dispersions were best described by the Weibull model showing parabolic release. The PEG formulation B1 (1:1) followed by formulation B3 (1:5) depicted the best dissolution profiles. The PEG based formulations had better dissolution and crystallinity characteristics over the ternary and PVP formulations. Quality by design principles proved vital in formulation of the solid dispersions providing a guide for formulation development and process design.

Conclusion

Preparation of loperamide solid dispersions via the melt method is a feasible dissolution enhancement technique and can be employed in the manufacture of solid dispersions through a continuous hot melt extrusion process.

CHAPTER 1: INTRODUCTION

1.1 Background

The rate-limiting step to absorption of drugs from the gastrointestinal (GI) tract is often dissolution from the dosage form. Dissolution is premised on solubility which is based upon the intrinsic physicochemical properties of the drug (aqueous solubility, crystallinity form, drug lipophilicity, solubilization by native surfactants, co-ingested food, and pKa) (Hörter and Dressman, 2001). Therefore, measurement of drug solubility is one of the key elements of active pharmaceutical ingredient (API) characterization during the drug discovery and development process (Murdande *et al.*, 2011). Poorly soluble drugs suffer from low and variable oral bioavailability and, therefore, are prone to variability in clinical response. Despite strategies to improve characteristics (including aqueous solubility) of drug candidates during lead optimization, approximately 40% of currently marketed compounds and most development candidates remain poorly water-soluble (Williams *et al.*, 2013).

The biopharmaceutical classification system (BCS) divides drugs into four classes in terms of their aqueous solubility and permeability (Figure 1.1). The BCS system correlates in vitro solubility and permeability to the in vivo bioavailability (Pobudkowska and DomańSka, 2014). The dissolution of BCS class II drugs is rate-limiting to oral absorption and is dependent on character (pH, ionic strength, and buffer capacity) of the GI fluid upon which it dissolves (Hamed *et al.*, 2016). Numerous bioavailability enhancement techniques have been widely employed on BCS class II and IV drugs (Brough and Williams, 2013) (Venkateswarlu, Preethi and Chandrasekhar, 2016).

Loperamide hydrochloride is an opiate agonist widely used for the control and symptomatic relief of acute non-specific diarrhea (Halder *et al.*, 2012). Loperamide hydrochloride is available in a range of orally administered formulations, including tablets, suspensions, capsules, a fixed-dose combination chewable tablet, and an oro-dispersible formulation (Wei *et al.*, 2016). Although an effective antidiarrheal, it is absorbed slowly and erratically after oral administration and thus requires higher dose (Ujwala, 2013; Dadhich, Kumar and Pathak, 2016). These limitations of loperamide intimate the use of biopharmaceutical techniques to overcome and to improve the biopharmaceutical performance of the API. The BCS classification is presented in Figure 1.1.

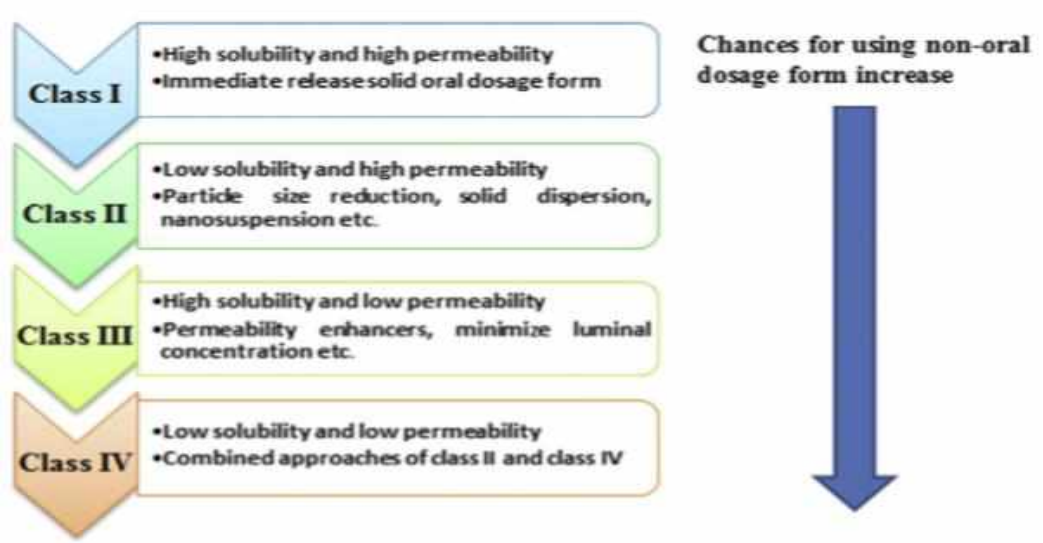

Figure 1.1: Biopharmaceutical classification with associated formulation approaches (Baghel, Cathcart and O'Reilly, 2016).

Solid dispersions are an established solubilization technology for poorly water soluble drugs and are defined as two component systems (can contain polymer mixtures or surfactants in addition) where the drug preferably in a molecular dispersed state is dispersed in an amorphous polymer matrix (Huang and Dai, 2014). Solid dispersions are a feasible approach to formulate poorly water-soluble drugs in the amorphous form, for the enhancement of dissolution rate and bio-performance (Qian, Huang and Hussain, 2010; Alonzo *et al.*, 2011). The crystalline to amorphous transition offers improved apparent solubility and dissolution rate due to the lower energy barrier required to dissolve the molecules (Karagianni, Kachrimanis and Nikolakakis, 2018).

1.2 Study problem

Loperamide is the most selective antidiarrheal opioid currently available for clinical use (Shaw, 2017). However, it is a BCS class II drug hence poorly water-soluble (Venkateswarlu, Preethi and Chandrasekhar, 2016). Drugs with low water solubility are predisposed to low and variable oral bioavailability and therefore, to variability in clinical response (Williams *et al.*, 2013). Its poor water solubility leads to a decrease in dissolution rate and as consequence absorption is reduced (Veeram, 2019). The reduced bioavailability is compounded by the fact that its oral absorption is strongly attenuated by intestinal P-gp-mediated efflux and significant first-pass metabolism by cytochrome P450 3A (CYP3A) isoform (Dufek, Bridges and Thakker, 2013). This necessitates the use of higher doses than would otherwise be necessary (Ujwala, 2013; Dadhich, Kumar and Pathak, 2016).

The study aims to address the problems by carrying out formulation development of loperamide hydrochloride using hydrophilic polymers to increase the solubility of the drug substance and thus deal with the inherent poor water solubility that is a character of the molecule. Various polymers

will be used to prepare solid dispersions through the fusion method resulting in a drug product that is envisioned to have enhanced solubility and hence in vivo bioavailability.

The study findings will aid in the manufacture of a solid dispersion with enhanced solubility with improved dissolution rate and therefore performance of the drug. The solubilized active can be used in the manufacture of other dosage forms, like oral disintegration tablets, capsules, and syrups.

1.3 Study justification

Drug–polymer solid dispersions have been demonstrated as a feasible approach to formulate poorly water-soluble drugs in the amorphous form, for the enhancement of dissolution rate and bio-performance (Qian, Huang and Hussain, 2010), (Alonzo *et al.*, 2011). The amorphous solid state offers improved apparent solubility and dissolution rate due to the lower energy barrier required to dissolve the molecules. Hence, transformation of crystalline drug into its amorphous form is widely employed for increasing solubility (Karagianni, Kachrimanis and Nikolakakis, 2018). Solid dispersions increase drug dissolution via several mechanisms including; a reduction in effective particle size, improved wetting, enhanced solubilization, and presence of the drug in its more soluble amorphous state (Williams *et al.*, 2013).

Preformulation studies are the foundation upon which formulation development takes place and ensure that teething issues are identified early and corrected or reduced using the formulation design. They play a vital role in formulation development and utilize instrumental and mathematical models to characterize material attributes as well as dictate possible formulation processes.

The study is expected to utilize predictive models and quality by design principles to prepare loperamide HCl solid dispersions that have a greater dissolution rate compared to the parent API.

1.4 Hypothesis

1. Prepared solid dispersions have greater dissolution rate compared to physical mixtures (co-milled) and the marketed product.
2. Ternary solid dispersions have superior dissolution compared to the prepared binary solid dispersions.

1.5 Objectives

The aim of the study was to formulate loperamide hydrochloride solid dispersion using hydrophilic polymers as a precursor for continuous manufacturing using hot melt extrusion.

1.5.1 Specific objectives

1. Utilization of Quality by Design principles to guide in preformulation studies of loperamide hydrochloride solid dispersion.
2. Physicochemical characterization of prepared solid dispersion through FTIR.
3. Perform in vitro dissolution studies of prepared solid dispersion in comparison with reference product and physical mixtures of drug and polymer.

CHAPTER 2: LITERATURE REVIEW

2.1 Diarrhea

Travelers' diarrhea remains a frequent health concern globally affecting those travelling from one geographical region to another. It can result in many adverse consequences including lost time and opportunity, changes to itinerary, overseas medical encounters and hospitalization (Riddle *et al.*, 2017). The tropical areas of Latin America, Africa, and southern Asia are considered high-risk areas for traveler's diarrhea (Valdez *et al.*, 2006). The incidence varies from about 8% for travel to highly developed countries to about 20% in southern Europe, Israel, Japan, South Africa, and some Caribbean islands. In most developing countries, the risk is 20% to 66% in the first 2 weeks abroad and then somewhat less thereafter (Freedman, 2014). Worldwide, approximately 20 million episodes of diarrhea occur annually in people traveling from industrial regions to developing countries (Shaw, 2017). Those often affected are usually young, healthy adults who develop mild or moderately severe, non-dehydrating illnesses that do not require hospitalization. However, the presentation in children under 4 years and those dehydrated can be more serious requiring hospitalization (Butler, 2008; Yi and Shane, 2017).

Risk factors for traveler's diarrhea are young age, season of travel, eating in restaurants, and duration of stay in a resource-limited country. Diverse enteric pathogens (bacteria, viruses, and parasites) are associated with traveler's diarrhea and can be identified in 50% to 94% of persons with symptoms (Ericsson, 2017; Yi and Shane, 2017). The most common infecting organism is enterotoxigenic *Escherichia coli*, which is primarily transmitted through oral-fecal route. Less common pathogens include *Shigella*, *Campylobacter*, *Giardia*, and nontyphoid *Salmonella* (Shaw, 2017).

Opioids are effective and prompt-acting antidiarrheal agents. They produce antidiarrheal effect by enhancing tone in the anal sphincter and in segments of the longitudinal muscle of the gastrointestinal tract, while inhibiting propulsive contraction of circular and longitudinal muscle. These effects increase the contact time of luminal fluid with mucosal cells leading to net intestinal absorption of water and electrolytes, reducing stool volume (Singh Bansi and Louis-Auguste, 2012; Shaw, 2017). Loperamide is the most selective antidiarrheal opioid currently available with non-significant CNS effect at therapeutic doses (Shaw, 2017). It has both antisecretory and antimotility effects and is widely used with 80% patient response in 24 hours when used in combination with an antibiotic, which is faster than sole antibiotic therapy (Freedman, 2014; Kantele *et al.*, 2016; Schiller, 2017).

2.2 Clinical indications of loperamide

Loperamide is FDA approved, widely available, effective, inexpensive, over-the-counter medication for control and symptomatic relief of acute nonspecific diarrhea, traveler's diarrhea, chemotherapy-related and protease inhibitor-associated diarrhea, as well as chronic diarrhea associated with inflammatory bowel disease (Adeyemo and Chang, 2008; Hanauer, 2008; Stanciu and Gnanasegaram, 2017). The recommended initial dose is 4 mg of loperamide followed by 2 mg after each unformed stool up to a maximum dose of 8 mg/day. Treatment is further continued for 1-2 days more if diarrhea still persists. The efficacy of loperamide in the treatment of inflammatory bowel syndrome with diarrhea is not well known. However, its use is recommended on a more prophylactic basis to prevent diarrhea (Adeyemo and Chang, 2008; Shaw, 2017). Butler reported that loperamide reduces frequency of loose stools by approximately one-half and shortens the average duration of diarrhea from ∼1.5 days to <1 day (Butler, 2008). Additionally, it has been successfully used in patients with chronic diarrhea for several years without evidence of tolerance (Regnard *et al.*, 2011). Improvement of fecal continence in patients with and without diarrhea, improving night-time continence in patients with ileo-anal pouches has been observed (Hanauer, 2008; Regnard *et al.*, 2011).

2.3 Loperamide pharmacology

The μ-opioid receptor plays a major role in the inhibition of gut transit and thus its agonist, loperamide, is widely used to treat acute and chronic diarrhea (Shi *et al.*, 2014). Opioids inhibit the firing of secretomotor and submucosal neurons as well as inhibit the release of transmitters from these neurons (acetylcholine). They increase sympathetic and decrease parasympathetic activity affecting propulsion in the GI tract. They also have a direct effect on smooth muscle opiate receptors (Yagasaki, Suzuki and Sohji, 1978; Miller *et al.*, 2017; Raffa, Ossipov and Porreca, 2017). Loperamide works directly on circular and longitudinal intestinal muscles to inhibit peristalsis and prolong transit time. Additionally, it also reduces fecal volume, increases viscosity, diminishes fluid and electrolyte loss as well as increasing anal sphincter tone (Singh Bansi and Louis-Auguste, 2012; Bodge and Cumpston, 2019). The decreased intestinal motility and secretion, allows for greater absorption of fluids in the GI tract. Hence, improving diarrhea symptoms, including stool consistency, frequency and urgency (Adeyemo and Chang, 2008).

Loperamide although highly lipophilic is actively excluded from the CNS by the p-glycoprotein efflux membrane transporter in the blood-brain barrier thus only has peripheral effects compared to other opioids (Regnard *et al.*, 2011). Loperamide is 50 times more potent and has a higher binding affinity to peripheral receptors than morphine (Baker, 2007; Cicci *et al.*, 2019). Loperamide has no analgesic effect in therapeutic and supratherapeutic doses and is the most potent antidiarrheal (Baker, 2007; Regnard *et al.*, 2011). It has been found to be a very high affinity inhibitor of the hERG channel. However, this is only evident on excessive misuse of the drug (Kang *et al.*, 2016).

2.4 Loperamide physicochemical properties

The International Union of Applied and Pure Chemistry (IUPAC) name for loperamide hydrochloride is 4-(p chlorophenyl)-4-hydroxy-*N, N*-dimethyl-diphenyl-1-piperidine butyramide hydrochloride, whose chemical structure is shown in Figure 2.1. It was launched by Janssen Pharmaceutica in 1973 (Halder *et al.*, 2012; Katselou *et al.*, 2017). Loperamide is a white or yellowish-white crystalline powder with poor flow properties and compressibility. It has limited aqueous solubility thus is absorbed slowly and erratically after oral administration (Ujwala, 2013; Dadhich, Kumar and Pathak, 2016). Loperamide HCl has three different crystalline forms: an anhydrous polymorphic form I representing the stable polymorph of isometric crystals and a metastable form (melting point approximately 224°C); an anhydrous polymorphic form II (melting point of approximately 218 °C) that exists as needles; and a tetrahydrate form whose melting point is around 190 °C (Woertz and Kleinebudde, 2015; Alejandro, Guillermo and Ángeles, 2020). An amorphous form has been reported (Weuts, Kempen, Decorte, *et al.*, 2005).

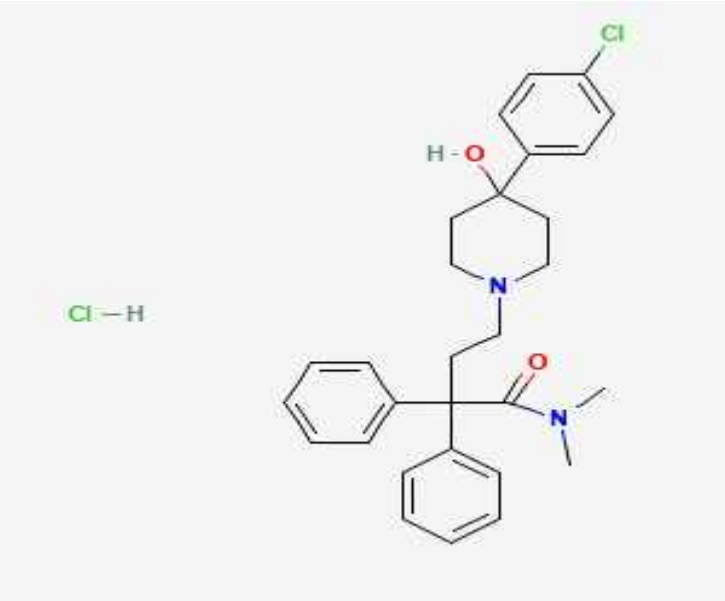

Figure 2.1: The chemical structure of loperamide hydrochloride from https://pubchem.ncbi.nlm.nih.gov/compound/71420#section=Structures.

It is a weakly alkaline molecule that forms salt at a low pH (1.2), which subsequently increases its solubility. The water solubility of loperamide is very limited (about 0.00086 mg/mL at 20°C). The lethal dose 50 of orally administered loperamide in rats is 185 mg/kg (Wei *et al.*, 2016). Loperamide and its salts are light sensitive thus are protected from light (Upadhyay and Ali, 2009). It has a molecular weight of 513.5 g/mol with the molecular formula $C_{29}H_{33}ClN_2O_2$ and a high

melting point of 222.1 °C. It has the following dissociation constants: pKa_1 9.41 (strongest basic); pKa_2 13.96 (strongest acidic).

2.5 Pharmacokinetics

Systemic bioavailability is about 0.3% because of substantial first-pass metabolism that occurs prior to systemic absorption. Peak plasma concentrations occur within 2.5 hours of oral administration of the solution and 5 hours of the gelatin capsule (Baker, 2007). Onset of action is 1 h and it takes up to 16-24 h for maximum effect, with a duration of action up to 3 days (Regnard *et al.*, 2011).

One hour after oral administration, 85% of the drug is distributed to the GI, 5% is distributed to the liver, and less than 0.04% is distributed to the brain (Shaw, 2017). Loperamides' slow oral absorption and inability to cross the blood-brain barrier is due to the highly expressed P-gp efflux transporter in the blood-brain barrier actively pumping out loperamide that reaches the central nervous system (Baker, 2007; Montesinos *et al.*, 2014; Miller *et al.*, 2017). Plasma protein binding of loperamide is 97%, thus loperamide has a large apparent volume of distribution (Lentini *et al.*, 2019).

Loperamide being highly protein bound, has reduced partitioning from the blood into tissues thus limiting its metabolism (Lentini *et al.*, 2019). It is hepatically metabolized by the cytochrome P450 (CYP) system, primarily by CYP3A4 and CYP2C8. It also undergoes metabolism through CYP2B6, and CYP2D6 (Bodge and Cumpston, 2019). Metabolism is through oxidative N-demethylation with the principal in-vivo metabolites *N*-desmethylloperamide and *N*-hydroxymethyl-mono-desmethylloperamide, having a potency that is two to three times less than that of loperamide (Baker, 2007; Vandenbossche *et al.*, 2010; Miller *et al.*, 2017).

Small amounts of loperamide are excreted unchanged in the feces (30% to 40%) and urine (2% to10%). The drug has an elimination half-life of 9.1–14.4 h (Yu *et al.*, 2004; Baker, 2007; Bodge and Cumpston, 2019).

2.6 Contraindications

The FDA does not recommend loperamide use in children <24 months of age, and use is contraindicated in patients with dysentery. Loperamide should not be given to patients with suspected or documented ileus or intestinal paresis (Chertow, Uyeki and Dupont, 2015). Shane *et al* further states that antimotility drugs should not be given to children <18 years of age with acute diarrhea (strong, moderate) and should also be avoided in patients with active inflammatory bowel disease, for they may cause paralytic ileus and toxic megacolon (Shane *et al.*, 2017). If symptoms

persist over 48 h, appearance of blood or mucus in the stool, then loperamide should be discontinued (Wolfe, 2012).

2.7 Loperamide abuse and inhibition of hERG channel

Loperamide is a high affinity inhibitor of the hERG channel (Kang *et al.*, 2016). With abuse of high-dose loperamide for its euphoric effects and to self-treat opioid use disorder (in place of evidence-based therapies, like buprenorphine or methadone), increasing (Eggleston *et al.*, 2019). Life-threatening loperamide toxicity through a syndrome of loperamide-induced cardiac toxicity presents with cardiac arrest or with unheralded, recurrent syncope in conjunction with ECG abnormalities, Additionally, features of conventional opioid toxicity may also present (Wu and Juurlink, 2017). Health options include switching over-the-counter loperamide to blister packs (the FDA-preferred method), making loperamide only available by prescription, or moving the product behind the pharmacy counter (White, 2019).

2.8 Biopharmaceutical classification profile of Loperamide

The BCS is a scientific framework that provides a basis for predicting the oral absorption of drugs based on their aqueous solubility and permeability (Varma *et al.*, 2012; Williams *et al.*, 2013). It necessitates that for high solubility, the highest strength dose must be soluble in 250 ml of water at all pH values that might be encountered in the GI tract. Therefore, drugs may be classified as class II even though they have good solubility at one end of this pH range (Williams *et al.*, 2013). Loperamide is a BCS class II drug, showing low aqueous solubility and high membrane permeability thus cannot dissolve in the gastrointestinal fluids, resulting in poor absorption. So it is necessary to improve its dissolution rate in gastrointestinal fluid so as to improve its bioavailability (Mehta *et al.*, 2014; Srimathkandala *et al.*, 2015; Venkateswarlu, Preethi and Chandrasekhar, 2016). Techniques tailored to improve its inherent solubility are utilized therefore to increase its apparent bioavailability.

2.9 Bioavailability

Bioavailability (F) is a measure of the systemic availability of a drug administered by a route other than IV. Bioavailability is determined by comparing the area under the plasma drug concentration curve (AUC) versus time for the extravascular formulation to the AUC for the IV formulation (Davis, 2018). It is the extent and rate to which the API from the drug product is absorbed and becomes available at the site of drug action (Chow, 2014). It is determined by three vital factors

namely dissolution, permeability, and solubility (Viswanathan, Muralidaran and Ragavan, 2017). Solubility is the maximum amount of material (e.g. solid) that will dissolve in a given volume of solvent, dependent on affinity of solute molecules to each other in relation to affinity of solute to solvent molecules (Wiedmann and Naqwi, 2016). Solubility is a critical factor as drug substances have to be dissolved before they can be absorbed. As absorption of passively transported drugs across the GI tract is the combined product of both permeability and solubility according to Fick's first law (Wang and Urban, 2004). Low aqueous solubility and low dissolution are a common property of many new drug candidates making inference that there is suitable confidence in techniques used to improve the solubility of the drug in the GI tract (Williams *et al.*, 2013).

Measurement of drug solubility is one of the key elements of API characterization during the drug discovery and development process (Murdande *et al.*, 2011). With low solubility (less than 100 mcg/ml) detrimental to dissolution and absorption (Hörter and Dressman, 2001; van de Waterbeemd and Gifford, 2003). It is paramount for increased bioavailability that dissolution is increased to formulate an optimized formulation (Chokshi *et al.*, 2007). Various technologies have been developed to increase the bioavailability of these active ingredients belonging to BCS II and IV classifications. Over the last decade, nano-crystal delivery forms and amorphous solid dispersions have become well established in commercially available products and industry literature (Brough and Williams, 2013; Mehta *et al.*, 2014).

2.10 Bioavailability enhancement techniques

Buffers adjust the pH of solutions resulting in an increase in polarity of weakly acidic/basic drugs and hence its aqueous solubility (Williams, Trevaskis and Charman, 2013; Wiedmann and Naqwi, 2016). For solid oral dosage forms, salt formation allows for solubility enhancement of drugs. It is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. As salts of acidic and basic drugs generally have higher corresponding solubilities than their acidic and basic forms and are often more stable than the drug itself (Serajuddin, 2007; Wiedmann and Naqwi, 2016). Salts provide a pH adjustment similar to buffers upon dissolution and dissociation due to generation of counterions of the salt resulting in increased solubility (Williams, Trevaskis and Charman, 2013). However, it is important to characterize the salts to ensure that acidic and basic forms do not precipitate out. As well as, to eliminate the presence of counterions resulting in reduced solubility (Serajuddin, 2007).Common counterions shown to increases solubility include; hydrochloride, mesylate, hydrobromide, acetate, and fumarate (Deepak Gupta , Deepak Bhatia , Vivek Dave, 2018). Loperamide is available as its hydrochloride form with another form loperamide oxide acting as a prodrug.

Polymorphism is the ability of a solid compound to exist in more than one crystalline form. Most drugs exhibit structural polymorphism. Small changes in the crystal packing may lead to significant differences in the chemical reactivity of polymorphs of the same drug. The amorphous form is less stable due to the lack of a three dimensional crystal structure, free volume, and greater

molecular mobility (Deepak Gupta , Deepak Bhatia , Vivek Dave, 2018). Different crystalline polymorphs (or the amorphous form) have different physicochemical properties (including solubilities) (Williams, Trevaskis and Charman, 2013). However, solubility differences between polymorphs is low (2-3 folds) due to relatively small differences in free energy (Gowardhane, Kadam and Dutta, 2014). Understanding the polymorphs of a compound and the conditions upon which polymorphic transitions are critical during formulation development (Williams, Trevaskis and Charman, 2013).

Cocrystals constitute a molecular complex between a drug and cocrystal former that result in changes to the crystal lattice. In the formed complex, unlike salts, proton exchange does not occur, it involves self-assembly of existing molecules without breaking or forming covalent bonds to generate new solid forms. The choice of the co-former has an influence on solubility as it can either increase or decrease solubility (Vishweshwar *et al.*, 2006; Williams, Trevaskis and Charman, 2013). Cocrystals can be classified into molecular cocrystals that contain only neutral co-formers and ionic cocrystals, which are comprised of at least one ionic co-former that is a salt (Duggirala *et al.*, 2016). Cocrystal selection is not only based on enhanced aqueous solubility but with the corresponding best physicochemical properties while not compromising structural integrity of the API (Schultheiss and Newman, 2009; Elder, Holm and De Diego, 2013). In contrast to the metastable nature of amorphous phases, cocrystals are stable owing to their crystalline nature. They can exhibit dramatic solubility advantage over the stable crystalline drug form, often comparable to amorphous pharmaceuticals (Babu and Nangia, 2011).

Cosolvents are water-miscible organic solvents widely used to increase the solubility of poorly water-soluble substances (Williams, Trevaskis and Charman, 2013).They are amphiphiles thus reduce the interfacial tension between the aqueous solution and hydrophobic solute (Nayak Amit Kumar and Panigrahi Prachi Prava, 2012). Through interactions with nonpolar solutes and aqueous polymers they stabilize the hydrophobic structures increasing its solubility (Van Der Vegt and Nayar, 2017). Cosolvents have been used with other solubilization techniques including surfactants, cyclodextrins, solid dispersions, pH manipulation, and lipids. With the most commonly used cosolvents including; ethanol, propylene glycol, and low-molecular weight polyethylene glycol (PEG)(Williams, Trevaskis and Charman, 2013).

Surfactants are amphiphiles that are used above their critical micelle concentration (CMC) upon which they incorporate drugs into micelles consequently solubilizing poorly water-soluble drugs. The lipophilic micelle core provides a nonpolar reservoir into which highly lipophilic compounds may partition, enhancing apparent aqueous solubility (Williams *et al.*, 2013). The increased wetting and penetration of solvent into the solid drug particles enhances its dissolution. Anionic surfactants such as SLS have the greatest influence on solubility followed by ionic then non-ionic surfactants (Gowardhane, Kadam and Dutta, 2014).

Lipid-based formulations improve bioavailability through stimulation of bile salt release and incorporation of drug and lipid digestion products into intestinal mixed micelles. They are consequently transported in the lymphatic system decreasing first pass metabolism and intestinal drug efflux or metabolism (Williams, Trevaskis and Charman, 2013). Lipids are the core ingredient of the formulation. However, surfactants as well as hydrophilic cosolvents are at times incorporated to aid solubilization and to improve dispersion properties (Shrestha Hina, Bala Rajni and Arora Sandeep, 2014). Lipids may be formulated into a range of delivery systems for oral or parenteral administration (solutions, suspensions, emulsions, microemulsions, nano-emulsions, micellar solutions, liposomes, lipid nanoparticles, and emulsion preconcentrates) (Williams, Trevaskis and Charman, 2013).

Solid lipid nanoparticles (SLNs) contain drug molecularly dispersed within a lipidic vehicle (Williams *et al.*, 2013). They include nanocrystals, nano emulsions, polymeric nanoparticles, self-nanoemulsifying drug delivery systems, dendrimers, carbon nanotubes, polymeric micelles and lipid nanocarriers. The nano sized (50–1000 nm) carriers enables overcoming of inherent poor pharmacokinetics and are biocompatible and biodegradable. SLNs have a lipidic core that is both solid at room temperature and physiologic temperature, and a surfactant-stabilized outer surface. (Wei *et al.*, 2016; Vijayanand *et al.*, 2018). They have a higher entrapment efficiency for hydrophobic drugs in the core compared with conventional liposomes due to phospholipids tails in the hydrophobic core (Kammari, Das and Das, 2017). They combine the advantages of various colloidal carrier systems by incorporating the advantages of the solid matrix of polymeric nanoparticles with the advantages of micro emulsions and liposomes in having low biological toxicity (Wei *et al.*, 2016). While minimizing some of their individual disadvantages (Kammari, Das and Das, 2017). Their small size, large surface area, high drug loading and the interaction of phases at the interfaces, offer advantages in improving performance of pharmaceuticals. However, disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage and relatively high-water content of the dispersions (70-99.9%) have been observed. Also drug loading capacity is limited by; solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of the lipid matrix (Mukherjee, Ray and Thakur, 2009).

Particle size reduction leads to an increase in the surface area available for solvation and an increase in the rate of dissolution for solid drug products. It is therefore routinely used to improve the oral bioavailability of poorly water-soluble drugs (Williams, Trevaskis and Charman, 2013). However, comminution is often incapable of effectively reducing the particle size of nearly insoluble drugs (<0.1 mg mL^{-1}). Micronization as well is not suitable for high-dose drugs as it does not change the saturation solubility of the drug (Gowardhane, Kadam and Dutta, 2014).

Adsorption of poorly soluble drugs to microporous adsorbents such as silica carriers have shown substantial increase in drug dissolution as drug is stabilized in the rapidly dissolving amorphous form (Ahuja and Pathak, 2009; Williams, Trevaskis and Charman, 2013). Drug at decreased particle size increases the surface area enhancing the thermodynamic activity of the drug in the

dispersed state leading to improved dissolution (Ahuja and Pathak, 2009).The dissolution rate of ibuprofen was significantly increased upon adsorption to porous calcium silicate and silica gel (Madieh *et al.*, 2007).

2.11 Solid dispersions

Solid dispersions have become an established solubilization technology for poorly water soluble drugs (Enose *et al.*, 2014; Huang and Dai, 2014). Solid dispersions as a bioavailability enhancement technique was first reported by Sekiguchi and Obi in 1961 (Sekiguchi and Obi, 1961). With the drug–polymer interaction the determining factor in its design and performance (Huang and Dai, 2014). Drug dissolution enhancement is via a reduction in effective particle size, increased powder porosity, improved wetting, enhanced solubilization, and low lattice energy of the mixture that stabilizes the drug in the more soluble amorphous state (Williams *et al.*, 2013). The amorphous state exhibits a lower energy barrier necessary to dissolve the molecules thus providing improved apparent solubility and dissolution rate (Karagianni, Kachrimanis and Nikolakakis, 2018).

They also enable achievement and sustained maintenance of drug supersaturation allowing for increased drug absorption and improved bioavailability of poorly soluble drugs (Laitinen *et al.*, 2017). Amorphous dispersions improved bioavailability in ~82% of the cases. In 8% of the cases, they had lower bioavailability and in 10% of the cases, amorphous dispersions exhibited similar bioavailability in comparison to the reference material (Newman, Knipp and Zografi, 2012). However, they have been found to be unstable during storage due to drug recrystallisation requiring high level of polymers (50-80%). During storage, absorption of moisture leads to polymer phase separation, polymer crystal growth or polymorphic conversions to crystalline form. Additionally, scale up, reproducibility and formulation into dosage forms is difficult (Mehta *et al.*, 2014).The physical form of the drug and the carrier differentiates various solid dispersions. Drug is either suspended in the carrier as phase-separated crystalline or amorphous particles, or it exists as a homogeneous molecular mixture of amorphous drug and carrier. The carrier can exist in either the amorphous or crystalline form (Williams *et al.*, 2013).

2.12 Classification of solid dispersions

The classification of solid dispersions is shown in Figure 2.2. Based on the type of carrier used in their production (Mir and Khan, 2017).

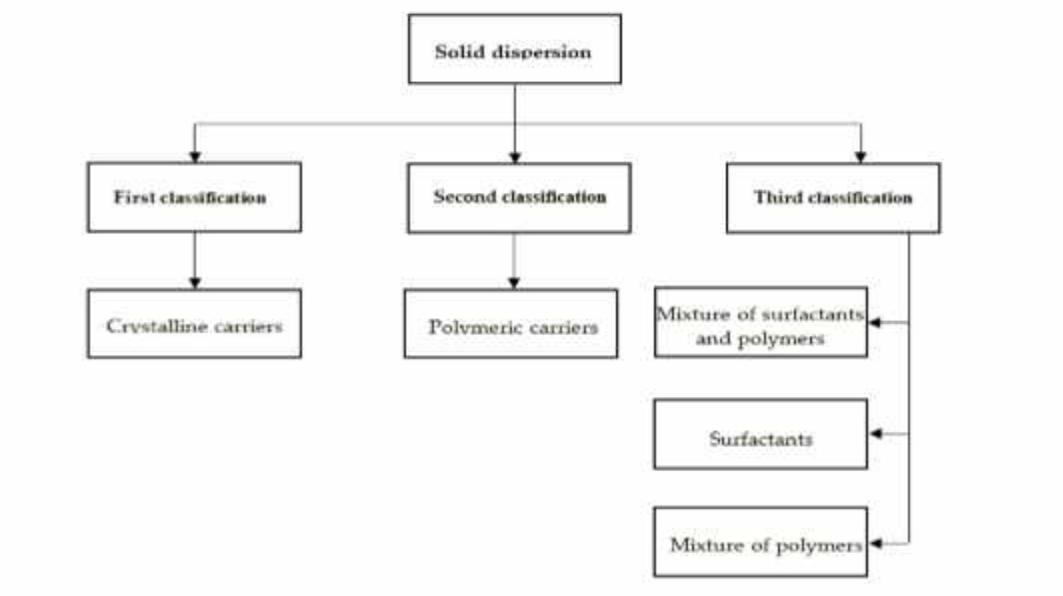

Figure 2.2: Classification of solid dispersions (Tran et al., 2019).

2.12.1 First generation solid dispersions

First generation solid dispersions utilized crystalline carriers. Formulation of eutectic mixtures or molecular dispersion using crystalline carriers such as urea, sugars and organic acids improved the dissolution of poorly water-soluble drugs (Mir and Khan, 2017; Kesharwani *et al.*, 2018). Sekiguchi and Obi showed that the use of urea as a hydrophilic carrier increased the bioavailability of sulfathiazole and chloramphenicol in the eutectic mixture compared to that of the conventional formulations (Sekiguchi and Obi, 1961). Succinic acid and citric acid have been used to enhance the dissolution of griseofulvin (Ghosh, Sharma and Boruah, 2018). However, this class is thermodynamically unstable.

2.12.2 Second generation solid dispersions

Because of thermodynamic instability of first generation solid dispersions, second generation solid dispersions were introduced using amorphous polymeric carriers (Tran *et al.*, 2019). They have been considered as the major advancement in overcoming limited aqueous solubility and oral absorption issues (Baghel, Cathcart and O'Reilly, 2016a). The amorphous state of carriers improves drug release. They include fully synthetic polymers such as; polyvinyl pyrrolidone (PVP), polyethylene glycols (PEG) and polymethacrylates. Natural product based polymers which mainly consist of cellulose derivatives such as; hydroxypropyl methylcellulose (HPMC), ethyl

cellulose, hydroxypropyl cellulose or starch derivates like cyclodextrins (Kumar, 2017; Mir and Khan, 2017; Kesharwani *et al.*, 2018).

2.12.3 Third generation solid dispersions

Single solubilization strategies are often inefficient and uneconomic compared to combination approaches (Williams *et al.*, 2013). Ternary solid dispersions are gaining greater utility and achieve the greatest increase in bioavailability (Prasad *et al.*, 2017). The carriers are often surface active, self-emulsifying or contain a mixture of polymers/ surfactants. Surfactants reduce surface tension, are wetting agents, re-crystallization inhibitors, detergents, emulsifiers, foaming agents, and dispersants e.g. Poloxamer 408, Tween 80, and Gelucire 44/14 (Kumar, 2017; Mir and Khan, 2017; Kesharwani *et al.*, 2018; Tran *et al.*, 2019). However, the surfactant must be carefully selected as it can interact with polymer and thereby increase the recrystallization of drugs (Chaudhari and Dugar, 2017).

2.12.4 Carrier materials for solid dispersions

Carriers used in solid dispersions produce a solubilization effect (Mehta *et al.*, 2014; Ghosh, Sharma and Boruah, 2018). Therefore, the choice of a carrier has a huge determination on the dissolution rate of the solid dispersion. Water soluble carriers enhance dissolution while poorly water-soluble carriers retard dissolution. Thus when the minor component of the matrix is the poorly soluble drug in a highly water soluble carrier, its dissolution is greatly enhanced (Mir and Khan, 2017; Ghosh, Sharma and Boruah, 2018). The ideal characteristics of a suitable carrier are enumerated in Box 1.

Box 1: Criteria for suitable carrier to increase the solubility/dissolution rate of a drug (Mir and Khan, 2017).

1. Freely water-soluble with intrinsic rapid dissolution properties.
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in different solvents and pass through a vitreous state upon solvent evaporation. Preferably able to increase the aqueous solubility of the drug.
5. Chemically compatible with the drug and should not bond strongly with the drug.

2.13 Types of solid dispersions

2.13.1 Simple eutectic mixtures

Eutectic mixtures were the first type of solid dispersions to be prepared. They consist of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. One of the components is sparingly water-soluble drug while the other is a highly water-soluble carrier. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution (Chivate *et al.*, 2012; Mir and Khan, 2017) the two components are melted at a single temperature known as the eutectic point which is lower than that of both components (Tran *et al.*, 2019). When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which gets solubilized rapidly. The increase in surface area is mainly responsible for increased rate of dissolution (Kumar, 2019).

2.13.2 Solid solution

They consist of a solid solute dissolved in a solid solvent (Chivate *et al.*, 2012) to form a single phase mixture independent of the number of components in the mixture. The particle size of the drug is reduced to an absolute minimum with the dissolution rate a factor of the dissolution rate of the carrier (Mir and Khan, 2017). Solid solutions are generally prepared via solvent evaporation or co-precipitation method (Kumar, 2019). Complete miscibility results in continuous solid solutions while discontinuous solid solutions have limited miscibility. They can further be classified into substitutional solid solutions where solute molecules substitute for solvent molecules in the lattice or interstitial solid solutions where the solute occupies the interstitial space within the lattice (Mir and Khan, 2017; Kumar, 2019; Tran *et al.*, 2019).

2.13.3 Glass solution/suspension

They are a homogeneous supersaturated amorphous system in which the drug molecule is dissolved in a glassy solvent. Glass suspension is a homogeneous system in which the drug molecule is suspended in a glassy solvent. Glass solutions and suspensions have low lattice energy with the glassy state characterized by transparency and brittleness below the glass transition temperature for both glass solutions and glass suspensions (Mir and Khan, 2017; Kumar, 2019; Tran *et al.*, 2019). However, they have poor processing ability due to their sticky nature (Karagianni, Kachrimanis and Nikolakakis, 2018).

2.14 Manufacturing methods of solid dispersions

The methods used in manufacturing of solid dispersions are shown in Figure 2.3 below.

Figure 2.3: Manufacturing methods of solid dispersions (Tran et al., 2019).

2.14.1 Kneading and co-grinding method

The carrier is dispersed in water and processed into a paste. Then, the drug is added and kneaded thoroughly. The final kneaded formulation is dried and passed through a sieve if necessary (Tran *et al.*, 2019). In co-grinding. physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill, steel balls are added and the powder mixture is then pulverized (Ghosh, Sharma and Boruah, 2018).

2.14.2 Melting method

Introduced by Sekiguchi and Obi it is the prototype solid dispersion method with pharmaceutical application. The drug and hydrophilic carrier are molten above the eutectic temperature, they are then rapidly cooled and solidified in an ice bath under vigorous stirring followed by pulverization to form a powder (Mir and Khan, 2017; Kumar, 2019). It is simple and economical but requires components that are miscible and compatible at the heating temperature. Phase separation and

thermolabile components are sources of instability. These drawbacks can be overcome by heating under vacuo or inert gas plus rapid cooling to prevent phase transitions (Chivate *et al.*, 2012).

In Melt agglomeration a binder acts as a carrier. The components are heated above the melting point of the binder or a dispersion of the drug is sprayed onto the heated binder (Tran *et al.*, 2019). A rotary processor allows for; better temperature control, incorporation of higher binder content in the agglomerates and homogenous drug distribution in formed agglomerates (Ghosh, Sharma and Boruah, 2018).

In hot melt extrusion, amorphous solid dispersions are formed without solvent, avoiding residual solvents in the formulation. It is a combination of the melting method and extrusion, in which a homogeneous mixture of drug, polymer, and plasticizer is melted and then extruded through the equipment (Tran *et al.*, 2019). Elevated temperatures are transient (1 min) thus suitable for thermolabile drugs (Mir and Khan, 2017). Extrudate can be modified to any shape desired (Kumar, 2019). Polymers with operable viscosity, thermoplastic character and suitable glass transition temperature (T_g) in the range of 50–180 °C are crucial for HME. The process is often run at a temperature 20–40 °C above the T_g but for thermostable drugs they can be undertaken above the melting point (T_m) of the API (Liu *et al.*, 2013). Plasticizers are often employed to modify polymer properties as they reduce the T_g and melt viscosity facilitating the extrusion process (Jani and Patel, 2014).

2.14.3 Solvent evaporation method

The drug and carrier are dissolved in a volatile solvent for homogeneous mixing. The solution is evaporated under constant agitation followed by crushing and sieving of the obtained solid. Thermal decomposition of drugs or carriers is prevented due to low boiling point of organic solvents. Therefore, very high melting point carriers can be used (Ghosh, Sharma and Boruah, 2018; Tran *et al.*, 2019). They have increased porosity that enhances dissolution compared to SDs prepared through melting methods (Bouchal *et al.*, 2015). However, the added step of removal of solvent increases their cost, residual solvents give rise to possible adverse effects, reproducibility is difficult, selecting a common low toxicity solvent is challenging and residual solvent can cause chemical instability (Chivate *et al.*, 2012). The limitations are overcome through; evaporation under vacuo, freeze drying for rapid solvent removal or use of an azeotropic mixture of solvent in water to overcome solvent selection dilemma (Kumar, 2019).

Spray drying is useful for drugs soluble in at least one volatile solvent (Huang and Dai, 2014).The drug is dissolved in a suitable solvent, and the carrier is dissolved in water to prepare the feed solution. Then, the two solutions are mixed by sonication or other suitable methods until the solution is clear. The feed solutions are then sprayed in a drying chamber that is under vacuum via a high-pressure nozzle to form fine droplets. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, fast

enough to prevent phase separation from taking place and forming particles of nano or micro size (Ghosh, Sharma and Boruah, 2018; Kumar, 2019; Tran *et al.*, 2019).

Through lyophilization, drug and carrier are co-dissolved in a common solvent, frozen often in liquid nitrogen and sublimed to obtain a lyophilized molecular dispersion. The advantage of freeze drying is the minimal thermal stress with the risk of phase separation minimized as soon as the solution is vitrified (Mir and Khan, 2017; Kumar, 2019).

Introduced in late 1980s and early 1990s. Supercritical fluid is a solvent free method where the drug and carrier are dissolved in a supercritical solvent (e.g., CO_2) and sprayed through a nozzle into an expansion vessel with lower pressure. Rapid expansion induces rapid nucleation of the dissolved drugs and carriers, leading to the formation of solid dispersion particles with a desirable size distribution in a very short time. Supercritical fluid can be performed by several methods such as; rapid expansion from supercritical solution (RESS), gas antisolvent (GAS), supercritical antisolvent (SAS), and solution enhanced dispersion by supercritical fluid (SEDS) (Mir and Khan, 2017; Kumar, 2019; Tran *et al.*, 2019).

Co-precipitation is useful for drugs with high melting point and low solubility in common organic solvents (Huang and Dai, 2014). The carrier is first dissolved in solvent to prepare a solution, and the drug is incorporated into the solution with stirring to form a homogeneous mixture. Then, water is added dropwise to the homogenous mixture to induce precipitation. With the drug and carrier co-precipitated to form micro particles. Finally, the precipitate is filtered and dried (Kumar, 2019; Tran *et al.*, 2019).

2.14.4 Melting solvent method

It combines the both the solvent and melting method. Where drug is dissolved in a suitable liquid solvent and then incorporated into the melt of polyethylene glycol, the solvent is then evaporated until a clear, solvent free film is left. It is useful for thermolabile drugs or those with high melting points. However, poor miscibility of drug or solvent in PEG melt, polymorphic transitions triggered by solvent and the necessity of low drug loading (below 50 mg) limits its use. (Chivate *et al.*, 2012; Mir and Khan, 2017; Ghosh, Sharma and Boruah, 2018).

2.15 Stability of solid dispersions

One of the critical drawbacks associated with this technology is the lack of physical stability. Recrystallization or phase separation occurs limiting a product's shelf life (Lu *et al.*, 2015; Chavan *et al.*, 2019). Therefore, crystallization tendency must be monitored during processing, storage and handling as it is detrimental to bioavailability (Chavan *et al.*, 2019). Polymers with high T_g, incorporation of surfactants, absence of water, drug- polymer miscibility and strong drug-polymer interactions improve stability of solid dispersions (Qian, Huang and Hussain, 2010; Chaudhari and Dugar, 2017; Xie and Taylor, 2017).

A single distinct T_g of amorphous solid dispersions is an indicator of the mixing uniformity and stability (Qian *et al.*, 2010). Hygroscopic polymers lead to immiscibility as drug polymer interactions are disrupted resulting in phase separation followed by crystallization (Marsac *et al.*, 2010). Loperamide is less susceptible to crystallization due to its intrinsic good glass forming properties (Weuts, Kempen, Decorte, *et al.*, 2005).

2.16 Glass transition temperature

The glass transition temperature (T_g) is the temperature measured by DSC at or above which the molecular structure exhibits macromolecular mobility, at which the transition between glassy and rubbery state occurs (Crawford and Throne, 2002; Meng and Zhang, 2013; Domínguez, 2018). It is a property of amorphous materials or the amorphous portion of semicrystalline materials. The glass transition temperature plays a critical role in determining the storage conditions of solid dispersions. In order to slow down the molecular mobility of amorphous materials, a rule of thumb is that the storage temperature of such materials should be 50 K lower than their T_g (T_g – 50 rule). Anti-plasticizing polymers are often used to raise the T_g of the resultant amorphous systems (Lin *et al.*, 2018; Qiang *et al.*, 2020).

Where dramatic changes in polymer chain mobility occur as a function of temperature. Below T_g, the molecular chains of amorphous materials are frozen in place and behave like solid glass. Semicrystalline polymers begin to soften above T_g, however, they do not demonstrate fluid behavior until the T_m range is achieved as shown in Figure 2.4 (Shrivastava, 2018; Bhushan and Kumar, 2019). Loperamide exhibited a $T_{g\ of}$ 121 ^{o} C following high velocity ball milling (Woodhead, 2014).

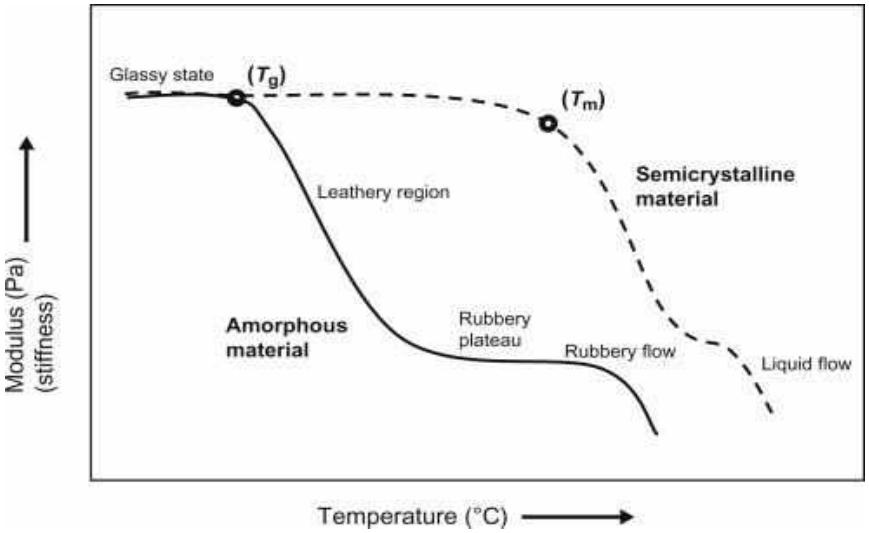

Figure 2.4: Melting and softening behavior of amorphous and semicrystalline materials (Shrivastava, 2018).

2.17 Quality by design in pharmaceutical process development

Quality by Design (QbD) is a concept outlined by Joseph M. Juran who believed that quality could be planned and that most quality crises and problems related to the way in which quality was planned (Jani and Patel, 2014). Quality by testing (QbT) involved extensive testing and minimal process flexibility that led to frequent unexplained batch failures. While an approved design space in QbD offers operational flexibility (Patil, Tiwari and Repka, 2016). QbD employs a systematic risk-based, proactive approach to pharmaceutical development whose outset begins with predefined objectives and follows a risk based approach centered on process understanding, control and sound science to guide process development to yield a product with predefined specifications (Basalious, El-Sebaie and El-Gazayerly, 2011).

Process development necessitates understanding of variables and their interaction as they influence critical product attributes. The different elements of QbD are shown in Figure 2.5. A statistics-based design of experiment (DoE) supports the development work and manages the relationship between the input and output variables. Essential elements of the pharmaceutical development are the quality target product profile (QTPP), the critical quality attributes (CQA), the critical material attributes (CMAs) and the critical process parameters (CPPs). Through relating the critical material attributes and critical process parameters (CPP) to the critical quality attributes (CQAs) of drug product a product of predetermined specifications and quality is prepared (Basalious, El-Sebaie and El-Gazayerly, 2011; Simões, Pinto and Simões, 2019).

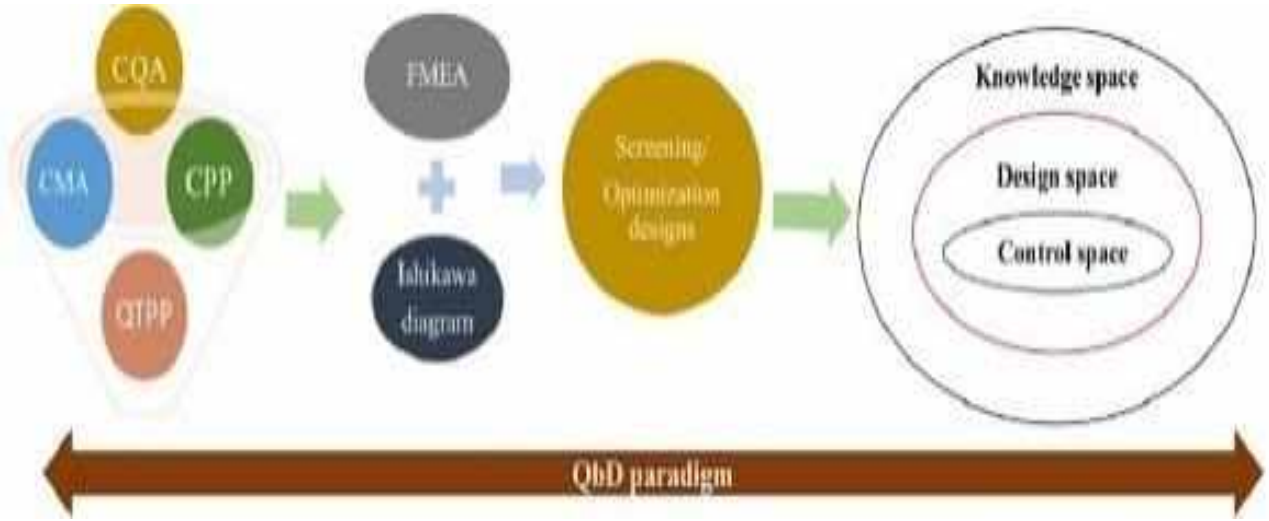

Figure 2.5: QbD process design (Butreddy, Bandari and Repka, 2021).

CHAPTER 3 : METHODOLOGY

3.1 Study design

The study design was a laboratory based comparative study.

3.2 Study location

The experiments were carried out at the Department of Pharmaceutics and Pharmacy Practice as well as at the Drug Analysis and Research Unit in the University of Nairobi.

3.3 Materials

Loperamide HCl was a kind donation from Biopharma Limited. USP reference standard Loperamide HCl was a kind donation from Mission for Essential Drugs and Supplies, Loperamide working standard was received as a kind donation from Laboratory and Allied. Other materials include PEG 4000, PVP k12, acetic acid, sodium hydroxide pellets, hydrochloric acid, ethanol, acetonitrile, methanol and orthophosphoric acid all of analytical grade were used.

3.4 Equipment

Dissolution tester (Electrolab), attenuated total reflectance ATR FTIR (Perkin Elmer Spectrum Two), High performance liquid chromatography-Photo diode array (PDA) (Shimadzu Nexera), potentiometric autotitrator (Titroline 6000), Ramtons hotplate, analytical balances, sieve mesh 50 µm, UV spectrophotometer (Spectrum SP-UV 500DB), mercury thermometer, were used during formulation and analysis.

3.5 Test for identity

Identity test was carried out using FTIR spectroscopy with comparison of spectra produced using Loperamide hydrochloride chemical reference substance (CRS). Any spectral differences were noted, with similar / superimposable spectra indicating a positive identification of the drug.

3.6 Loperamide Ishikawa fishbone

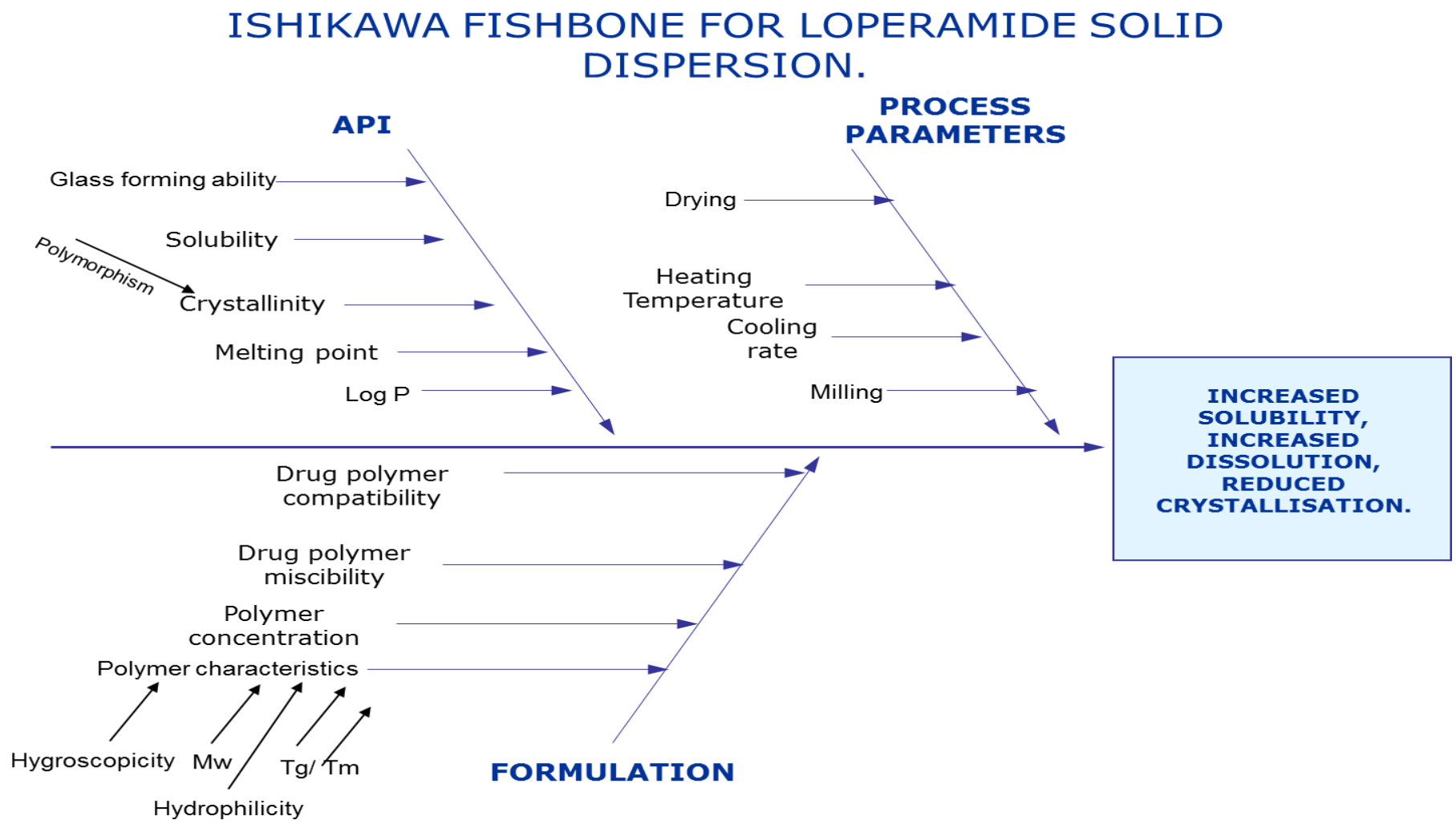

Figure 3.1: Ishikawa Fish diagram for preparation of solid dispersion.

3.7 QbD guided development of loperamide solid dispersion

Figure 3.2: Quality by Design (QbD) process flowchart.

QbD provides a risk based systematic process for formulation development. The QTTP provided the basis for the formulation and design, it envisions the final product and guided the QbD process that is displayed in Figure 3.2. The selected elements of the QTTP based on the desired character of the drug product are shown in Table 3.1 describing the expected output and justification for the parameters chosen. A risk-based system outlined by the Ishikawa fish bone (Figure 3.1) and section 3.7.1 was used in formulation development to ensure that the QTTP was attained using a scientific step wise approach to formulation.

Table 3.1: Loperamide solid dispersion quality target product profile (QTTP).

QTTP element	**Target**	**Justification**
Dosage form	Powder	Flexibility to prepare oral suspension, tablets, capsules.
Dosage design	Immediate release	Pharmaceutical equivalence.
Strength	2 mg	Pharmaceutical equivalence.
Stability	Stable at Accelerated stability conditions (40 ^{o} C, 75% RH) for 3 months	For stability determination of whether the formulation is stable.
Drug product quality attributes	Appearance Identification Dissolution Crystallinity	Quality indicating parameters.

To form a quality product the quality specifications of the SDs had to be defined as they affect the formulation development and selection of excipients. The CQA as shown in Table 3.2 was developed to characterize the desired quality attributes of the drug product (Sangshetti *et al.*,

2017). The attributes were ranked based on a risk ranking system (section 3.7.1) and Table 3.3 to ensure the key quality attributes were either controlled or tested.

Table 3.2: Solid dispersion critical quality attributes (CQA).

Quality attribute	**Target**	**Is this a CQA?**	**Justification**
Appearance	powder	Yes*	The color of povidone and polyethylene glycol darkens upon heating showing decomposition and weight loss. Brittleness of cooled melt shows drug is below its glass transition temperature.
Identification	Positive for loperamide	Yes*	A critical parameter though is managed through FTIR comparison with chemical reference standard prior to analysis. Therefore, there is no need to monitor during the study.
Dissolution	NLT 80% at 30 minutes	Yes	A critical parameter affecting bioavailability, therefore must be monitored and will be investigated based on specifications in the United States pharmacopeia (USP).
Moisture content	Low Humidity	Yes*	Water has a plasticizing effect on solid dispersions. Moisture is however controlled in the product through a desiccator thus further investigation is not warranted.
Crystallinity	Reduced crystallinity	Yes	Increased amorphicity is indicant of increased solubility. Will be investigated through FTIR analysis.

- CQAs such as Appearance, moisture content, identification are important variables though they will not be investigated as control strategies were employed to limit or control their effect on product quality, they are likely not to impact CQA of solid dispersions.

The risk ranking system outlined in section 3.7.1 was used throughout the QbD process to ensure a quality product was produced by selection of parameters that have a greater probability to influence product quality tested and their risk mitigated.

3.7.1 Risk ranking system

Low	Broadly Acceptable risk, no further investigation required.
Medium	Risk is acceptable, further investigation may be required to reduce risk.
High	Risk is unacceptable, further investigation needed to reduce risk.

Table 3.3: Critical quality attribute risk ranking system.

3.7.2 Critical material attributes (CMA)

Understanding of material attributes was used to guide process development. Loperamide has a log p of 4.77 which is borderline with materials described as having good ADME and physicochemical properties (more than 1 but less than 4) (Gao, Gesenberg and Zheng, 2017). Glass forming ability obtained via the Hruby parameter is the ability of a material to vitrify from its melted state upon cooling. Good glass formers have been identified as those having a molecular weight of more than 300 g/mol. With crystallization tendency greater for poor glass formers (Baird, Van Eerdenbrugh and Taylor, 2010; Mahlin and Bergström, 2013; Alhalaweh *et al.*, 2014; Kawakami, 2019). Loperamide HCl with a Mw of 513.5 g/mol is further classified as a class III glass former which is significant as it can be quench cooled at a lower rate compared to class I glass formers maintaining its amorphicity (Alhalaweh *et al.*, 2014). Risk assessment of the drug substance was done as shown in Table 3.4 below with the justification for the ranking given elucidated further in Table 3.5.

Table 3.4: Risk assessment of drug substance attributes on CMAs.

Drug product CQA	**Drug Substance Attributes**					
	Solubility	**Melting point**	**Lipophilicity**	**Glass forming ability**	**polymorphism**	**Hygroscopicity**
Crystallinity	High	Low	Medium	Low	High	Low
Dissolution	High	Low	Medium	Low	High	Low

Table 3.5: Justification for Risk assessment.

Drug substance attributes	**Drug product CQA**	**Justification**
Solubility	Dissolution	Solubility is a factor of dissolution; thus, API solubility influences its dissolution. Inherent drug solubility of LPM (0.00086 mg/mL at 20°C) will affect the solubility characteristics of the product. Risk is high. Formulation into solid dispersion will mitigate this risk.
	Crystallinity	Reduction in crystallinity in favor of amorphicity signifies an increase in solubility due to the higher energy of the amorphous form, highly crystalline drugs are less soluble than amorphous drugs. Risk is high. Formulation into solid dispersion will mitigate this risk.
Melting point	Dissolution	The high melting point of drug has no effect on its dissolution, thus will not affect product solubility. Risk is low.
	Crystallinity	Substance has a high melting point; thus, melting point plays a diminished role in drug crystallinity. Risk is low.
Lipophilicity	Dissolution	Lipophilicity has influence on drug dissolution, though its value approaches ideal value for best physicochemical and ADME properties, parameter cannot be

		modified directly therefore the risk is Medium. Risk will be mitigated through excipient selection.
	Crystallinity	Affects choice of excipients used to formulate the product. Risk is medium. Risk will be mitigated through excipient selection.
Glass forming ability	Dissolution	Plays a critical role in dissolution as the formation of glass and its maintenance is inherently linked to dissolution. Loperamide has good glass forming ability thus risk is Low.
	Crystallinity	Maintenance of glassy state is vital for viability or maintenance of performance during product shelf life. Loperamide has good glass forming ability thus risk is Low.
Polymorphism	Dissolution	Stable polymorph I which is anhydrous is the predominant form, conversion of this polymorph to the amorphous form is part of the formulation process. Risk is high Formulation process will be used to mitigate this risk.
	Crystallinity	
Hygroscopicity	Dissolution	Loperamide is non hygroscopic. Risk is low.
	Crystallinity	

Parameters assessed and found to be high and medium i.e., solubility, lipophilicity and polymorphism were further investigated.

3.7.3 Justification of excipient selection

Despite extensive research selection of carries for solid dispersions is complex due to difficulty in prediction of the resultant physical stability, phase behavior and dissolution rate (Van Duong and Van den Mooter, 2016). Polymers were assessed using the 6th edition of the handbook of

pharmaceutical excipients, to screen for incompatibilities and any safety concerns. The polymers were found suitable for development of LPM SDs.

PVP is used for immediate release formulations as it is water soluble and a recrystallisation inhibitor. Solid dispersions with PVP generally exhibit increased dissolution rates and drug solubilities compared to the parent compound. PVP k12 is a high T_g polymer shown to increase dissolution with increasing concentration (Knopp et al., 2015). It is more suitable for preparation by the solvent method compared to the melt method because it decomposes at around 180 ^{o} C in air (Chivate *et al.*, 2012; Rahman *et al.*, 2013; Ghosh, Sharma and Boruah, 2018). PVP k12 has a Mw of 2000-3000 with a T_g of 90 (Kolter and Gryczke, 2012). The solubility of the higher Mw PVPs reduces due to an increase in melt viscosity which also reduces its processability (Chivate *et al.*, 2012; Alsulays *et al.*, 2015; Knopp *et al.*, 2015). High polymer fractions in SDs have resulted in absence of crystallinity and high drug solubility. Spray dried formulations of Loperamide with PVP k30 and PVP-VA64 were completely amorphous, however the PVP k30 exhibited high hygroscopicity at humid conditions (Weuts *et al.*, 2004; Weuts, Kempen, Verreck, *et al.*, 2005; Ghosh, Sharma and Boruah, 2018).

PEG is semicrystalline having both crystalline and amorphous domains. With good glass formers such as LPM the polymer recrystallisation tendency can be arrested (Ibrahim, 2009; Nair *et al.*, 2020). PEGs of Mw 4000-6000 have low hygroscopicity and melting point of around 50 ^{o} C making them suitable for formulation of solid dispersions especially by the melt method. Additionally, they do not form sticky products compared to the relatively lower PEGs. A high PEG fraction reduces SDs crystallinity increasing its dissolution (Bartsch and Griesser, 2004; Ghosh, Sharma and Boruah, 2018). However, the concentration increase is only up to an optimum amount after which no additional dissolution improvement is achieved (Adeli, 2016). PEG solid dispersions are limited by their physical stability. Despite increasing dissolution, at elevated temperature and humidity, a crystallization tendency with reduction in dissolution was observed in a Loperamide and PEG 6000 SD (Weuts, Kempen, Verreck, *et al.*, 2005).

Surfactants have a solubilizing effect and increased wetting in solid dispersions (Mura *et al.*, 2005). They act as plasticizers with the beneficial effect of reducing product melt viscosity increasing its extrudability (Ghebremeskel, Vemavarapu and Lodaya, 2007). Surfactants increase dissolution when their concentration is above their critical micelle concentration (CMC). Anionic surfactants have the greatest solubilization effect. SLS is often used to enhance solubility of poorly-soluble drugs (Jin *et al.*, 2021) thus it was selected at its CMC of 8.1 mM (Stanley *et al.*, 2009; Williams, Trevaskis and Charman, 2013; Gowardhane, Kadam and Dutta, 2014).

3.8 Group contribution method and its use in estimating properties of polymers

Mathematical methods have proved helpful in excipient screening as predictive tools for miscibility. Group contribution methods (Equation 3.1) as postulated by Hildebrand are often used to determine properties of polymers as it is presumed that the effect of each group is additive upon

the compound. Its simplicity allows for the profiling of many groups of compounds. However, it has some variation with the polar and hydrogen bonding components determined by experimental trial and error yielding different results thus its nature is more qualitative (Welker, 2012; Fink, 2013; Walden *et al.*, 2021). It is a good tool for preformulation but for accuracy should be backed up with experimental data (Medarević *et al.*, 2019).

$$F = \sum_{i} niFi$$

Equation 3.1: Group contribution equation (Medarević et al., 2019).

Where F is the group value for a property F, n_i is the number of groups of type i and F_i is the corresponding group value

$$\delta = (E_{coh})^{1/2} = \left(\frac{\Delta Hvap - RT}{V}\right)^{\frac{1}{2}}$$

Equation 3.2: Hildebrand solubility parameter (Gao, 2014).

where E_{coh} is the cohesive energy density
; ΔH_{vap} is the heat of vaporization; R is the universal gas constant; T is the absolute temperature; and V_m is the molar volume.

The solubility parameters of different polymers are calculated using Equation 3.2. The total Hildebrand solubility parameter as shown in Equation 3.3 and extended by Hansen (Burke, 1984) is obtained by addition of the three types of polar interactions: dispersion, polar and hydrogen interactions.

$$\delta_t^{2=} \delta_d^{2+} \delta_p^{2+} \delta_h^{2}$$

Equation 3.3: Hansen solubility calculation (Burke, 1984).

where;

- $\delta_t^{2=}$ Total Hildebrand parameter
- $\delta_d^{2=}$ dispersion component
- $\delta_p^{2=}$ polar component
- $\delta_h^{2=}$ hydrogen bonding component

3.8.1 Calculation of solubility parameter for loperamide

Hoftyzer- Van Krevelen reference values were used to calculate the solubility parameter of LPM using Equation 3.4 below via the group contribution method (Gardon and Teas, 1976).

$$\delta h = \sqrt{\frac{\sum Ehi}{V}}$$

$$\delta p = \frac{\sqrt{\sum F^2 pi}}{V}$$

$$\delta d = \frac{\sum Fdi}{V}$$

Equation 3.4: Hoftyzer- van Krevelen group contribution method (Baghel, Cathcart and O'Reilly, 2016b).

where E_{hi}, F_{pi}, and F_{di} are the molar group attraction constants due to hydrogen-bonding, polar, and dispersion components, respectively, and V is the molar volume.

The contribution of each group to the total solubility parameter of LPM is summarized in Table 3.6. With the total parameter used to calculate the drug-polymer miscibility (Table 3.8) and the drug-polymer interaction parameter (Table 3.10).

Table 3.6: Calculation of solubility parameter of Loperamide using Hoftyzer and Van Krevelen reference values.

Groups	**F_{di}**	**F^2_{pi}**	**E_{hi}**	**$\sum^z V/cm^3mol^{-1}$**
2 -CH3	840	0	0	67
6 CH2	1620	0	0	96.6
2 >C<	-140	0	0	-28.4
2-Phenyl	2860	24,200	0	104.8
1-subd phenyl	1270	12,100	0	52.4
2 –N<	40	1,280,000	10,000	-18
1 -Cl	450	302,500	400	28
1-COH	470	640,000	4500	10
1 C= O	290	592,900	2000	10.8

3 rings	570	-	-	48
∑	8270	2851700	16,900	361.2
	8270/361.2	√2851700/361.2	√ (16,900/361.2)	
	δd =22.89	δp =4.68	δh =6.84	
	$\delta_t^{2=} \delta_d^{2+} \delta_p^{2+} \delta_h^2$			
δt	24.34			

To ascertain the level of miscibility Table 3.7 and 3.8 below were used to calculate miscibility based on the difference between solubility parameters of the API and the polymer in the mixture. Miscibility plays a key role as highly miscible systems are more resistant to drug crystallization (Baghel, Cathcart and O'Reilly, 2016a; Venkatram *et al.*, 2019; Walden *et al.*, 2021).

Table 3.7: Solubility parameters evaluation criteria (Walden et al., 2021).

$\Delta\delta$ **API-polymer**	**Miscibility**
< 7 $MPa^{1/2}$	Miscible
7-9 $MPa^{1/2}$	Borderline miscible
> 10 $MPa^{1/2}$	Immiscible

Table 3.8: Materials solubility parameters and their calculated estimated solubility with respect to Loperamide.

Material	**Solubility parameter**	**Difference in relation to API**
Loperamide	24.34	0
PEG 4000	20.40	3.94
Povidone K12	19.40	4.94
Sodium lauryl sulphate	17.07	7.27

The calculated solubility parameters (Table 3.8) indicate that there is good miscibility between loperamide and the two polymers i.e., PEG 4000 and PVP k12. While in the case of SLS there is borderline miscibility.

Table 3.9: Materials solubility parameters and their calculated estimated solubility with respect to Sodium lauryl sulphate.

Material	**Solubility parameter**	**Difference in relation to API**
Sodium lauryl sulphate	17.07	0.00
Povidone K12	19.40	2.33
PEG 4000	20.40	3.33

Table 3.9 above suggests that surfactant SLS will tend to aggregate more towards the polymers compared to the API based on the results yielded. The table was used to evaluate the effect of surfactants based on their miscibility as internal surfactants have a different character to external

3.8.2 Flory-Huggins parameter for drug-polymer blends

Estimation of Flory Huggins parameters from Hansen's solubility was done using Equation 3.5. The parameter evaluates the drug-polymer interaction. A negative as well as slightly positive X values correlate with ease of mixing due to reduction in free energy (Ousset *et al.*, 2018).

$$X = 0.34 + \frac{V_{drug}}{RT} \times (\partial_{drug} - \partial_{polymer})^2$$

Equation 3.5: Flory-Huggins parameter (Ousset et al., 2018).

Where R is the molar gas constant

T is room temperature in kelvin (K)

V is the molar volume of drug

∂ is the Hansen solubility parameter for drug or polymer

X is the Flory Huggins interaction parameter

Table 3.10: Loperamide- polymer miscibility based on Flory Huggins Method.

Material blend	**Flory Huggins parameter**	**Comments**
LPM- PEG 4000	2.60	Positive value, low interaction
LPM-PVP K12	3.90	Positive value, low interaction
LPM-SLS	8.05	Large positive value, lower interaction

A positive value obtained from the Flory Huggins parameter as shown in Table 3.10, indicates that the polymer tends to self-associate rather than to interact with the API. A relatively larger positive value for PVP K12 indicates that PEG preferentially has better interaction and hence solubility compared to PVP k12. The Large positive value calculated with SLS indicates low miscibility, hence the SLS would be more inclined to self-associate or to associate with the polymer compared to the API (Jarray *et al.*, 2016).

3.9 Prediction of glass transition temperature of drug polymer blends fox equation

The Fox equation (Equation 3.6 below) was used to predict the glass transition temperature of the drug-polymers blend. The predicted weight ratios were used as a measure of stability based on the stability rule of thumb (i.e., storage temperature should be 50 K below the T_g). The T_g of the API and polymers utilized are summarized in Table 3.11.

Table 3.11: Glass transition temperatures (T_g) of materials obtained from literature (Kolter and Gryczke, 2012; Woodhead, 2014).

Material	**T_g (° C)**
Loperamide hydrochloride	121
PEG 4000	-22.37
PVP k12	90

The values in Table 3.12-3.13 are calculated from the Fox equation:

$$\frac{1}{Tg} = \frac{w1}{Tg1} + \frac{1 - w1}{Tg2}$$

Equation 3.6: Fox equation (Brostow et al., 2008).

Where w1 is the weight fraction of component 1

1- w1 is the weight fraction of component 2

Tg1 is glass transition temperature of component 1 (K)

Tg2 is glass transition temperature of component 2 (K)

Tg is the glass transition temperature of the polymer mix (K)

The predicted glass transition temperatures shown in Table 3.12 (PEG 4000) and Table 3.13 (PVP k12) were used to select the polymer range for study.

Table 3.12: Predicted glass transition temperature of polymer blends at different drug and PEG 4000 ratios using Fox equation.

Design Table			
Run	**Loperamide Hcl (%w/w)**	**PEG 4000 (%w/w)**	**T_g predicted (^{o} C)**
1	1.00	0.0	121
2	0.9	0.1	99
3	0.8	0.2	80
4	0.7	0.3	63
5	0.6	0.4	47
6	0.5	0.5	33
7	0.4	0.6	20
8	0.3	0.7	9
9	0.2	0.8	-2
10	0.1	0.9	-13
11	0.0	1.0	-22

Experimental studies were undertaken at 50-83.3 % w/w PEG levels. Figure 3.3 shows that increasing concentrations of PEG significantly lowers the polymer blend T_g with expected T_g between -2 to 33 ^{o} C. The low glass transition temperatures pose a stability concern as they are well below the recommended storage temperature.

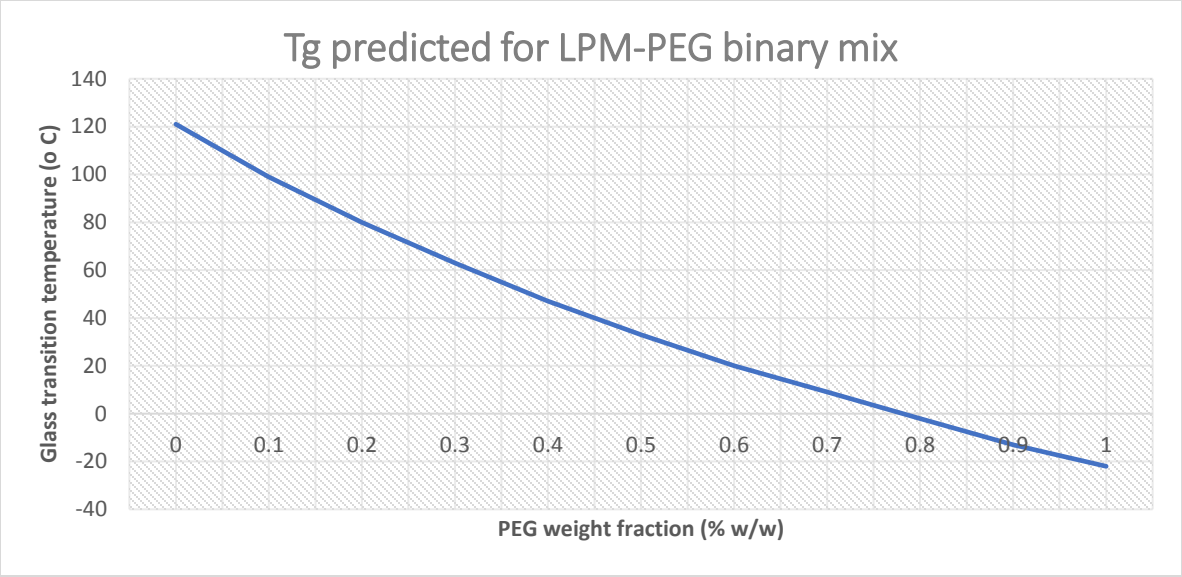

Figure 3.3: Predicted glass transition temperatures at different PEG 4000 weight ratios (%w/w).

The predicted T_g of the LPM-PVP blend at different weight ratios (Table 3.13) was used to select the polymer concentration range as well as to predict the T_g of the resultant SD and hence its stability.

Table 3.13: Predicted glass transition temperature of polymer blends at different drug and PVP k12 ratios using Fox equation.

Design Table			
Run	**Loperamide Hcl (%w/w)**	**PVP k12(%w/w)**	**T_g predicted (^{o} C)**
1	1.00	0.0	121
2	0.9	0.1	117
3	0.8	0.2	114
4	0.7	0.3	110
5	0.6	0.4	107
6	0.5	0.5	104
7	0.4	0.6	101
8	0.3	0.7	99

Design Table			
Run	**Loperamide Hcl (%w/w)**	**PVP k12(%w/w)**	**T_g predicted (° C)**
9	0.2	0.8	96
10	0.1	0.9	93
11	0.0	1.0	90

Experimental studies were undertaken in the polymer range 50-83.3% w/w. Increasing PVP concentrations slightly reduce the mixtures T_g. With expected glass transition temperature of between 96-104 ° C in the experimental range as shown in Figure 3.4 below

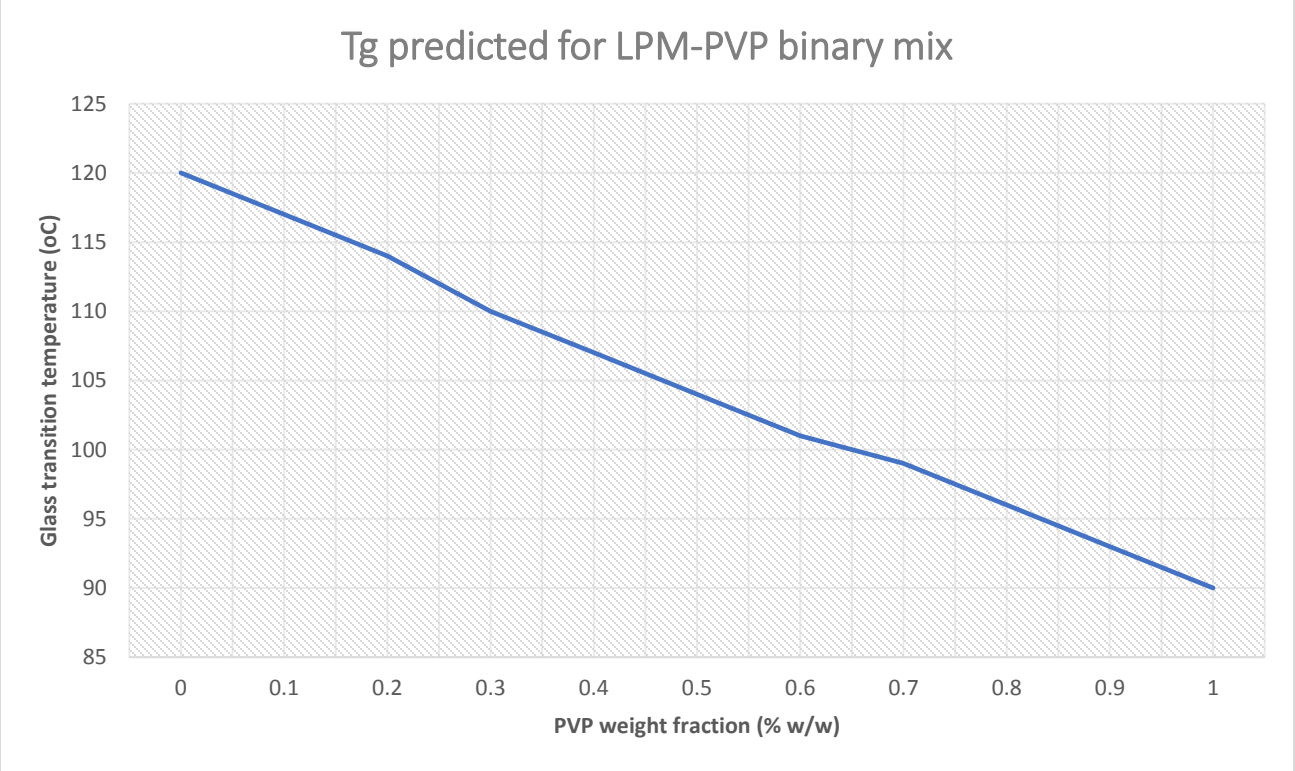

Figure 3.4: Predicted glass transition temperatures at different PVP k12 weight ratios (%w/w).

Based on the obtained T_g the PVP formulations were expected to be more stable than the PEG formulations. However, the model does not factor in the hygroscopicity of the materials, which upon absorption of water plasticizes the polymer blend reducing its T_g.

3.10 Formulation and process development

Risk assessment of formulation variables suggested in the Ishikawa fish bone diagram (Figure 3.1) was done as per Table 3.14.

Table 3.14: Risk assessment of formulation and process variables.

Drug product CQA	**Formulation variables**					
	Heating temperature	**Excipient choice**	**Drug polymer miscibility**	**Polymer weight fraction**	**Milling**	**Drying**
Dissolution	High	High	High	High	Medium	Medium
Crystallinity	High	High	High	High	Medium	Medium

The apportioned risk to each formulation variable was justified as shown in Table 3.15 below. With the variables found to be high and medium risk reasonably mitigated through the formulation process and predictive mathematical tools.

Table 3.15: Justification of risk assessment for formulation and process variables.

Formulation variable	**Drug product CQA**	**Justification**
Heating temperature*	Dissolution	Heating is carried out at the melting temperature of polymer and above its Tg. Polymers used are thermolabile degrading with weight loss. Therefore, the risk is high, mitigated by using a temperature monitored oil bath.
	Crystallinity	
Excipient choice	Dissolution	The choice of excipient affects the characteristics of formed SD. The risk is High and is mitigated by careful selection of excipients using the Ishikawa fish diagram.
	Crystallinity	
Drug polymer miscibility*	Dissolution	Drug polymer miscibility ensures SD stability and dissolution. Poorly miscible systems tend to phase separate or crystallize at the detriment of dissolution. The risk is high, therefore techniques such as Flory Huggins, Hansen

	Crystallinity	solubility parameters are used for excipient screening.
Polymer weight fraction	Dissolution Crystallinity	The ratio of the polymers compared to drug will impact the dissolution and crystallinity. The polymer fraction should be sufficient for miscibility and to significantly affect character of the formed matrix. Analytical balances were used to ensure accuracy of measurements, Risk is High.
Milling*	Dissolution Crystallinity	Particle size uniformity ensures dissolution can be attributed to the process rather than variable surface area available for dissolution. The risk is high, though will be mitigated through sieving to form a uniform particle blend.
Drying*	Dissolution Crystallinity	Water has a plasticizing effect leading to devitrification of SDs therefore risk is High but will be mitigated through placing in a desiccator.

- *Adequate process and formulation control variables are instituted to control these variables, reducing their overall effect on the quality attributes of the drug product. Therefore, these variables will not be further investigated during formulation study.

3.11 Process selection

A melt/fusion technique was employed in the preparation of the solid dispersions. The drug and polymer blend (1g) were heated to a temperature just above the melting temperature of the polymer and below its degradation temperature to form a fused melt. The solid was rapidly cooled by placing on an ice pack then stored in a desiccator for 24 hours to reduce any moisture that may have been absorbed during the process. The product was consequently pulverized and passed through sieve mesh 50 μm to give a uniform particle size distribution.

3.11.1 Formulations

Formulation development was done to produce Loperamide solid dispersions with increased dissolution and reduced crystallinity. Prepared dispersions were made in the following ratio 1:1,

1:2 and 1:5. To investigate the drug polymer ratio and its effect on the dissolution and crystallinity of loperamide solid dispersions.

8 solid dispersions were formulated according to Table 3.16 below;

Table 3.16: Composition of loperamide solid dispersions.

Drug-carrier ratio	**PEG 4000**	**PVP k 12**
1:1	B_1	B_4
1:2	B_2	B_5
1:5	B_3	B_6
1:5 With 2% w/w SLS	T_1	T_2

Controls (PM1 PEG and PM2 PVP) were prepared by triturating physical mixtures (1 g) of LPM- polymer mix at a ratio of 1:5 and passing them mixture through sieve mesh 50 μm. They were also stored in a desiccator.

3.11.2 Infrared spectroscopy study

FTIR spectroscopy was used to detect formation of new bonds between drug and polymer. The test samples of physical mixtures, loperamide hydrochloride, PVP k12, PEG 4000 and SLS were measured using ATR-FTIR. Where a small quantity sufficient to occlude, the orifice was added to the sample holder and analyzed. The measurements were recorded in terms of % transmittance in the wave number range of 450 to 4,000cm^{-1}. The FTIR spectra were checked for peak shifts, changes in transmittance and absence of peaks.

3.12 Crystallinity index

The crystallinity of a material is expressed as the crystallinity index (CI) which is inversely proportional to crystallinity. FTIR was used to calculate crystallinity through measuring relative peak heights via a tangent baseline method of those representing crystallinity to those not representing crystallinity within the same spectrum. Broad peaks point out to amorphicity while sharp peaks illustrate crystallinity. The peak at around 1624 was compared to the peak at around 1373 cm^{-1} using Equation 3.7.

$$K_i = a/b,$$

Equation 3.7: Calculation of crystallinity index (Razva et al., 2014).

where, K_i is the crystallinity index

a/b – ratio peak intensity

3.13 Potentiometric titration

Assay of the API used was done using the method specified in the British Pharmacopeia 2019. Through dissolving 0.400 g in 50 ml ethanol 96% R, then adding 5 ml of 0.01 M Hcl. The titrant added by an autotitrator was 0.1 M sodium hydroxide. With the volume added between the two inflexion points taken.

The equivalence: 1 ml of 0.1M standardized sodium hydroxide is equivalent to 51.35 mg of Loperamide hydrochloride

3.14 Loperamide calibration curve

Accurately weighed 50mg Loperamide hydrochloride was weighed and transferred in to 50 ml volumetric flask. Methanol was added to dissolve and made up to the mark to prepare stock solution with drug concentration of 1000 µg/ml. Which was further diluted with methanol to yield concentrations of 50, 100, 200, 300, 400, 500 µg/ml. The absorbance was measured at λ max of 248.8 nm using UV-VIS spectrophotometer against a blank of methanol.

3.15 Solid dispersion assay

Assay was done using UV spectroscopy at lambda max 248.8 nm. A weight equivalent to 25 mg of Loperamide was weighed and diluted with methanol R to yield solutions expected to contain 250 mcg/ml of loperamide which were subsequently assayed spectrophotometrically with a suitable blank.

3.16 Drug release profiles and modelling

Dissolution studies were done to evaluate change in dissolution characteristics of binary solid dispersion compared to reference market product, physical mixture and prepared ternary solid dispersions. Samples equivalent to 2 mg of loperamide were selected for dissolution studies. The

studies were conducted using type I (basket) USP dissolution apparatus with 500 ml acetate buffer pH 4.7 ± 0.05 as dissolution media. The temperature of the media was maintained at 37 ºC ± 0.5 and RPM set at 100. Samples were withdrawn at 5,10, 15, 30, 45 and 60 minutes. With the drug assayed spectrophotometrically at 220 nm.

The results from the in vitro study were fitted into DD solver software so as to obtain the drug release kinetics and modelling. With the dissolution data obtained characterized using Equation 3.8-3.9.

3.16.1 Mean dissolution time

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

where; where j is the sample number, n is the number of dissolution sample times, $t\hat{}_j$ is the time at midpoint between t_j and t_{j-1} (easily calculated with the expression $(t_j + t_{j-1})/2$) and ΔM is the additional amount of drug dissolved between t_j and t_{j-1}

Equation 3.8: Mean dissolution time (Lobo and Costa, 2001).

The mean dissolution time (Equation 3.8) reflects the time the drug takes to dissolve (Giri, 2013)

3.16.2 Dissolution efficiency

$$D.E. = \frac{\int_0^t y \times \mathrm{d}t}{y_{100} \times t} \times 100\%$$

where, y is the drug percent dissolved at time t.

Equation 3.9: Dissolution efficiency (Lobo and Costa, 2001).

Dissolution efficiency (Equation 3.9) is described as the area under the curve up to a specific time point. Expressed as a percentage of a rectangle describing 100% dissolution at the studied time, t.

The acceptance criteria were (Table 3.17) used for differentiating the different loperamide formulations, enabling selection of the best dissolution profiles and were derived from the DD solver excel add in.

Table 3.17: Acceptance criteria for model independent approaches.

Criterion	**Remarks**
Mean dissolution time (MDT)	The mean time drug takes to dissolve under dissolution conditions. The higher the value the more the polymer retaining capacity, is affected by polymer characteristics. It is directly proportional to dose and inversely proportional to solubility.
Dissolution Efficiency (DE)	The closer the value to 1 the greater the dissolution efficiency.
Mean residence time (MRT)	The residence time of the drug substance within the dosage form. The larger the value the greater is its retention within the dosage form.
Area under curve (AUC)	The larger the AUC the greater the cumulative drug release.

3.16.3 Dissolution profiles modelling

The dissolution data was analyzed using model dependent methods using the DDSolver excel add in. The data was fitted into the following mathematical models shown by Equation 3.10-3.15:

3.16.3.1 Zero order kinetics

The model described in Equation 3.10, suits modified release dosage forms and states that drug release is independent of concentration represented by the equation:

$$Q_t = Q_0 + K_0 t$$

Equation 3.10: Zero order kinetics model (Lobo and Costa, 2001).

where;

Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug and K_0 is the drug zero order release constant

3.16.3.2 First order kinetics

$$lnQ_t = lnQ_0 + K_1 t$$

Equation 3.11: First order release kinetics (Lobo and Costa, 2001).

Where; ln presents natural logarithm, Q_t is the quantity released at time t, Q_0 is the initial quantity of drug and K_1 is the first order release constant.

Pharmaceutical dosage forms following this model, release water soluble drugs from a porous matrix in such a manner that the quantity in the interior diminishes over time. A natural log straight line defined by Equation 3.11 describes this model.

3.16.3.3 Higuchi model

$$Q_t = k_H t^{1/2}$$

Equation 3.12: Higuchi model (Lobo and Costa, 2001).

Where Qt is the quantity released at time t. k_H is the Higuchi dissolution constant

The Higuchi model (Equation 3.12) is often used to define release in matrix dosage forms that have a modified release (Dash *et al.*, 2010).

3.16.3.4 Korsemeyer-Peppas model

$$\frac{M_t}{M_\infty} = kt^n$$

Equation 3.13: Korsemeyer-Peppas equation (Lobo and Costa, 2001).

Where $\frac{M_t}{M_\infty}$ is the fraction of drug released at time t, k is the function incorporating the structural and geometric characteristics of the dosage form, n is the release component as per equation 3.13.

Table 3.18: Interpretation of Korsemeyer-Peppas using the release component (n).

Release exponent (n)	**Drug release mechanism**	**Rate as a function of time**
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case II transport	Zero order release
>1.0	Super case transport	t^{n-1}

Korsemeyer-Peppas model was additionally used to describe the drug release mechanism as specified in Table 3.18.

3.16.3.5 Hixson-Crowell

The model described in Equation 3.14 is an erosion-based model that illustrates that there is a change in surface area of the particles as drug dissolves. With drug release occurring on a plane parallel to the drug surface (Dash *et al.*, 2010).

$$(1-f_t)^{1/3} = 1 - K_\beta t$$

Equation 3.14: Hixson- Crowell kinetics (Lobo and Costa, 2001).

Where; f_t is the drug dissolved fraction at time t

K_β is the release constant

$f_t = 1-(W_t/W_o)$

3.16.3.6 Weibull model

The Weibull model in Equation 3.15 was used to characterize drug release of the formulations, it additionally contains a shape parameter which describes the shape of the curve and hence the release character as shown in Table 3.20.

$$\log[-\ln(1-m)] = b \log(t - T_i) - \log a$$

Equation 3.15: Weibull model (Lobo and Costa, 2001).

Where; a is the scale parameter,

m is the accumulated fraction of drug in solution at time t,

location parameter, T_i which is the lag before the onset of dissolution,

b is the shape parameter.

The shape parameter identifies the type of release in Table 3.19

Table 3.19: Weibull model shape parameter model (b).

b	case	Shape
1	I	Exponential
>1	II	Sigmoidal
<1	III	Parabolic (steep increase)

Case I (Table 3.19) signifying exponential release, with b<1 indicating steeper increase than b=1. While b>1 presenting sigmoidal release character having a turning point (Dash *et al.*, 2010)

3.16.3.7 Mathematic criterion for selection of best dissolution profile

Mathematical criterion in Table 3.20 was used to select the model of best fit based on the regression coefficient R^2. The coefficient of determination R^2 adjusted was used to obtained the model of best fit, because the different models don't have the same number of parameters (Zhang *et al.*, 2010). The model with the greatest R^2 adj was used to describe the release characteristic of the SD (Lobo and Costa, 2001).

Table 3.20: Acceptance criteria for Goodness of fit.

Criterion	Value	Remarks
R^2 adjusted	1	Profile with highest R^2 adjusted signifies the model of best fit. A value of 1 indicates perfect fit.

3.16.3.8 f_1 (difference), f_2 factor (similarity) and p value for dissolution profile comparison

The f1 factor was used to ascertain difference of dissolution curves at each time point while the f2 factor indicates the level of similarity of two dissolution profiles. Additionally, the p value obtained through analysis of variance was used to corroborate the results through evaluating if the difference between the two profiles is significant, as shown in Table 3.21.

Table 3.21: Acceptance criteria f1, f2 and p value on dissolution performance.

Criterion	**Value**	**Remarks**
F_1 (difference factor)	0-15	A value of zero indicating zero percent error between curves is indicant of similarity. With dissimilarity increasing with increasing value from 0.
F_2 (similarity factor)	50-100	A value of 100 indicates similarity and reduces towards 0 with increasing dissimilarity. Values of 50 and above indicate that average difference is less than 10%
P value	<0.05	An obtained p value from an analysis of variance (ANOVA) is used to evaluate whether the hypothesis is false. A p value >0.05 means no effect is observed.

CHAPTER 4 : RESULTS AND DISCUSSION

4.1 Test for identity

Identity testing, carried out through attenuated FTIR, gave a positive identity for loperamide hydrochloride drug substance. The peak positions between the reference and the API sample were congruent (Appendix I). Significant wave numbers and responsible functional groups are summarized in Table 4.1. With overlay plots for loperamide HCl formulations also displayed.

Table 4.1: FTIR spectral characteristics of loperamide hydrochloride.

Wave number (cm^{-1}).	**Functional group.**
3248	O–H stretch.
1624	C=O
1476	C-O
1373	C-H bend alkanes (CH_3)
837	C-Cl stretching halo compound.
709	Benzene derivative.

The wave numbers obtained are similar to those found in literature (Dadhich, Kumar and Pathak, 2016; Venkateswarlu, Preethi and Chandrasekhar, 2016).

4.2 FTIR spectroscopy study

The loperamide formulations showed regions of overlap between the excipients and API, with peak enlargement and shifts occasioned by intermolecular bonding (dipole-dipole interactions and hydrogen bonds) between the API and excipients. The overlay plots in Annexure I (Figure 7.3-7.6) show reduced crystallinity at the peak at 3248 cm^{-1} for both the PEG and PVP formulations with broadening indicant of reduced crystallinity and hydrogen bonding of the OH group.

Changes in peak intensity was noticed in the different PVP formulations at 1651 cm^{-1} PM1 had the largest intensity then B4, T2, B6, and B5 respectively due to relative PVP content as well as the intermolecular bonding taking place.

Formulation B1, B2, B3 and T1 had shifts from larger wavenumbers to lower ones (negative shift). The peak at 3248 cm^{-1} shifted to 3237 cm^{-1}, peak at 1476 to 1466 cm^{-1}, peak at 1624 to 1622 cm

$^{-1}$ and the peak at 1373 to 1341 cm $^{-1}$. Formulation B4 had a broad peak at 3235 cm $^{-1}$ while the rest had flat peaks that were similar to the PEG spectra at that wavenumber. The shifts are occasioned by intermolecular bonding such as dipole-dipole interactions and hydrogen bonds.

Formulation B4, B5, B6 and T2 had a notable peak shift at 1651 cm-1 from 1624 with formulation B6 having a doublet with one peak at 1651 and the other at 1622 cm^{-1}. This could be due to the content of PVP which has a peak at 1662 cm^{-1} (Figure 7.10).

4.3 Crystallinity index

The crystallinity index as calculated by Equation 3.7 and shown in Table 4.2 depicts the crystallized order state in mixed crystalline and non-crystalline system. Small crystallinity index values indicate high crystallinity while high values indicate low crystallinity (Ramasamy and Suresh, 2009; Razva *et al.*, 2014). The PEG based formulations had the least crystallinity in the following order $B_3>T_1>B_1>B_2>PM_1$. The PVP based formulations had low crystallinity in the order $B_4>T_2>B_6>B_5>PM_2$. All formulations had less crystallinity compared to loperamide and the physical mixtures showing that the development of SDs reduces the crystallinity of loperamide. The lowest crystallinity was obtained in the PEG formulations signifying they formed SDs more readily, this can be attributed to their greater miscibility with loperamide compared to PVP which had higher crystallinity.

Table 4.2: Crystallinity index of loperamide formulations.

Sample	**Crystallinity index (CI)**
B1	1.220
B2	1.021
B3	**3.890**
B4	0.534
B5	0.416
B6	0.451
LPM API	0.378
T1	2.714
T2	0.523
PM1 PEG	0.531
PM2 PVP	0.116

4.4 Assay of loperamide hydrochloride drug substance

The content of loperamide HCl in the drug substance raw material (Table 4.3) complied with the specifications of the British Pharmacopeia (2019).

Table 4.3: Potentiometric assay of Loperamide HCl.

Sample	**Assay (99-101%)**
A	**94.9975**
B	**100.0041**
C	**102.8669**
Average	**99.2895 (**RSD: 4.0115)

4.5 Assay of loperamide hydrochloride in the formulated solid dispersions

Figure 4.1 displays the calibration curve of loperamide HCl at 249 nm. The R^2 value of 0.9998 illustrates good linearity of the calibration curve in the experimental range of 50 to 500 mcg/ml.

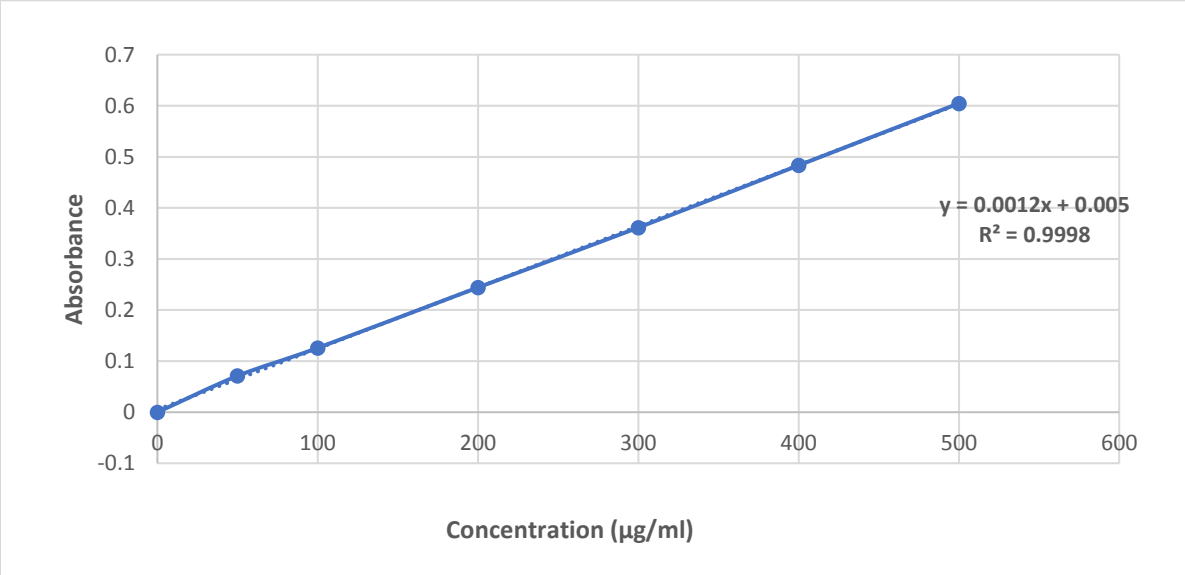

Figure 4.1: Loperamide hydrochloride calibration curve using working reference standard.

The calibration curve was used to determine the content of loperamide HCl in the formulated solid dispersions as shown in Table 4.4.

Table 4.4: Content of loperamide hydrochloride in solid dispersions.

Sample	Average weight per capsule (mg)	Assay (% label claim)
B_1	4.143 ± 0.063	90.16
B_2	6.102 ± 0.037	95.85
B_3	11.990 ± 0.102	96.83
B_4	4.060 ± 0.071	93.88
B_5	6.085 ± 0.070	108.41
B_6	11.953 ± 0.065	105.14
T_1	11.988 ± 0.031	104.81
T_2	11.937 ± 0.083	107.76
PM $_1$ PEG	13.133 ± 0.029	92.33
PM $_2$ PVP	12.527 ± 0.035	91.58

PM= physical mixture at ratio of 1:5

All formulations (Table 4.4) were within the Assay range specified in the USP 2021 (90-110 %). The formulations without bulking agent/filler added were filled into capsules size 3, to contain a weight equivalent of loperamide HCl of 2 mg.

4.6 Dissolution at specific time points

The dissolution characteristics of each formulation at the time points 5, 30 and 60 min are presented in Table 4.5 showing the percent dissolved at the initial sampling time, at the intermediate stage and the final sampling time. The Q_5 parameter illustrates formulations with rapid release or solubilization within the in vitro dissolution. The parameter is however affected by gelatin capsule disintegration with some capsules degrading faster than others therefore affecting the Q_5 value obtained. However, T1 formulation had the highest initial release of API from the matrix (highest solubilization effect) followed by the marketed formulation, then the PVP based formulation B_6 which has the highest concentration of hydrophilic polymer having a great initial solubilization effect on the API.

The Q_{30} parameter is the USP acceptance criteria for dissolution (not less than 80% at 30 min). Formulation B5, T2 and PM 1 failed to attain the acceptance criteria, with the formulations having a low release of 57%, 77% and 79% respectively after 30 min of dissolution testing. The

formulations with the highest cumulative increase include B1, B2 and B3, which are all PEG based formulations. They have much better dissolution at that time point compared to binary PVP formulations and also the ternary formulations. The better solubility parameter of LPM in PEG compared to LPM in PVP may have led to an increased solubilization effect of the solid dispersion. Additionally, the PEG formulations with the low glass transition, maintained their glassy state increasing its solubility. The Q_{60} parameter looks at completeness of dissolution and is ascertained through similarity with the value reported at Q_{45} illustrating a reduction in the rate of drug release. The PEG based formulations (B1, B2, B3 and T1) once again had the highest cumulative drug release at 60 minutes.

Table 4.5: Dissolution- time character comparison of loperamide formulations.

Formulation	**Quantity of loperamide hydrochloride released**		
	5 min (Q_5)	**30 min (Q_{30})**	**60 min (Q_{60})**
B_1	3.506911	101.6023	106.4965
B_2	17.12158	96.93015	**108.1769**
B_3	10.72102	**101.9397**	106.6372
B_4	0.944892	84.07537	89.37477
B_5	6.252237	57.75257	81.4775
B_6	25.60025	91.76349	99.48027
T_1	**34.00655**	88.55765	102.5585
T_2	12.03604	77.64616	89.20025
PM $_1$ PEG	6.148204	79.7709	99.06552
PM $_2$ PVP	2.696145	84.06696	91.68935
Loperamide marketed product	30.85513	80.31061322	88.96118

4.7 Drug dissolution profiles

The dissolution profiles of loperamide HCl solid dispersions of weight equivalent 2mg were summarized in Table 4.6 below. The mean dissolution time (MDT), dissolution efficiency (DE), mean residence time (MRT), area under the curve (AUC). Were used as parameters to evaluate the dissolution characteristics of each formulation.

Table 4.6: Drug dissolution profiles of Loperamide HCl solid dispersions, physical mixtures and market product.

Time	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**T1**	**T2**	**Market product**	**PM 1 PEG**	**PM 2 PVP**
0	0	0	0	0	0	0	0	0	0	0	0
5	3.507	17.12	10.72	0.945	6.252	25.60	34.01	12.04	30.86	6.148	2.696
10	66.64	44.93	57.17	28.36	22.66	52.73	53.13	35.65	54.06	12.74	16.92
15	85.50	66.13	83.73	63.84	35.38	70.39	65.93	50.41	70.54	48.51	60.22
30	101.6	96.93	101.9	84.08	57.75	91.76	88.56	77.65	80.31	79.77	84.07
45	106.2	108.2	106.0	88.55	71.00	97.51	97.09	82.74	84.62	95.69	89.46
60	106.5	108.2	106.6	89.37	81.48	99.48	102.6	89.20	88.96	99.07	91.69
MDT	**11.91**	**15.08**	**12.22**	**14.74**	**22.68**	**12.95**	**14.67**	**17.21**	**11.99**	**20.08**	**16.47**
DE	0.853	0.809	0.849	0.674	0.507	0.780	0.775	0.636	0.712	0.659	0.665
MRT	-1.760	1.820	-1.204	15.93	21.23	10.83	11.15	18.06	18.89	13.13	15.22
AUC	5121	4860	5095	4045	3041	4681	4649	3817	4271	3955	3991

The AUC was further illustrated by figure 4.2 showing the formulations with the greatest dissolution.

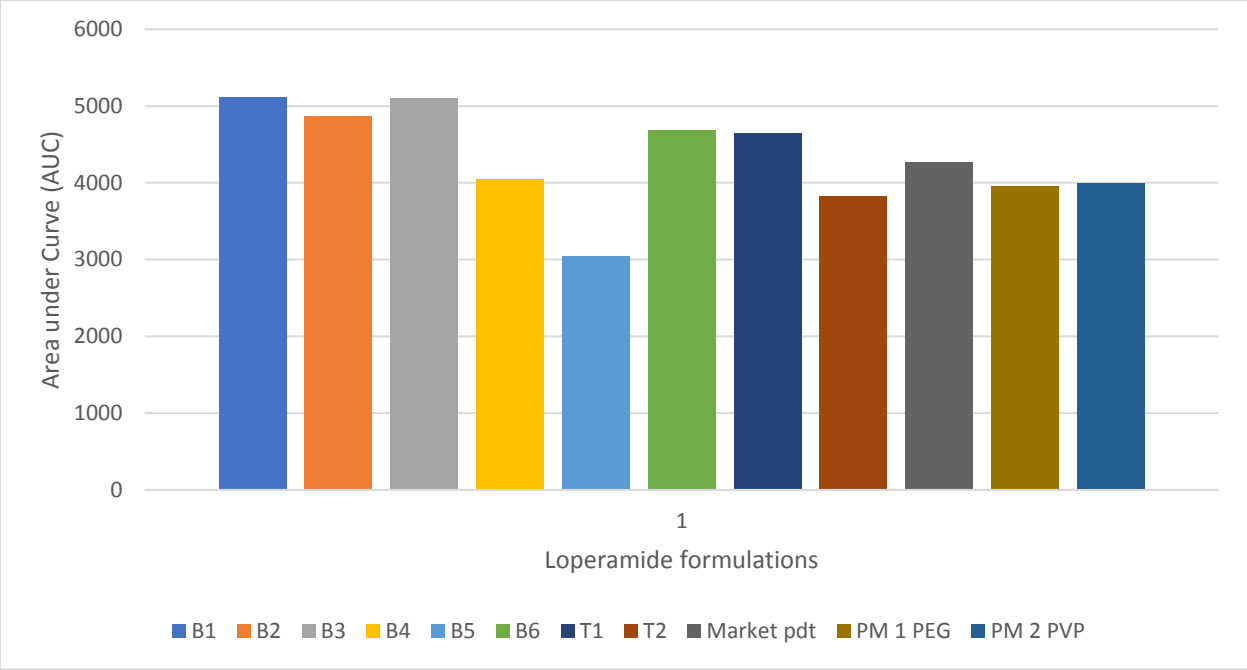

Figure 4.2: Area under the dissolution time curve.

Formulation B1 has the lowest -mean dissolution time, the lowest (negative) mean residence time and its dissolution efficiency is the closest to 1, indicating the formulation has the lowest retention of loperamide in the polymer matrix and the best drug release. The rapid release especially once the capsule disintegrates shows the high solubilizing effect present in the formulation. The marketed formulation has a slightly greater mean dissolution time probably occasioned by the dissolution enhancing excipients present in the blend, however it has a high mean residence time indicating that the effect of high dissolution is probably occasioned by the excipients rather than the interactions within the mixture or its attained nature. Formulation B3 also has a very low (negative) mean residence time indicating a rapid release of LPM from the polymer matrix and a low MDT signifies its superiority as a formulation over the PVP based formulations. It also has the greatest AUC followed by formulation B3 indicating the two PEG based formulations had the highest dissolution within the study. This is supported by their dissolution efficiency which at 0.8534 and 0.8492 respectively are the highest within the formulations under study. Once again, the PEG based formulations had the best dissolution characteristics compared to the PVP based formulations. However, formulation B6 was noticed to be superior to T1 based on its MRT, DE, MDT and AUC.

Of the PVP based formulations, formulation B6 had the least MDT of 12.94 min with the lowest MRT of 10 min with formulation B4 having better dissolution characteristics than formulation B5. The ternary formulations expected to have better release than the binary formulations performed poorer as indicated by the Higher MDT and MRT values. The highest MDT of 22.68, 20.08, 17.21

corresponds to formulations B5, PM1 PEG and T2 respectively which correlates with their failure to obtain a Q_{30} of 80% in Table 4.5 with the lowest dissolution (B5,57% Q_{30}) corresponding to the highest obtained MDT of 22.68.

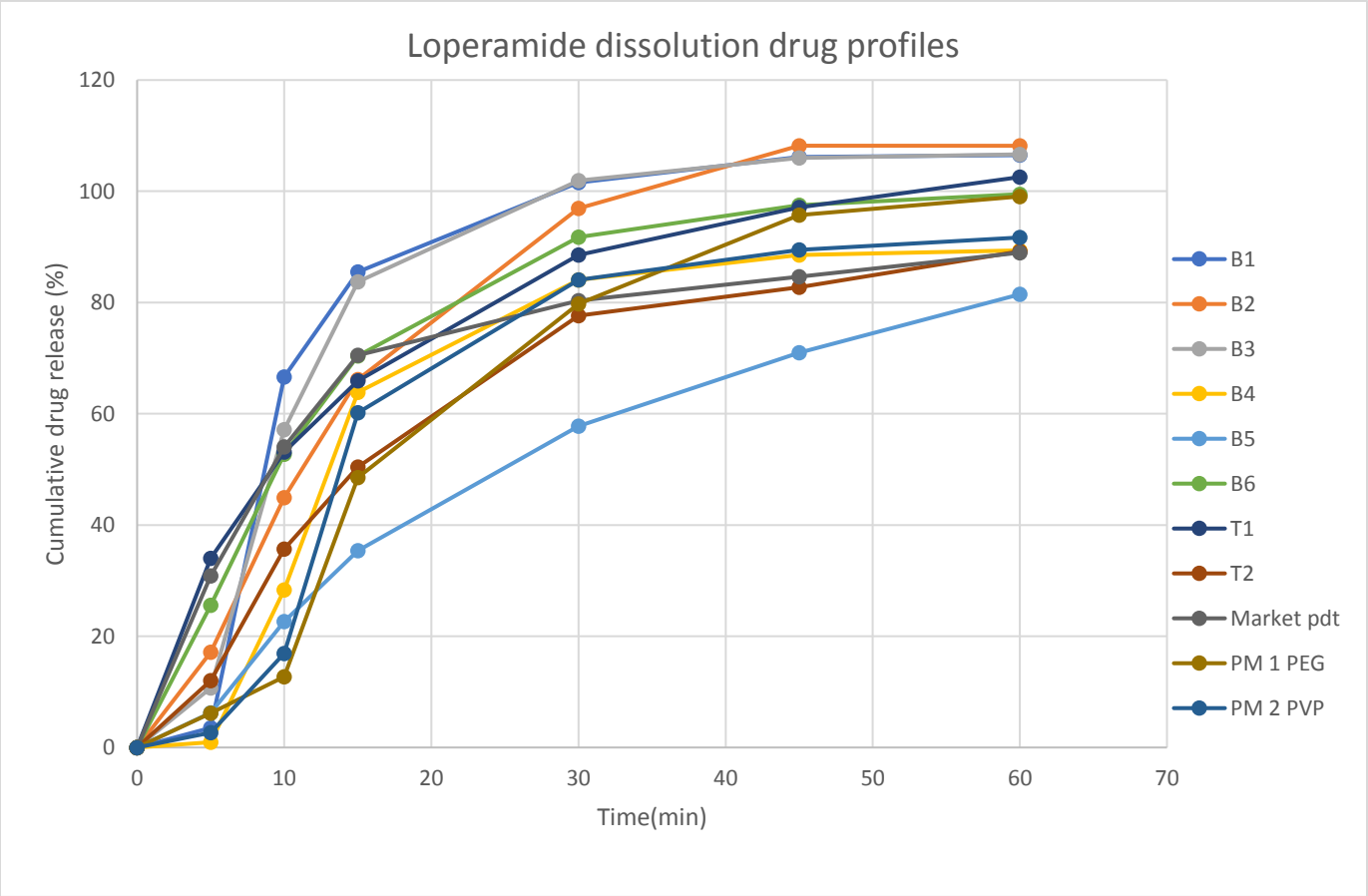

Figure 4.3: Dissolution profiles of loperamide HCl solid dispersion formulations.

The dissolution profiles (Figure 4.3) of the various formulations are displayed. Formulation B5 had the least cumulative drug release after 60 minutes with formulation B1 and B2 having the largest cumulative release. While at the initial sampling time of 5 minutes formulation T1, market product and B6 had the greatest initial release of LPM.

4.7.1 Drug dissolution modelling and kinetics

Equation 3.10-3.15 were used to evaluate the dissolution profiles of the different formulations using the DD solver excel add in. The obtained parameters are summarized in Table 4.7.

Table 4.7: Evaluation of model independent approaches for characterization of loperamide formulations.

Model	**Parameter**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**T1**	**T2**	**Market product**	**PM 1 PEG**	**PM 2 PVP**
Zero order	k_0	2.354	2.297	2.343	1.908	1.542	2.156	2.163	1.829	1.936	1.968	1.911
First order	k_1	0.089	0.070	0.086	0.047	0.028	0.075	0.076	0.043	0.069	0.042	0.044
Higuchi	k_H	16.020	15.340	15.905	12.642	9.978	14.690	14.728	12.158	13.393	12.655	12.506
Korsemeyer-Peppas	kKP	20.191	14.398	19.529	9.711	4.736	20.643	21.627	10.452	25.226	5.201	7.553
	n	0.435	0.518	0.442	0.573	0.706	0.404	0.392	0.542	0.321	0.746	0.640
Weibull	β	0.928	1.665	1.374	0.380	0.833	0.957	0.965	0.737	0.433	1.375	0.460
Hixson-Crowell	kHC	0.024	0.019	0.024	0.014	0.008	0.021	0.021	0.012	0.020	0.012	0.013
Model of best fit	R^2 adj	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	First order	Weibull	Weibull	Weibull	Weibull

The dissolution data was further evaluated using Equation 3.10-3.15 and the data presented in Annexure II, Figure 8.1-8.11 and Table 8.1-8.11. The zero-order model applies for formulations whose release rate is independent of concentration. The R^2 obtained indicates poor fit of the data to this model. The first order model applies for formulations whose release rate is dependent upon the concentration of the drug in the formulation. The goodness of fit R^2 in formulation B5, B6, T1 of 0.9916,.0.9947, 0.9970 respectively indicates the dissolution process of those formulations is concentration-dependent. The Higuchi model and Korsemeyer-Peppas models do not have good fit with the experimental data attributed to their low R^2 value obtained in Annexure III. The n value suggests formulation B1, B3, B6, T1 and market product release LPM through a quasi Fickian mechanism corresponding to the formulations with the best dissolution character. While B2, B4, B5, T2, PM1 PEG, PM2 PVP show anomalous transport. The Weibull model had the best fit for the dissolution data except for formulation T1. Nevertheless, the Weibull model has been criticized for a lack of a kinetic parameter for assessing drug release (Lobo and Costa, 2001). The shape parameter indicates that the formulations predominantly have a parabolic release (steeper than exponential) except for formulation B2, B3 and PM1 PEG. The Hixson-Crowell model has a good R^2 value in formulation B2, B5, B6, T1, T2 of 0.9790,0.9891,0.9956,0.9889 and 0.9714 respectively. Indicating an erosion type of drug release from a matrix that takes place on the particle surface in planes parallel to the drug surface.

4.7.2 Difference (f1), similarity factor (f2) and ANOVA (p value) on dissolution profile comparison

Table 4.8: f1 factor for ternary and binary formulations with physical mixtures as the reference sample.

Reference sample	**Test sample**	**F1**	**Remarks**
PM 1 PEG	B1	38.97	Reject
	B2	29.12	Reject
	B3	36.34	Reject
	T1	29.05	Reject
PM 2 PVP	B4	5.81	Accept
	B5	25.83	Reject
	B6	26.79	Reject
	T2	15.51	Reject

The f_1 difference factor is a measure of similarity used in comparison of two dissolution profiles. Table 4.8 shows the physical mixtures used as the reference sample against both binary and ternary formulations with each formulation having the same proportion of loperamide in relation to polymer. The table assesses the effect of surfactant and formulation on the dissolution of LPM.

The PEG based formulations showed dissimilarity with their control. This was also noted for the PVP based formulations which had f1 values larger than 15 except for formulation B4 which had a similar release profile to the control. Formulation T2 had borderline similarity with the control showing the surfactant SLS had a detrimental effect on LPM dissolution in the formulation when compared to B6 which was only subjected to heat. Formulation B5 performed worse than the reference product. The p value in Table 4.9 corroborated the f1 data better as the ANOVA method is more discriminative (Yuksel, Kanik and Baykara, 2000). Formulation B1, B4, B5, T2 had a p value greater than 0.05 (the level of significance) showing they were not significantly different to the physical mixture PM1 PEG.

Table 4.9: p value of solid dispersions compared with controls.

Reference sample	**Test sample**	**p value**	**Remarks**
PM 1 PEG	B1	0.054815	No effect
	B2	0.004616	Effect
	B3	0.035081	Effect
	T1	0.044593	Effect
PM 2 PVP	B4	0.362717	No effect
	B5	0.093689	No effect
	B6	0.022532	Effect
	T2	0.927278	No effect
B3	T1	0.513434	No effect
B6	T2	0.000102	Effect

Table 4.10: f2 comparison tests (similarity factor) between binary and ternary loperamide concentrations at ratio 1:5.

Reference sample	**Test sample**	**f2**	**Remarks**
B3	T1	44.54	Reject
B6	T2	42.44	Reject

The f_2 factor indicated in Table 4.10 shows the similarity between dissolution profiles. The studied comparison involved that between the binary and ternary formulations of equal polymer weight

fraction to check for similarity between the two, this was done to check the effect of addition of surfactant to the formulations. The f_2 factor attained showed the binary and ternary profiles were dissimilar with the profiles close to similarity indicating that addition of surfactant SLS had a significant effect on the dissolution of LPM. The way the surfactant is incorporated affects its influence on drug solubility, with internally incorporated surfactants having greater dissolution compared to external ones (Dave *et al.*, 2013). Additionally, surfactants can give reduced dissolution due to molecular interactions (Guo *et al.*, 2019). The p value (Table 4.9) obtained showed that formulation B3 and T1 are similar showing the addition of surfactant did not appreciably change the dissolution character of the polymer blend. The p value of B6 and T2 shows that addition of surfactant had a significant effect on dissolution even though the observed effect is a detrimental one.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

Loperamide solid dispersions were successfully prepared. The process showed that the PEG based formulations were more readily formulated by the melt method and the results obtained signify they more readily formed solid dispersions compared to the PVP formulations. QbD principles and mathematical models proved to be important tools in the formulation process. The addition of SLS to form ternary solid dispersions did not yield the results expected with binary formulations B1 (1:1) and B3 (1:5) having superior dissolution. The results from FTIR showed that the crystallinity was lowest in the PEG formulations which correlated with the dissolution data obtained. The preparation of solid dispersions however showed that the process reduced the overall crystallinity of loperamide. Preparation of solid dispersions is a viable method for improving the bioavailability of loperamide.

5.2 RECOMMENDATIONS

Additional studies should be done to improve the formulation process. The use of physicochemical characterization tools such as thermogravimetric analysis to determine preformulation melting and degradation temperatures, x-ray powder diffraction for crystallinity and differential scanning calorimetry to obtain the glass transition temperature of blends. Should be used to obtain detailed physicochemical properties of the prepared solid dispersions. Additionally, scale up and manufacturing using hot melt extrusion, 3D print technology, melt granulation can be undertaken. The net effect of implementing the recommendations would result in the greater characterization of the prepared solid dispersions, the formulation of an optimized solid dispersion and an assigned shelf life or storage conditions for the solid dispersions.

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7 ANNEXURE I: LOPERAMIDE FTIR SCANS

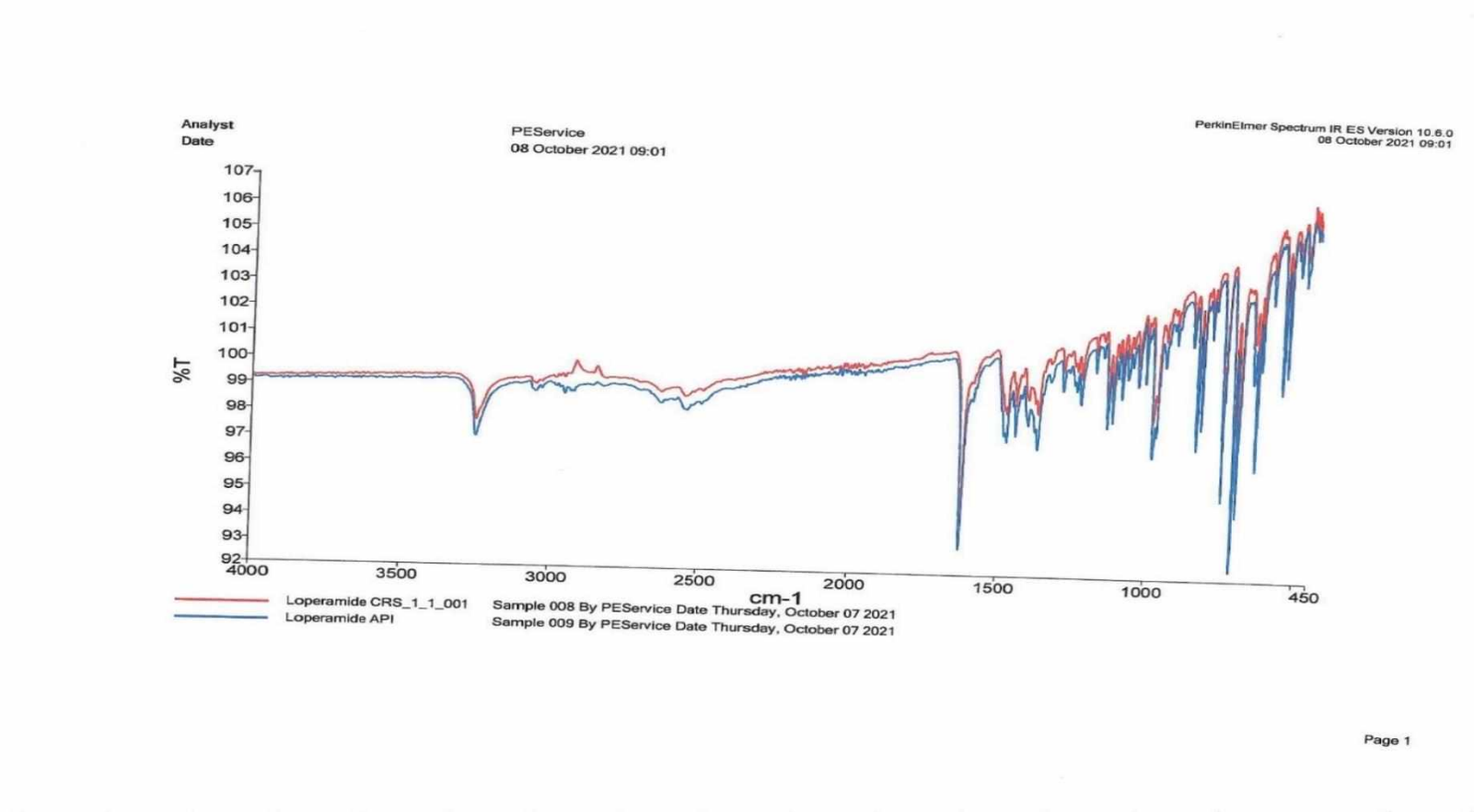


Figure 7.1: Loperamide API and CRS overlay plot.

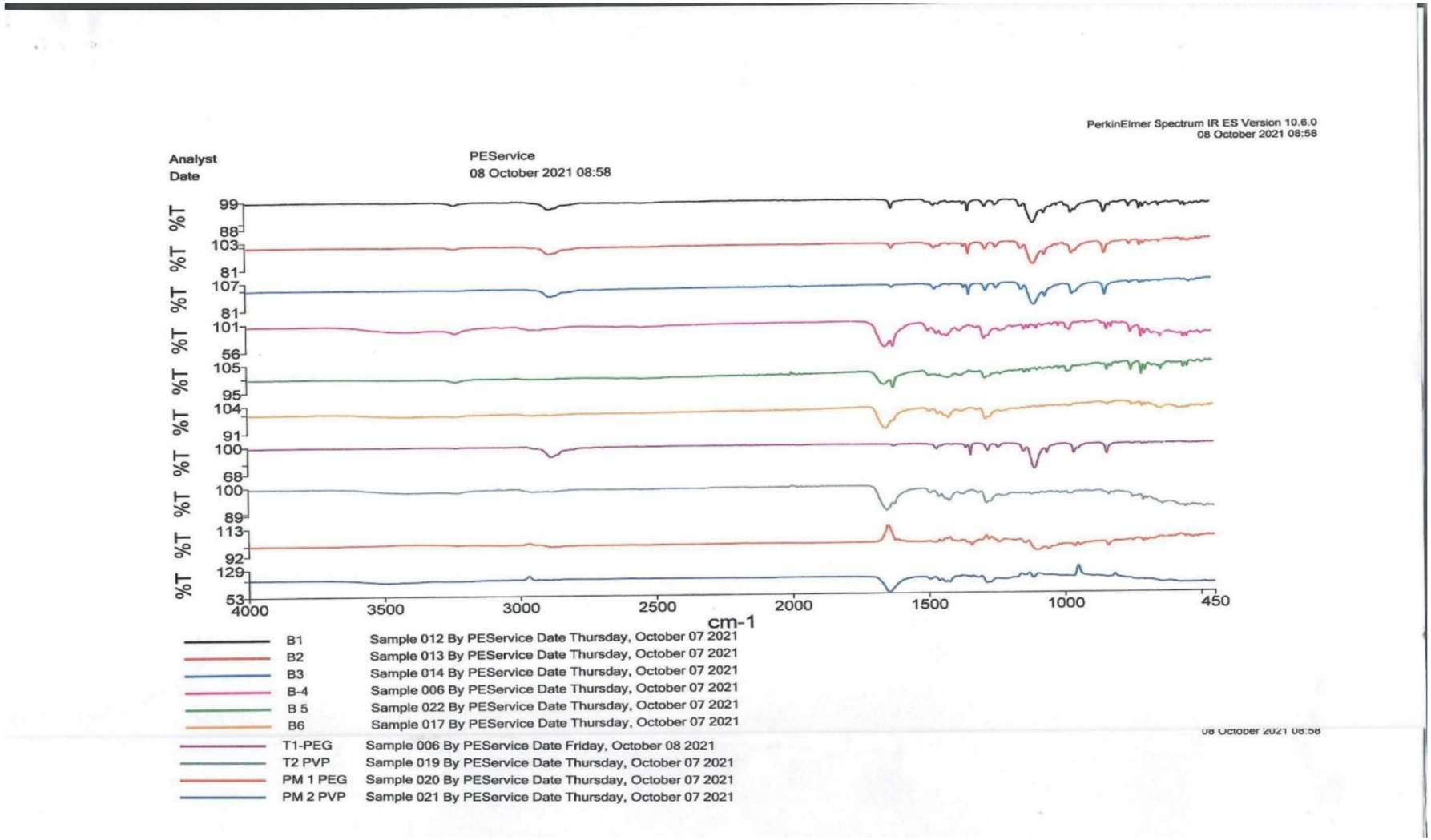


Figure 7.2: Loperamide formulations overlay plot.

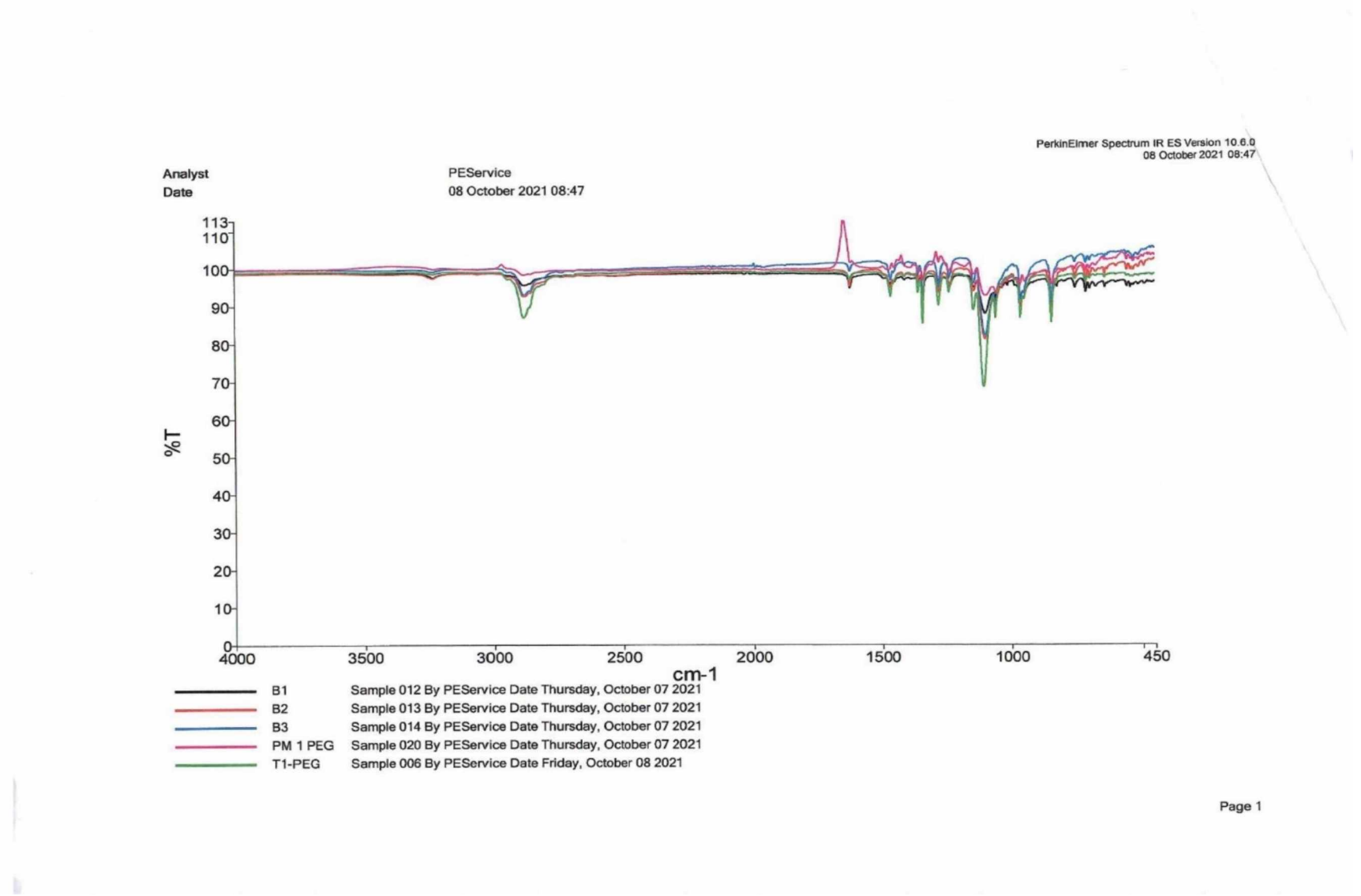


Figure 7.3: Loperamide PEG samples overlay plot (combined view).

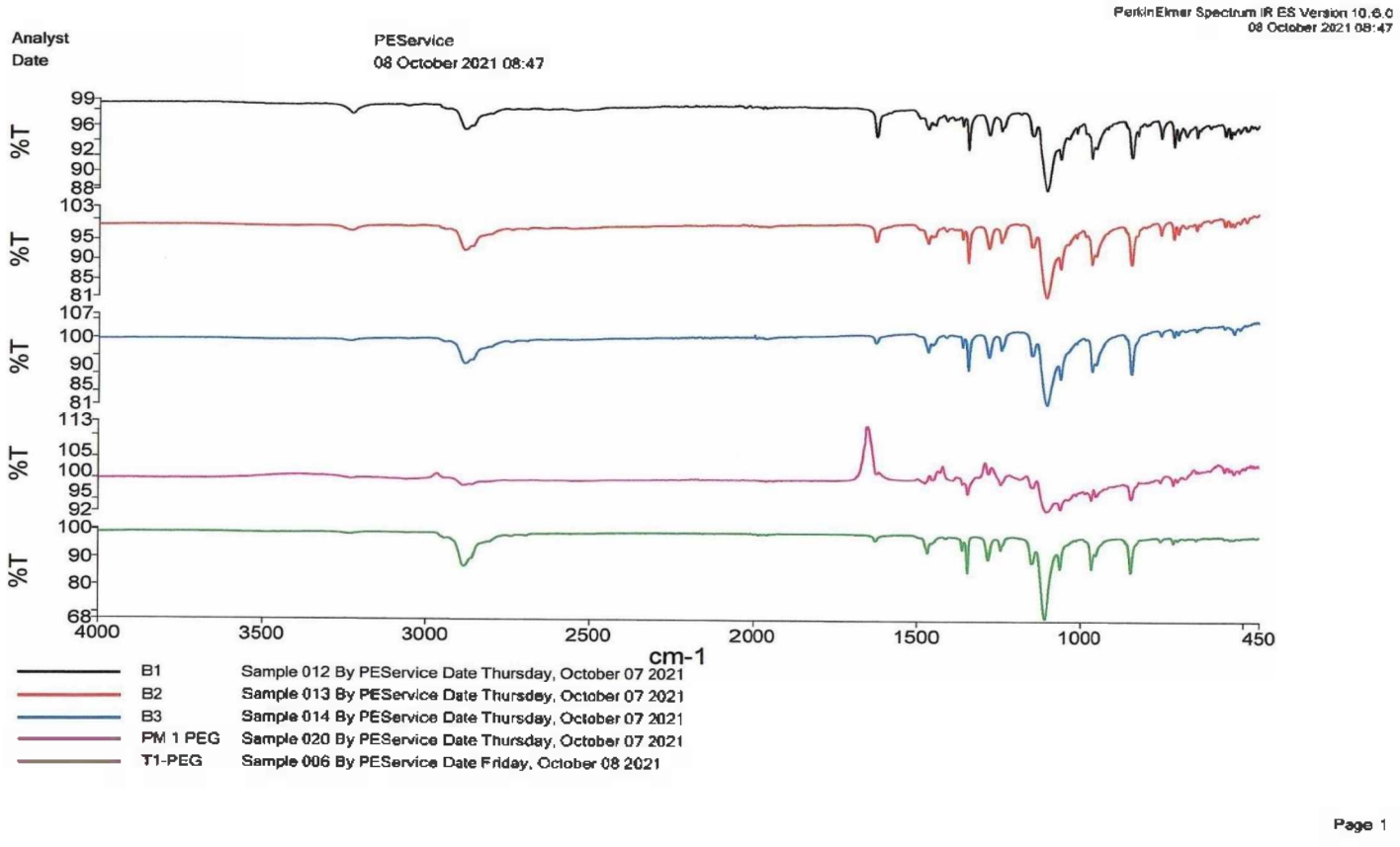


Figure 7.4: Loperamide PEG overlay plots (split view).

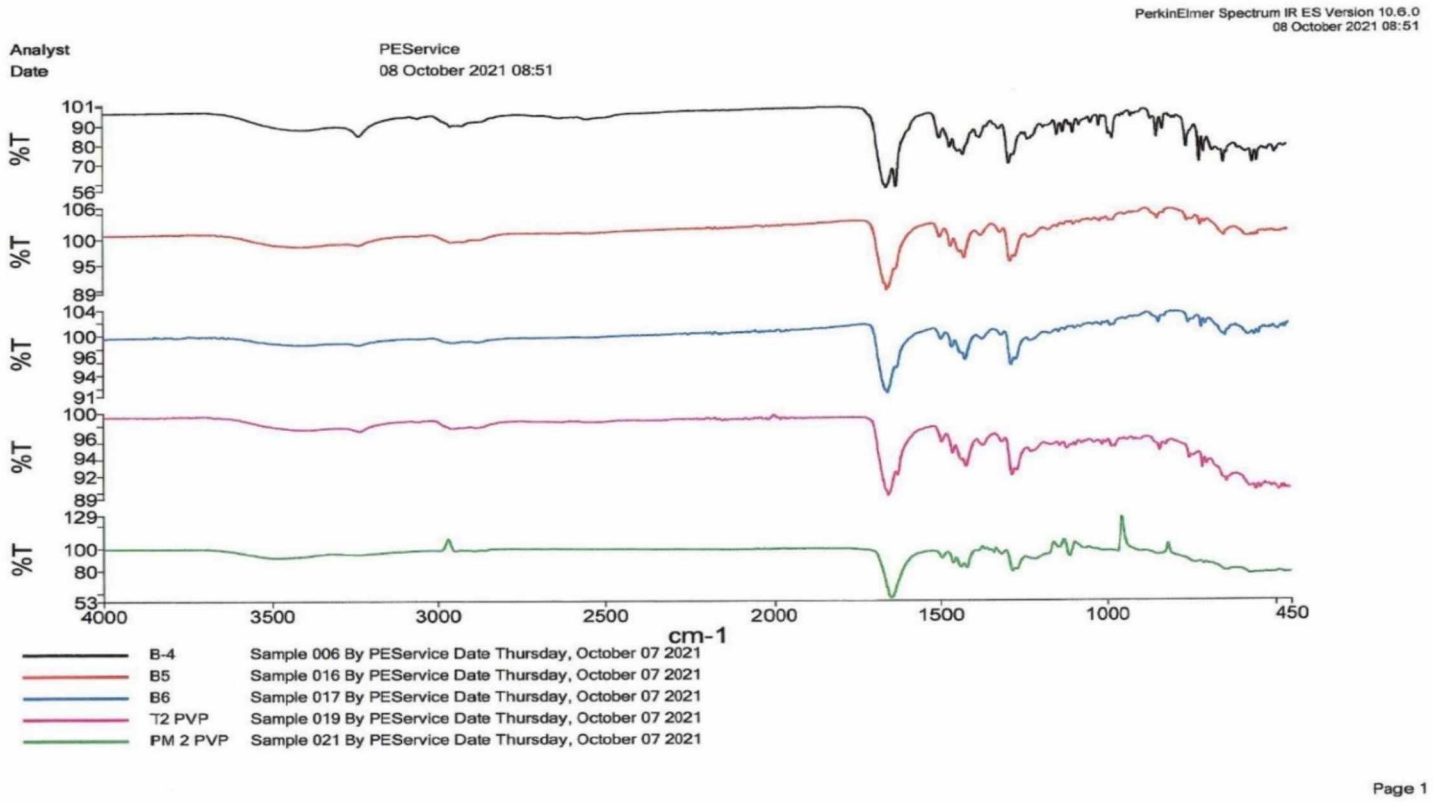


Figure 7.5: Loperamide PVP overlay plots (split view).

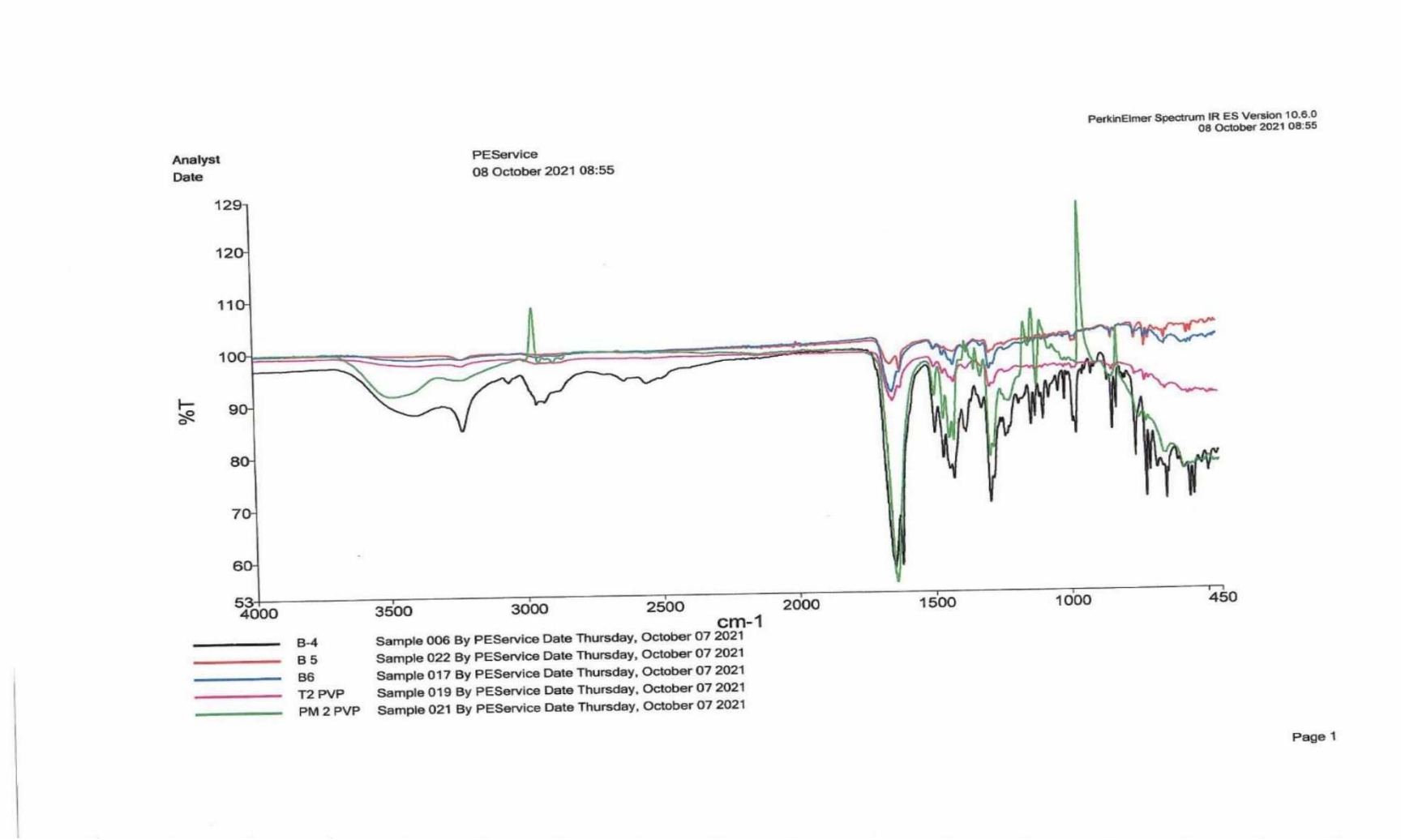
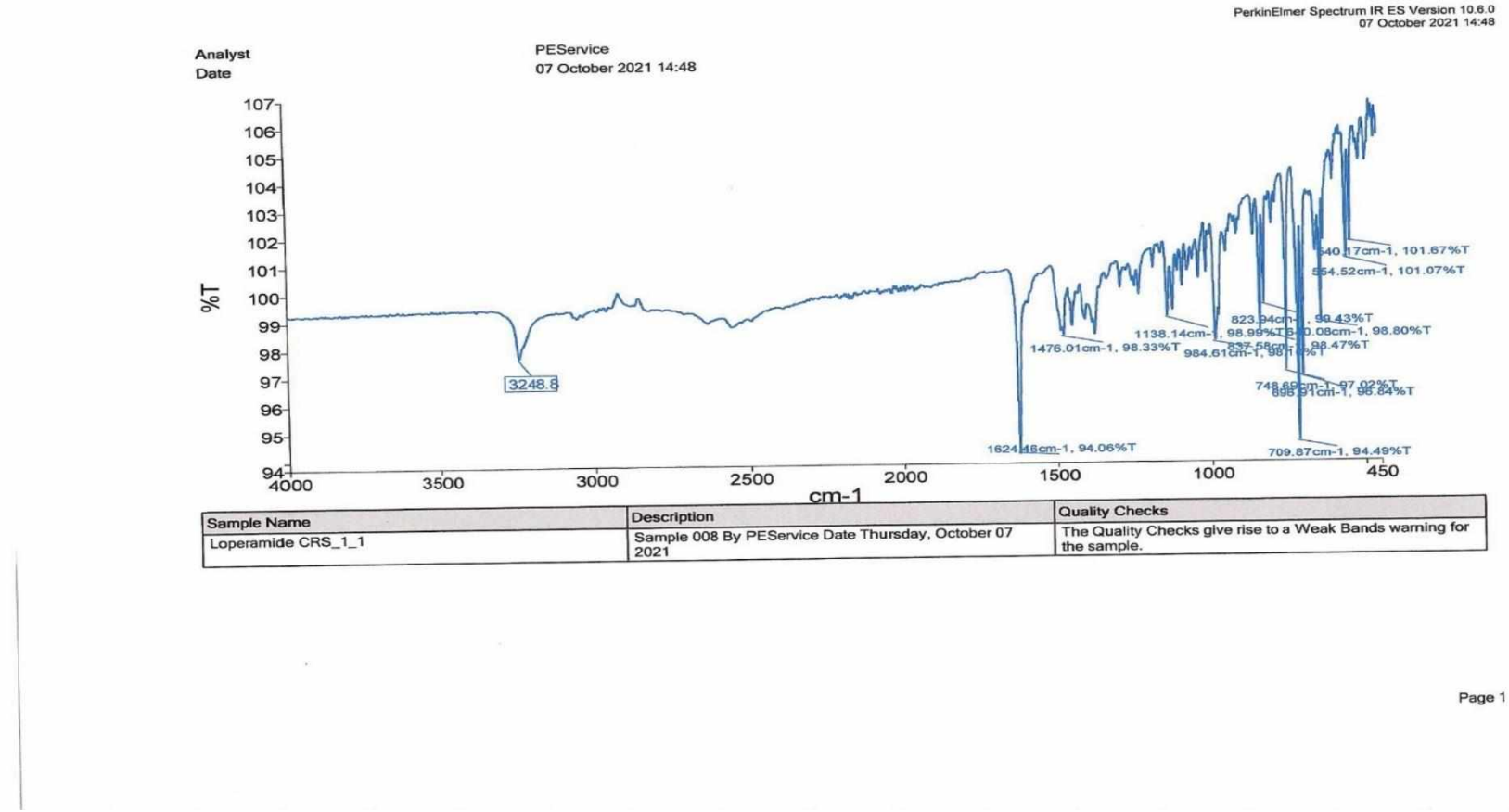


Figure 7.6: Loperamide PVP overlay plot (combined view).



Sample Name	Description	Quality Checks
Loperamide CRS_1_1	Sample 008 By PEService Date Thursday, October 07 2021	The Quality Checks give rise to a Weak Bands warning for the sample.

Figure 7.7: Loperamide CRS spectrum.

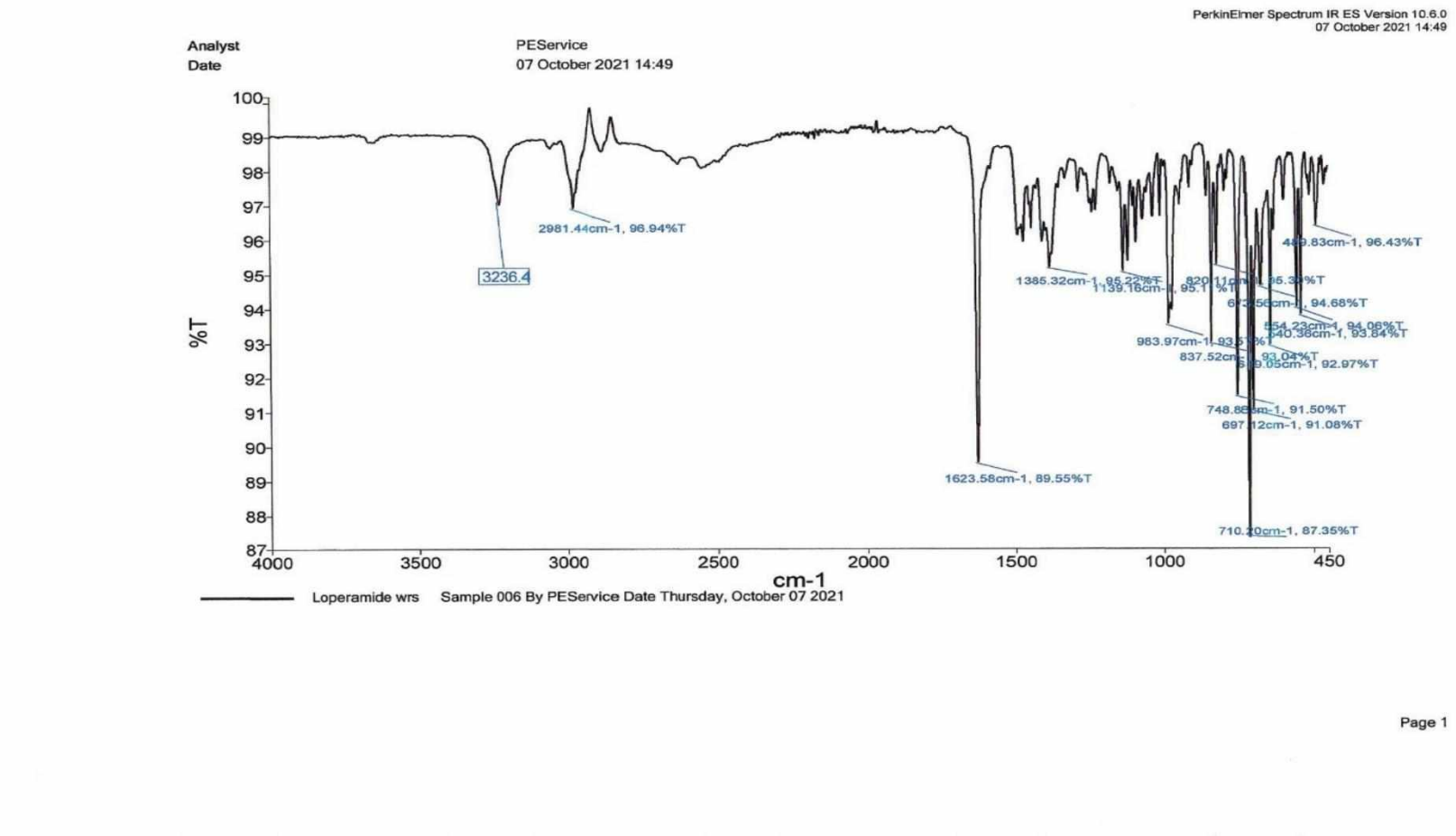


Figure 7.8: Loperamide WRS spectrum.

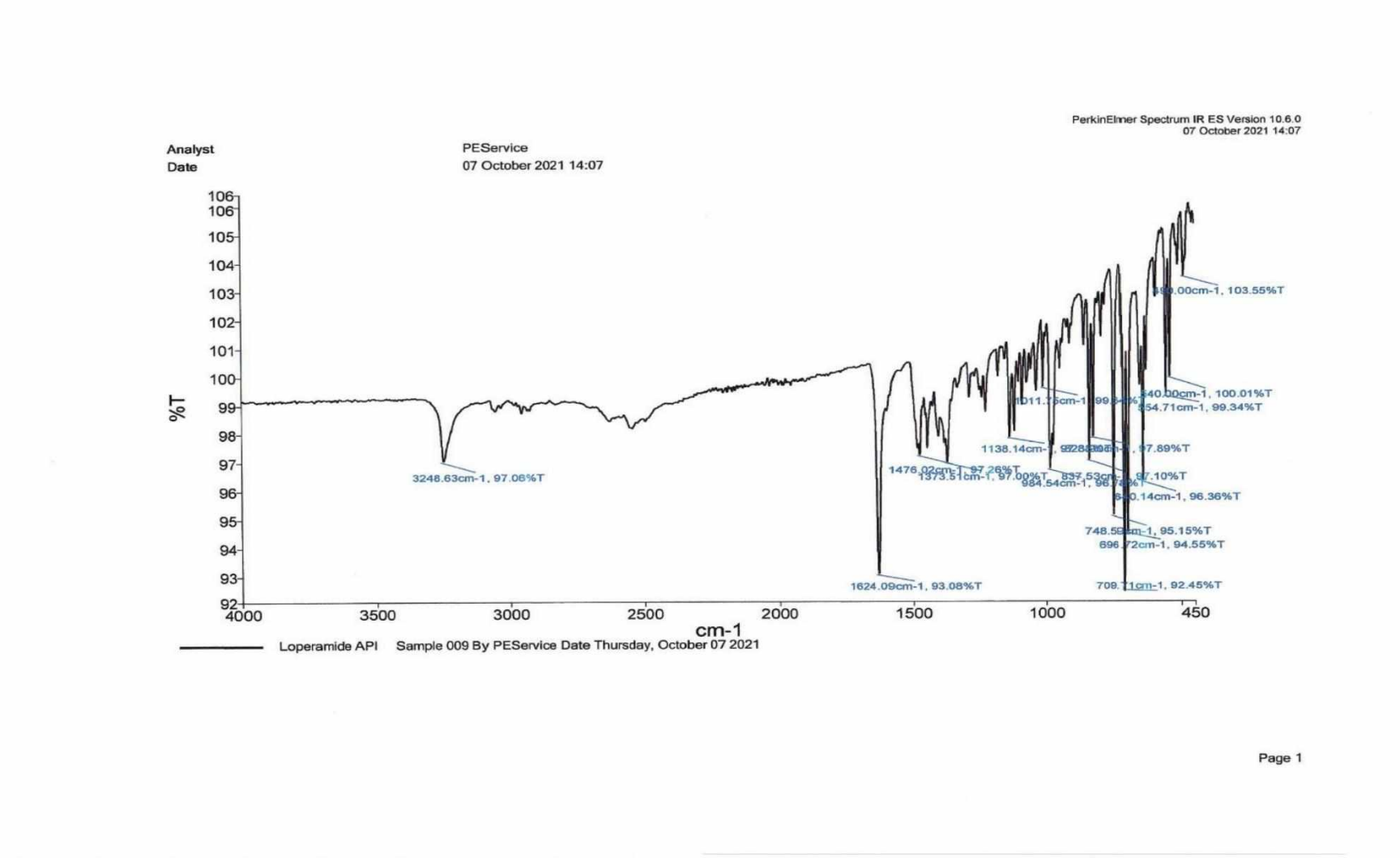


Figure 7.9: Loperamide API spectrum.

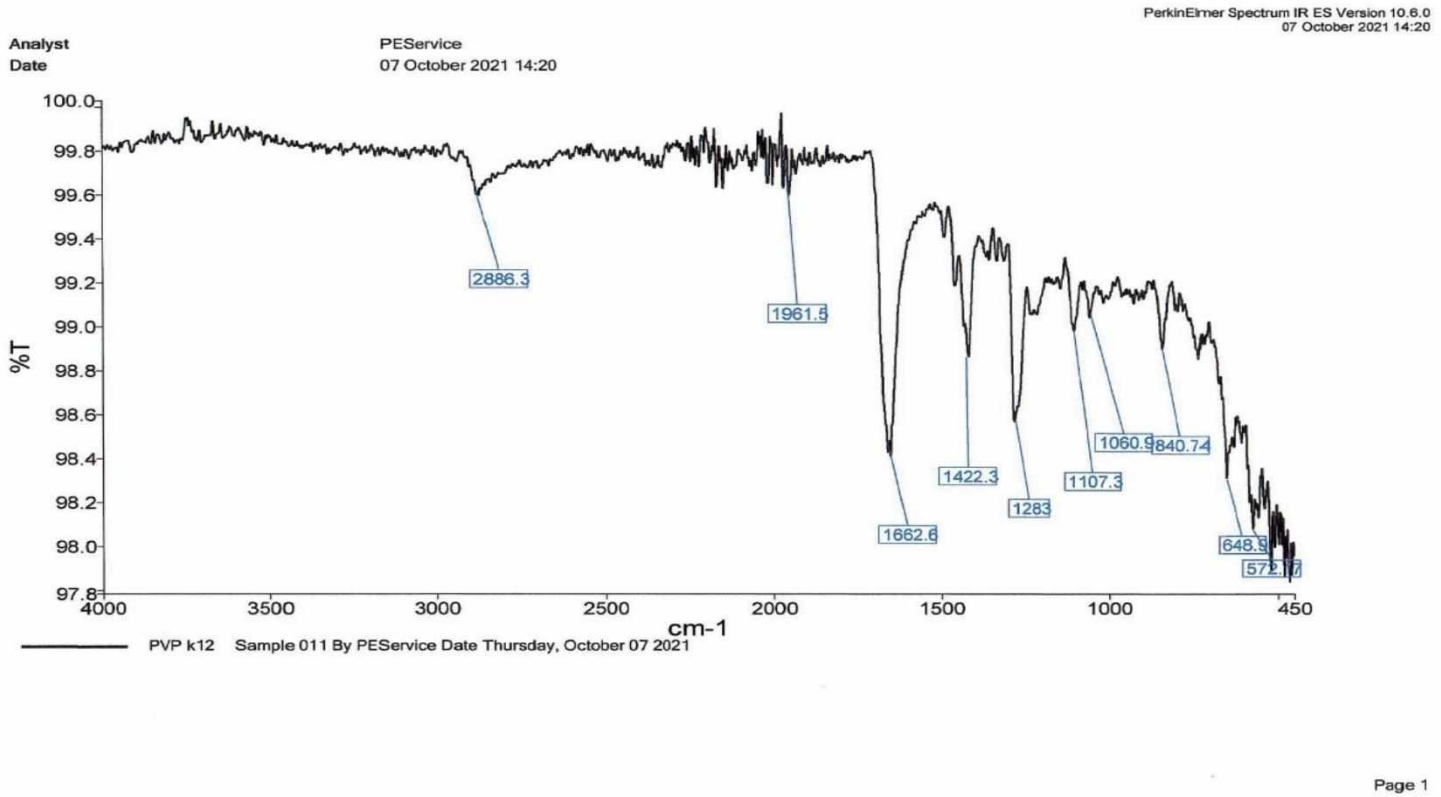


Figure 7.10: Poly vinylpyrrolidone (PVP) k12 spectrum.

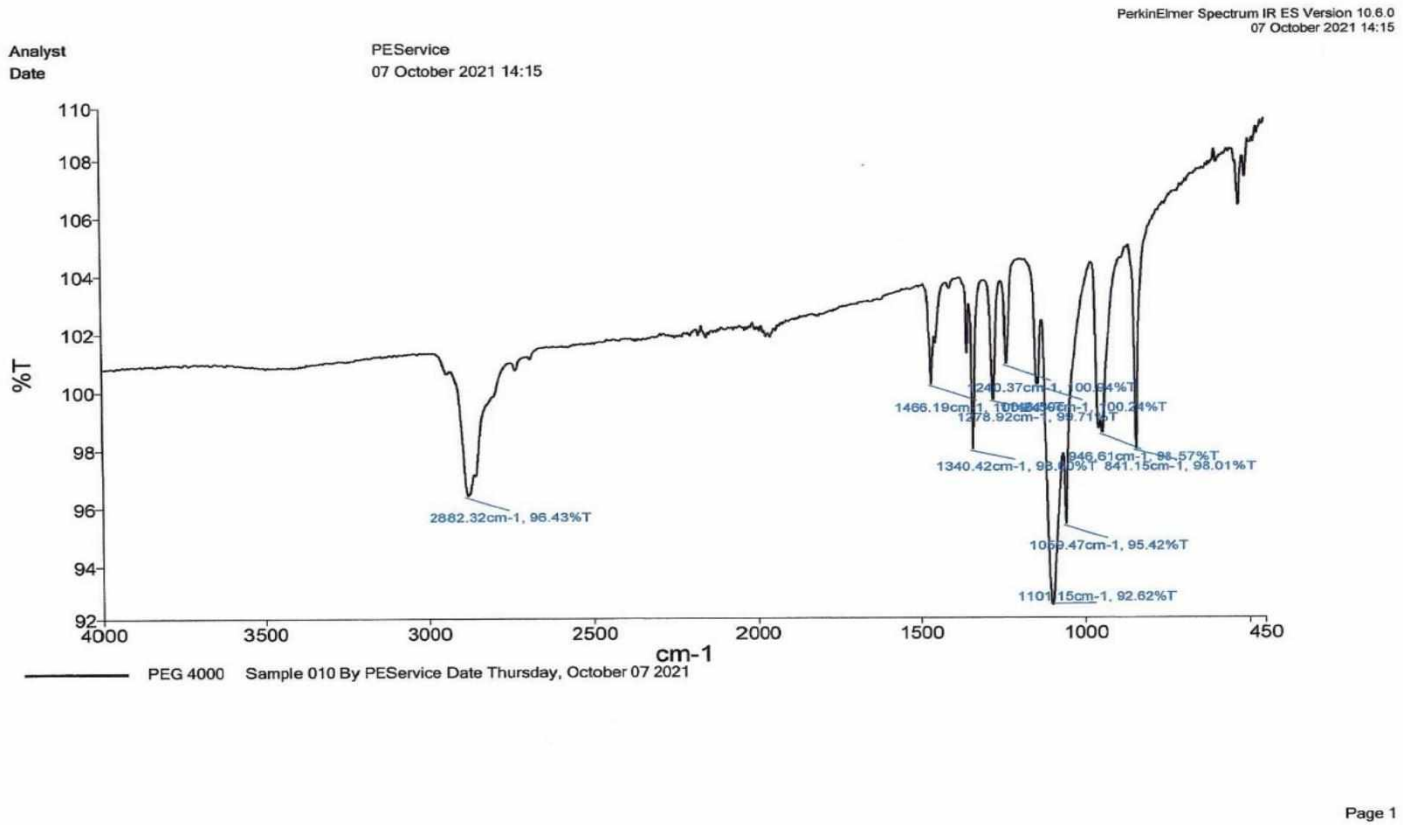


Figure 7.11: PEG 4000 spectrum.

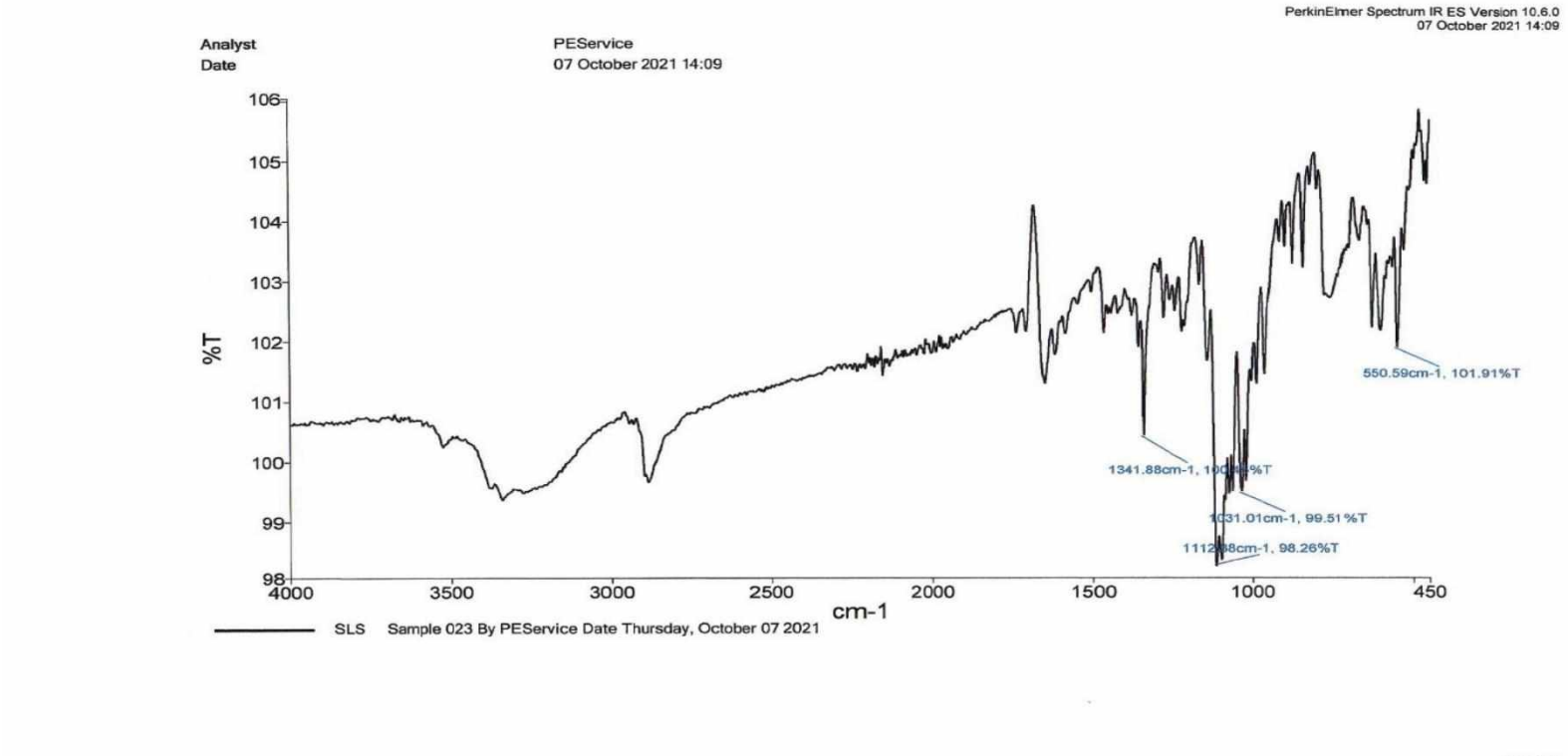


Figure 7.12: Sodium lauryl sulfate spectrum.

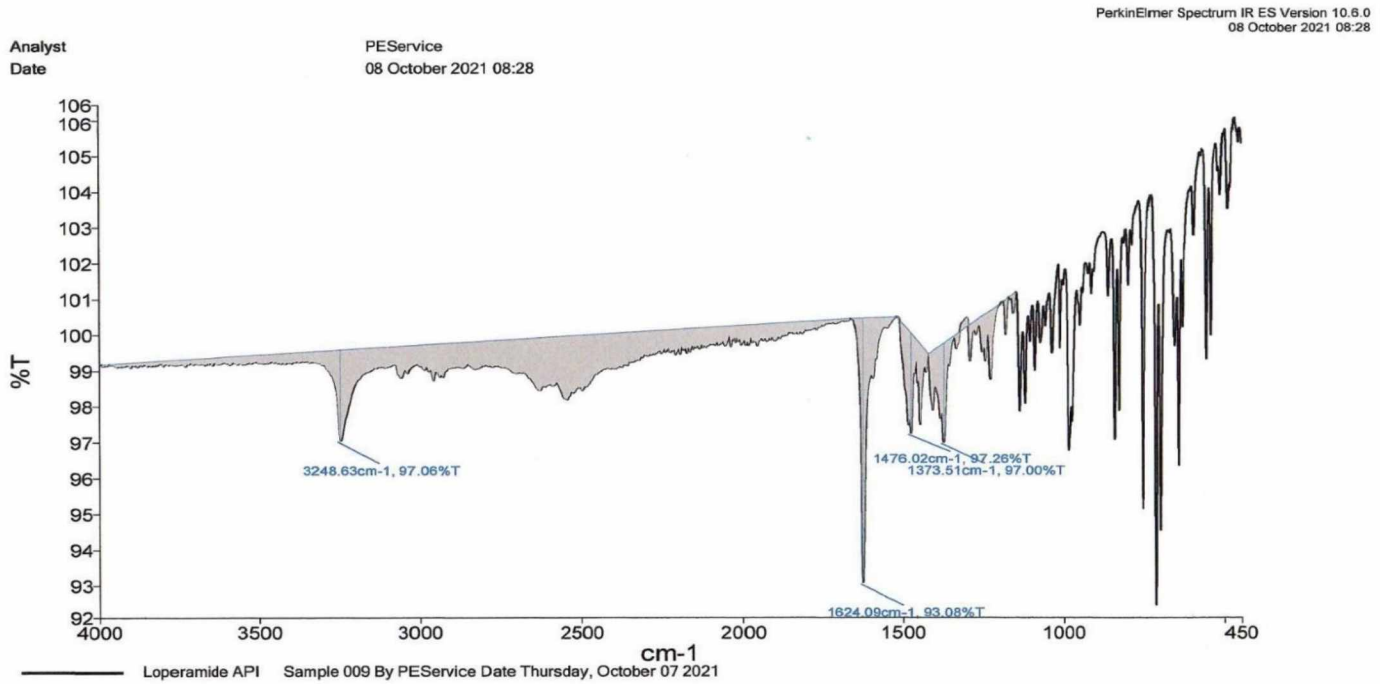


Figure 7.13: Loperamide API crystallinity index with tangent base lines selected.

PerkinElmer Spectrum IR ES Version 10.6.0
08 October 2021 08:28

Source Spectra Results																	
Spectrum Name	Number Of Peaks	Area_1	Height_1	X_1	Y_1	Area_2	Height_2	X_2	Y_2	Area_3	Height_3	X_3	Y_3	Area_4	Height_4	X_4	Y_4
Loperamide API	4	-1330	-2.53	3248.63	97.06	-187.95	-7.39	1624.09	93.08	-112.37	-2.79	1476.02	97.26	-165.67	-2.77	1373.51	97

List of Peak Area/Height												
Peak Number	Area (%T)	Height (%T)	Start	End	Base1	Base1 Left	Base1 Right	Base2	Base2 Left	Base2 Right	X (cm-1)	Y (%T)
1	-1330	-2.53	4000	1664.8	3999	4000	3999	1664.8	1665.8	1663.8	3248.63	97.06
2	-187.95	-7.39	1664.8	1519.12	1664.8	1665.8	1663.8	1519.12	1520.12	1518.12	1624.09	93.08
3	-112.37	-2.79	1519.12	1421.54	1519.12	1520.12	1518.12	1421.54	1422.54	1420.54	1476.02	97.26
4	-165.67	-2.77	1421.54	1149.16	1421.54	1422.54	1420.54	1149.16	1150.16	1148.16	1373.51	97

Page 2

Figure 7.14: Loperamide API crystallinity index with selected peak heights.

8 ANNEXURE II: DD SOLVER MODEL DEPENDENT RELEASE MODELLING

Figure 8.1: Formulation B1 release kinetics.

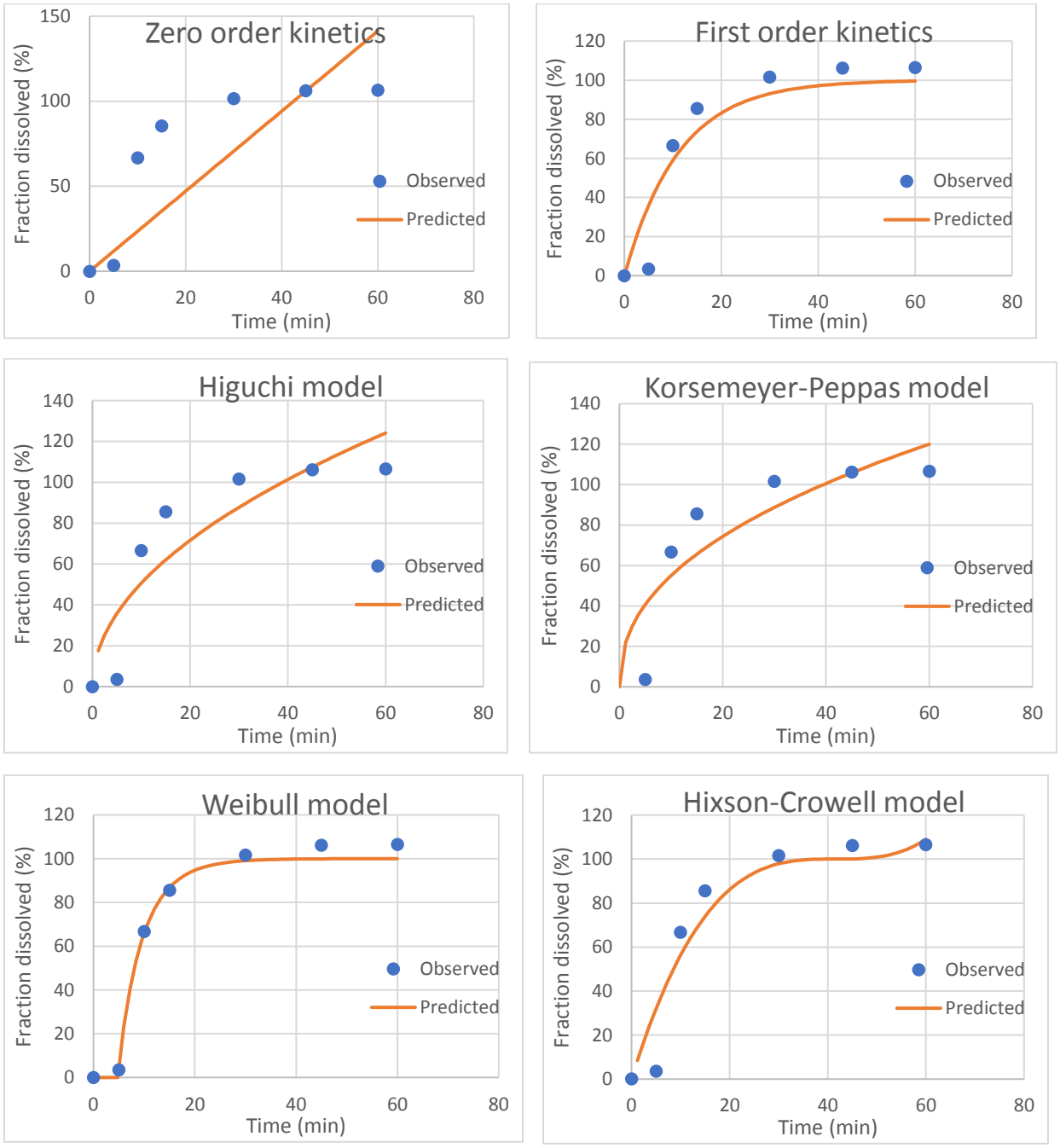


Table 8.1: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from formulation B1.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.4973	0.8909	0.8211	0.6423	**0.9898**	0.9158

Figure 8.2: Formulation B2 kinetics.

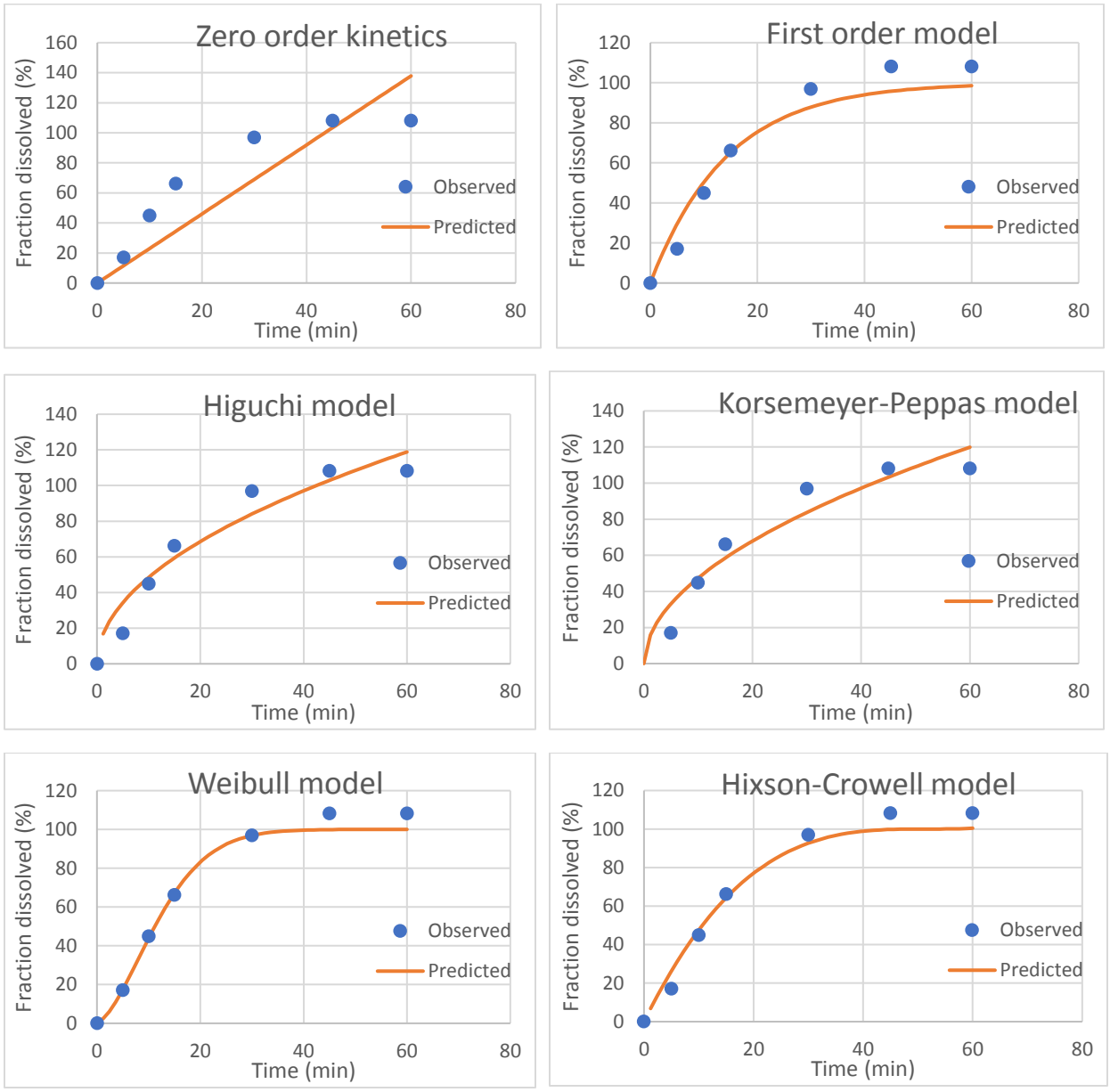


Table 8.2: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from formulation B2.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.7248	0.9555	0.9432	0.8830	**0.9822**	0.9790

Figure 8.3: Formulation kinetics B3.

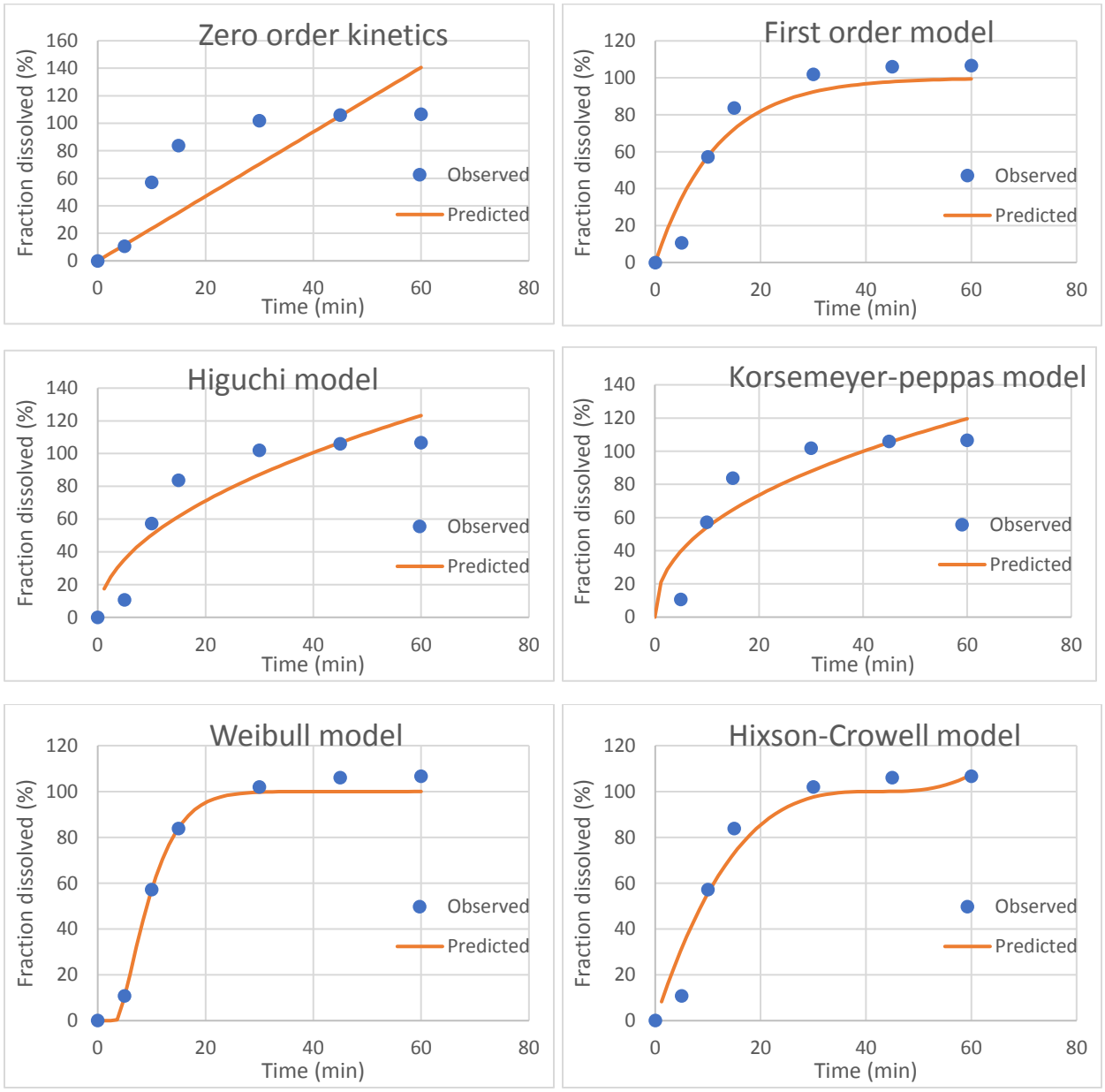


Table 8.3: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from formulation B3.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.5420	0.9253	0.8664	0.7247	**0.9896**	0.9514

Figure 8.4: Formulation kinetics B4.

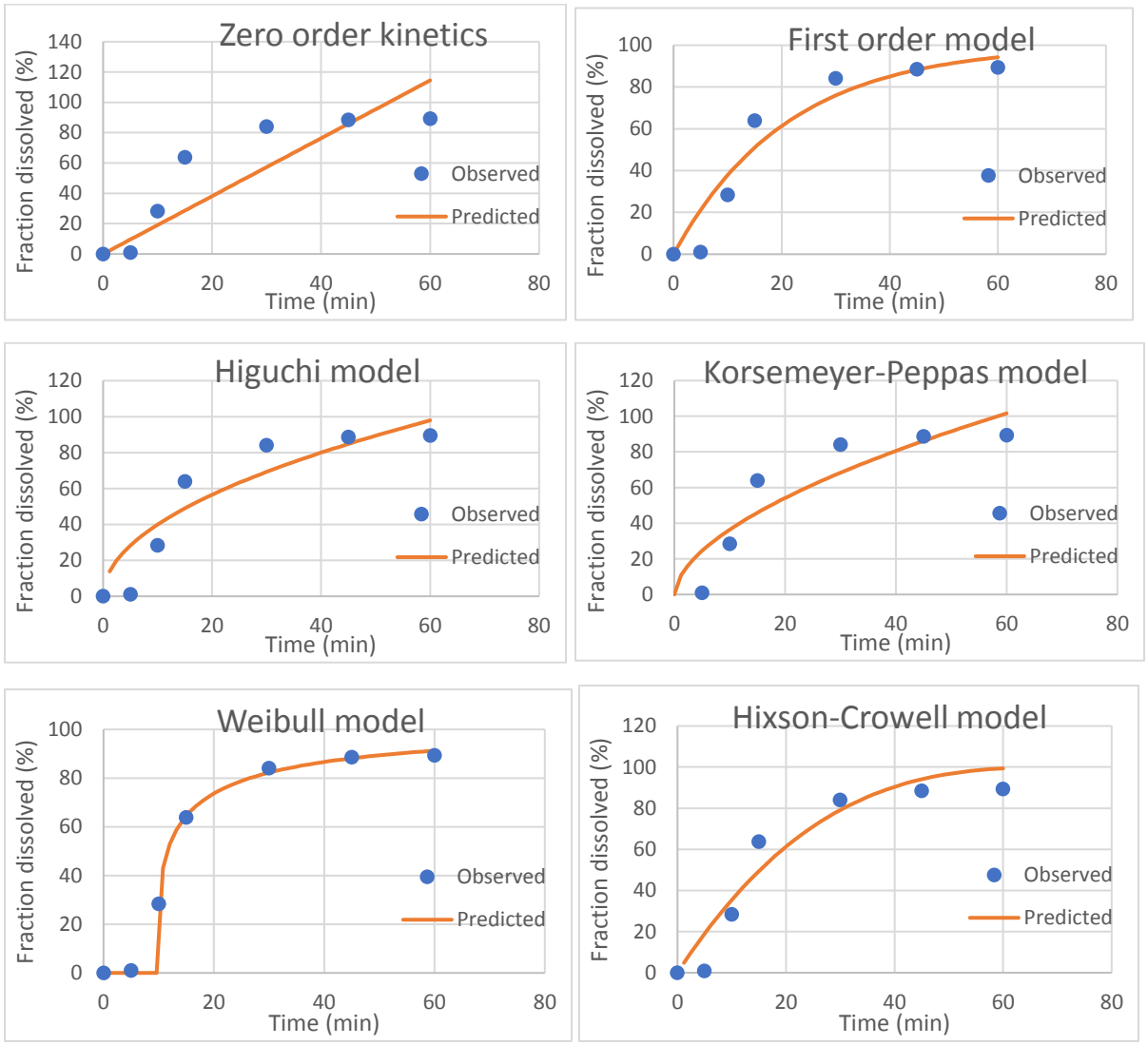


Table 8.4: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of loperamide from formulation B4.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.7174	0.9229	0.8555	0.7515	**0.9987**	0.9245

Figure 8.5: Formulation kinetics B5.

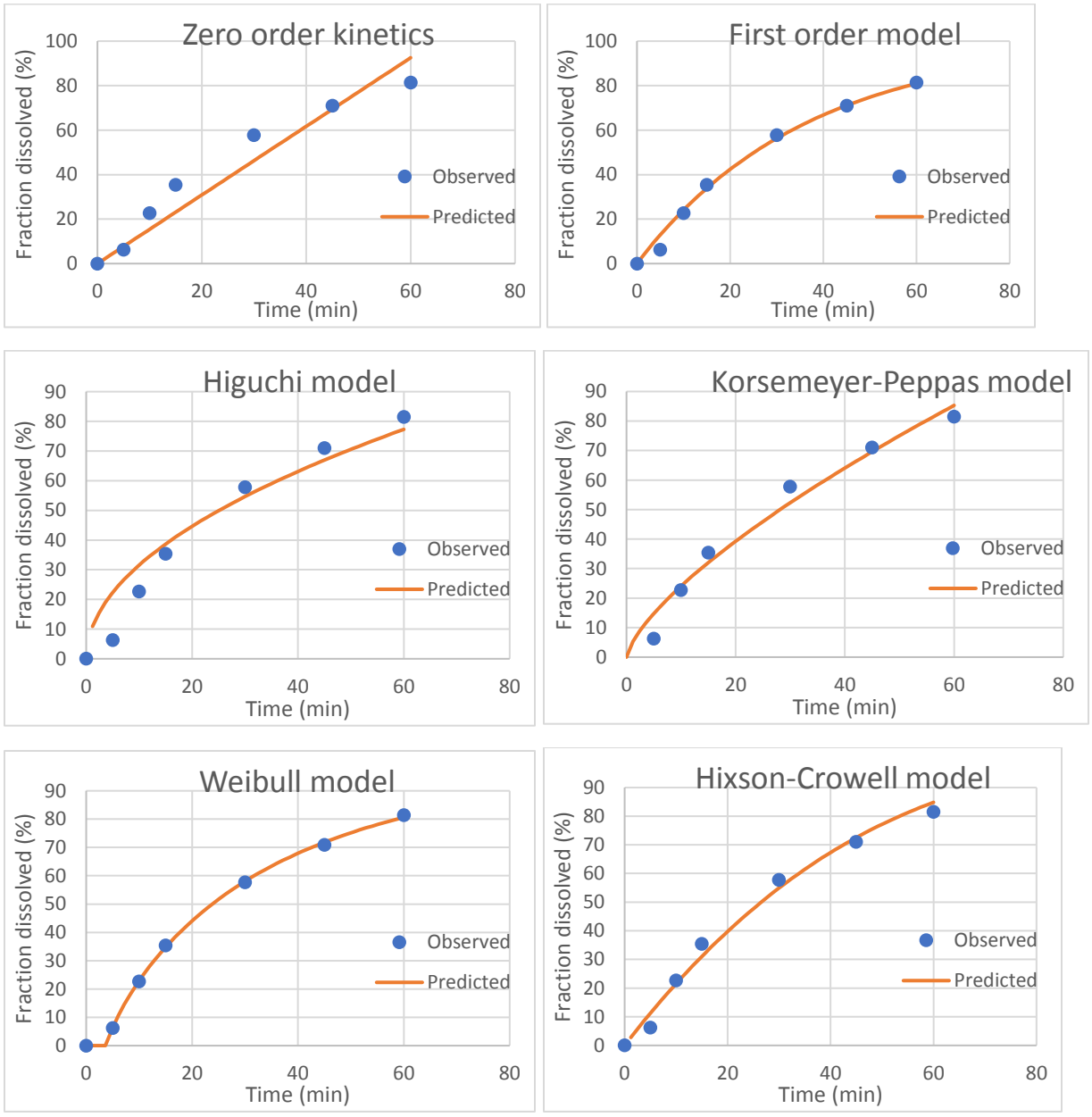


Table 8.5: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from formulation B5.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.9238	0.9916	0.9354	0.9613	**0.9995**	0.9891

Figure 8.6: Formulation kinetics B6.

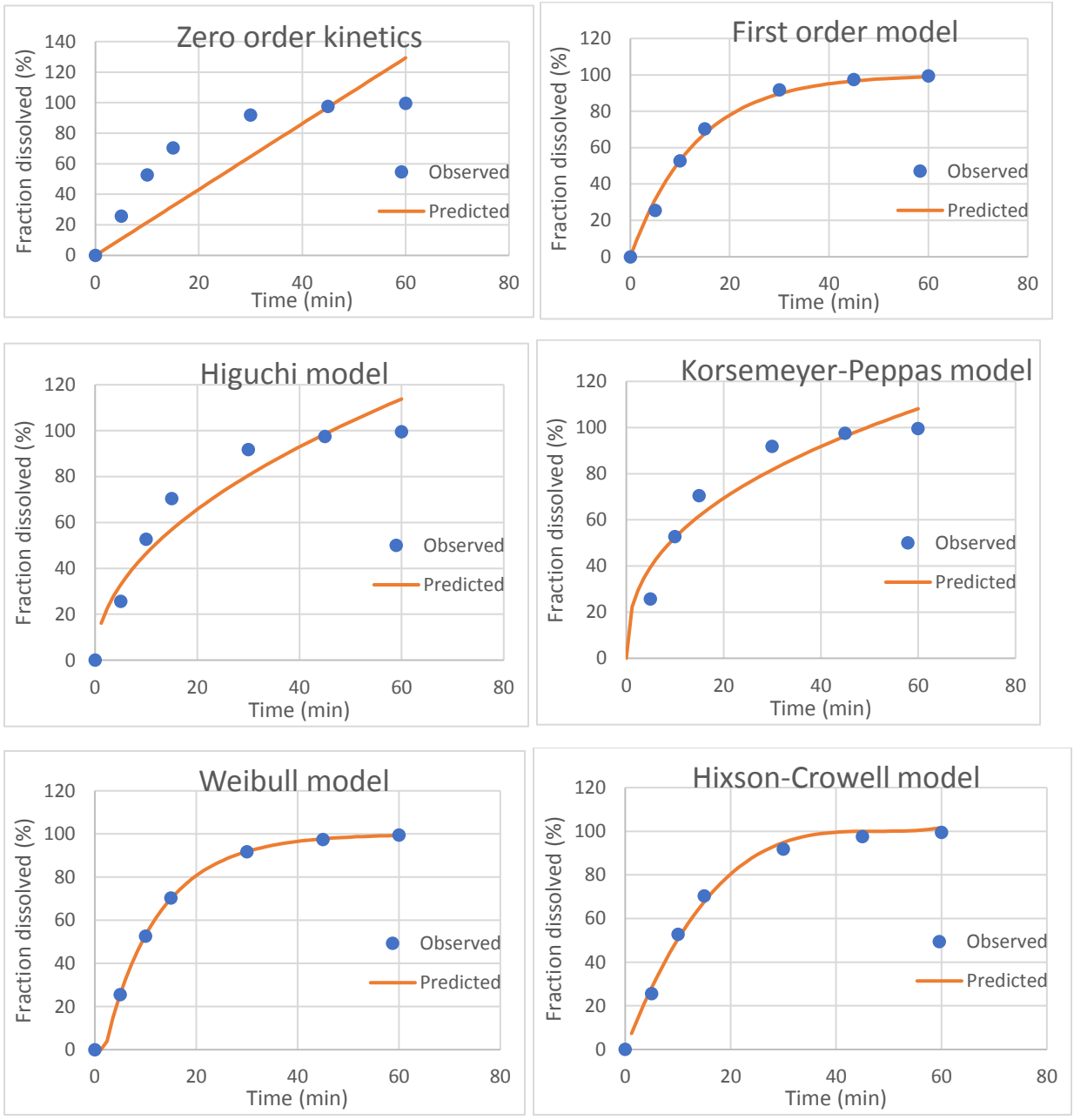


Table 8.6: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of loperamide from formulation B6.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.5194	0.9947	0.9316	0.8702	**0.9999**	0.9956

Figure 8.7: Formulation kinetics T1.

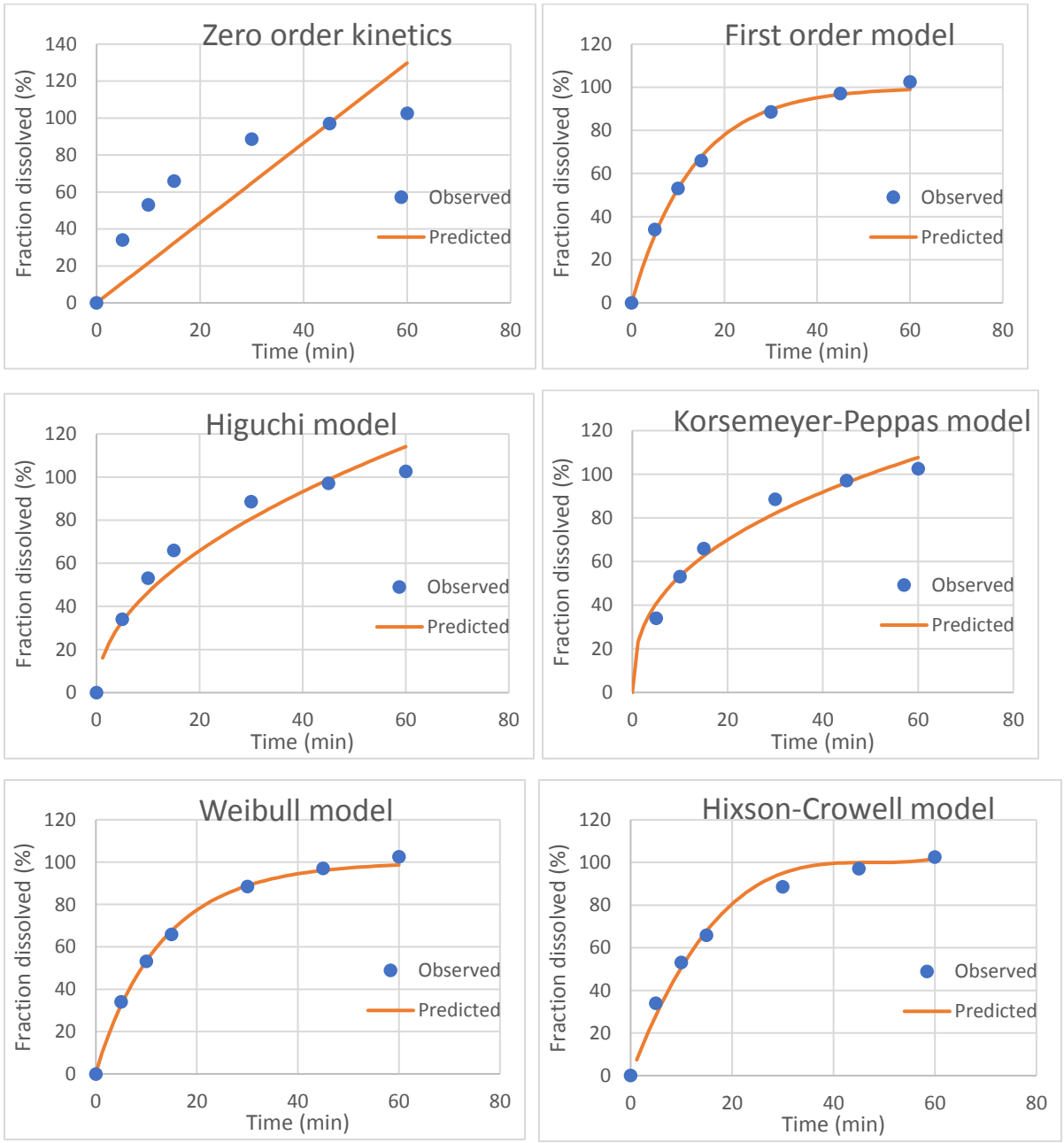


Table 8.7: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of loperamide from formulation T1.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.5235	**0.9970**	0.9613	0.9573	0.9960	0.9889

Figure 8.8: Formulation kinetics T2.

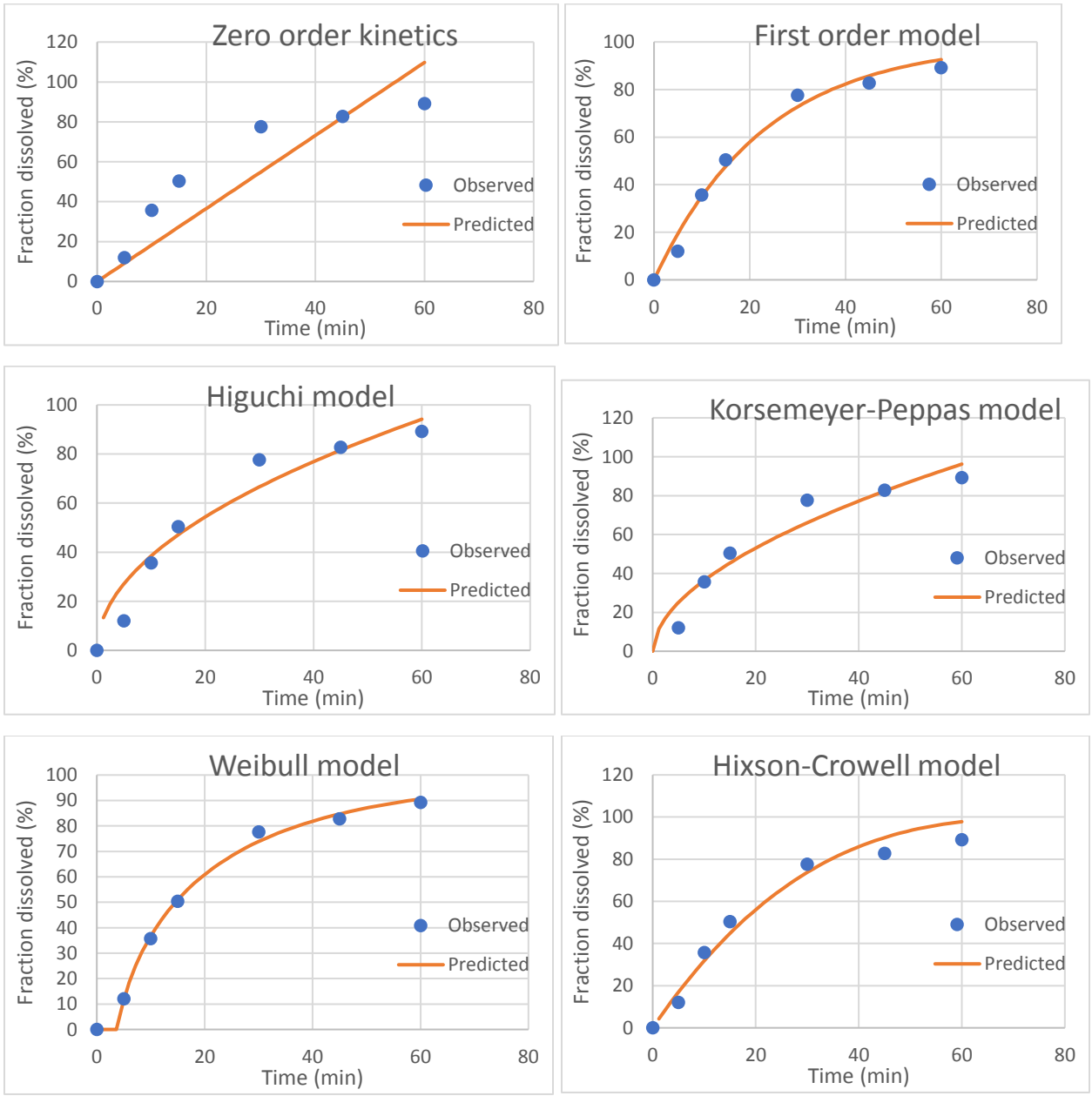


Table 8.8: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from formulation T2.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.7635	0.9858	0.9472	0.8983	**0.9957**	0.9714

Figure 8.9: Formulation kinetics market product.

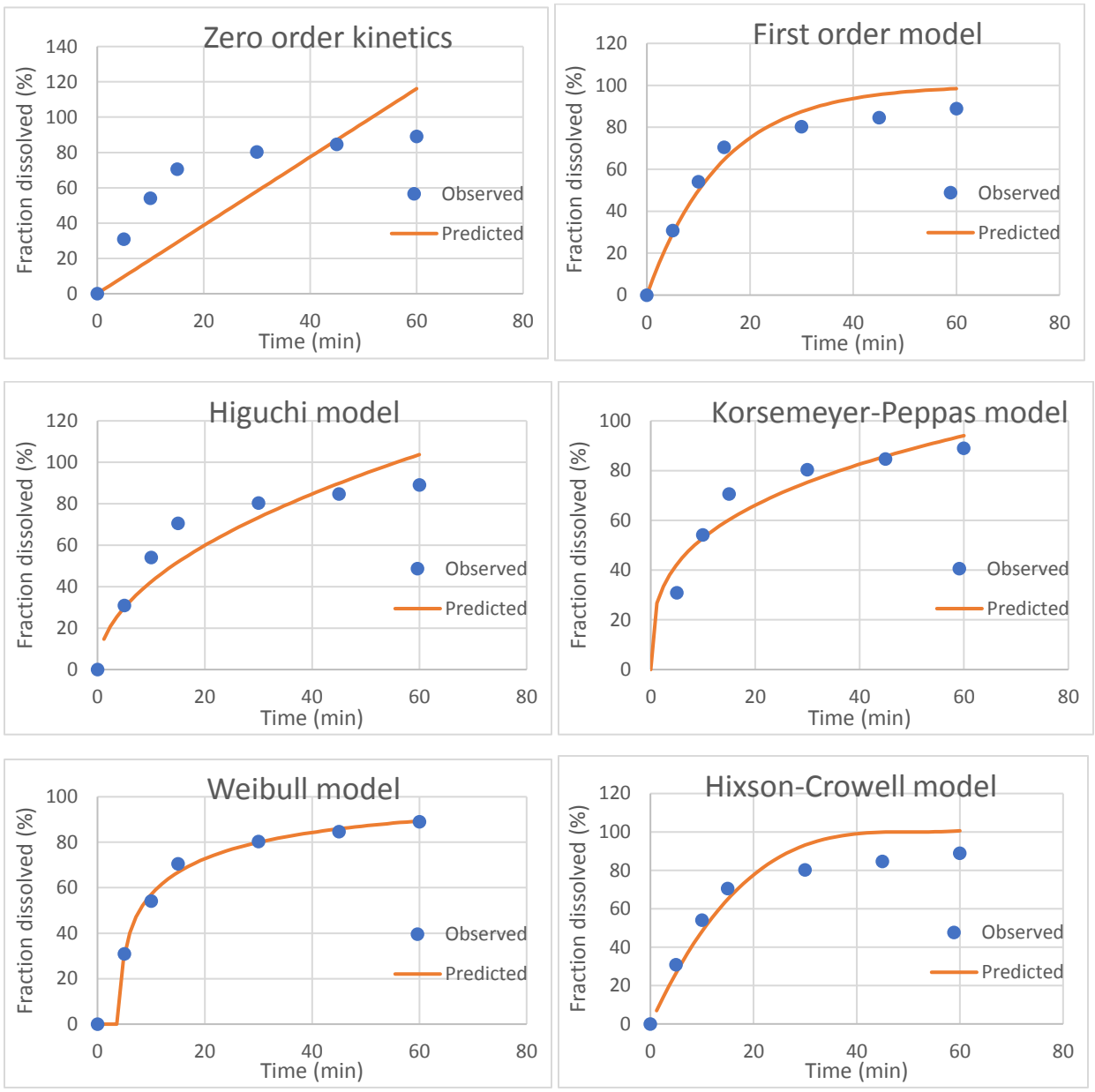


Table 8.9: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from market product.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.2831	0.9510	0.8788	0.8511	**0.9943**	0.9046

Figure 8.10: Formulation kinetics PM1 PEG.

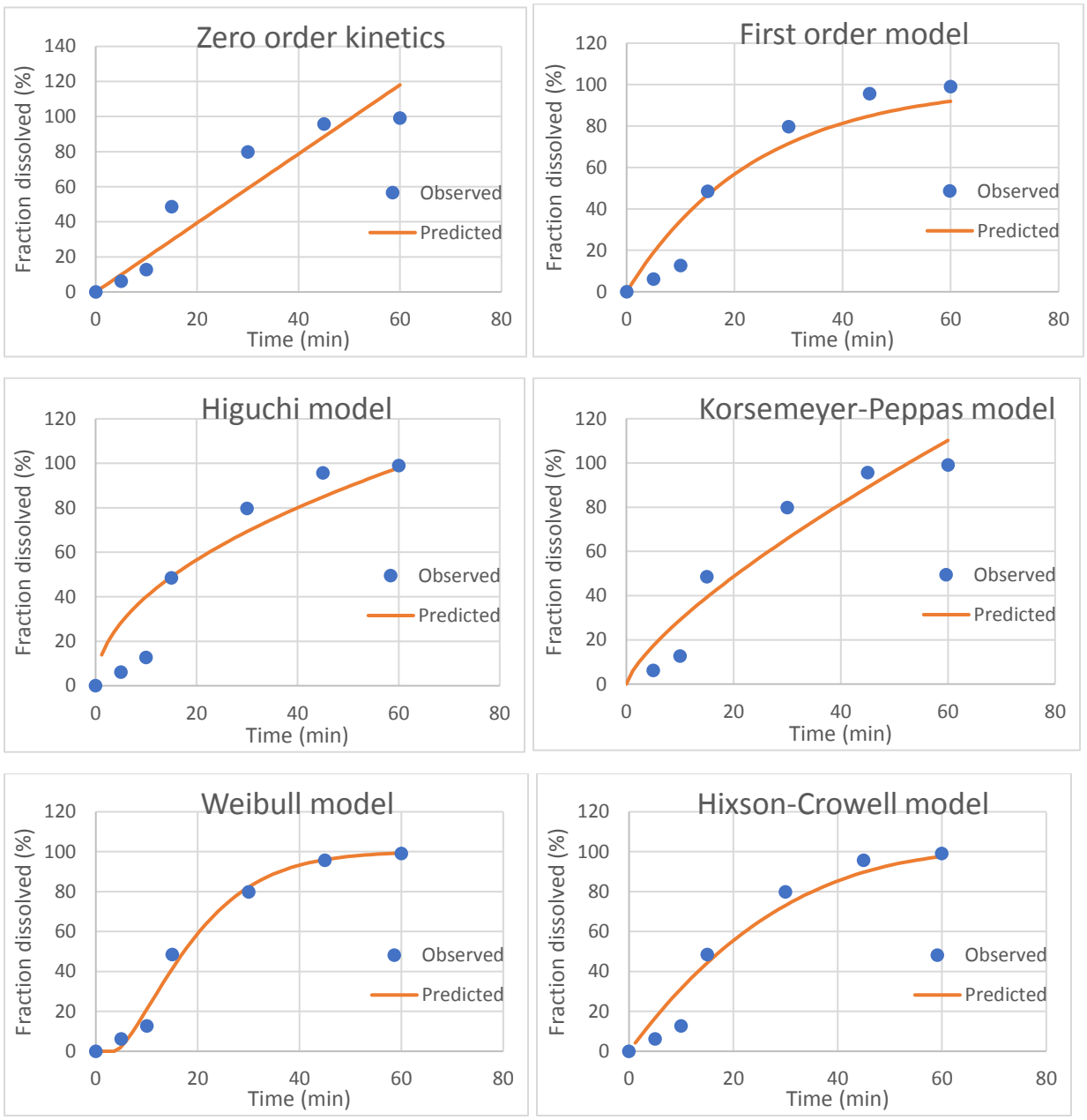


Table 8.10: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of Loperamide from formulation PM1 PEG.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.8869	0.9227	0.8693	0.8748	**0.9813**	0.9499

Figure 8.11: Formulation kinetics PM2 PVP.

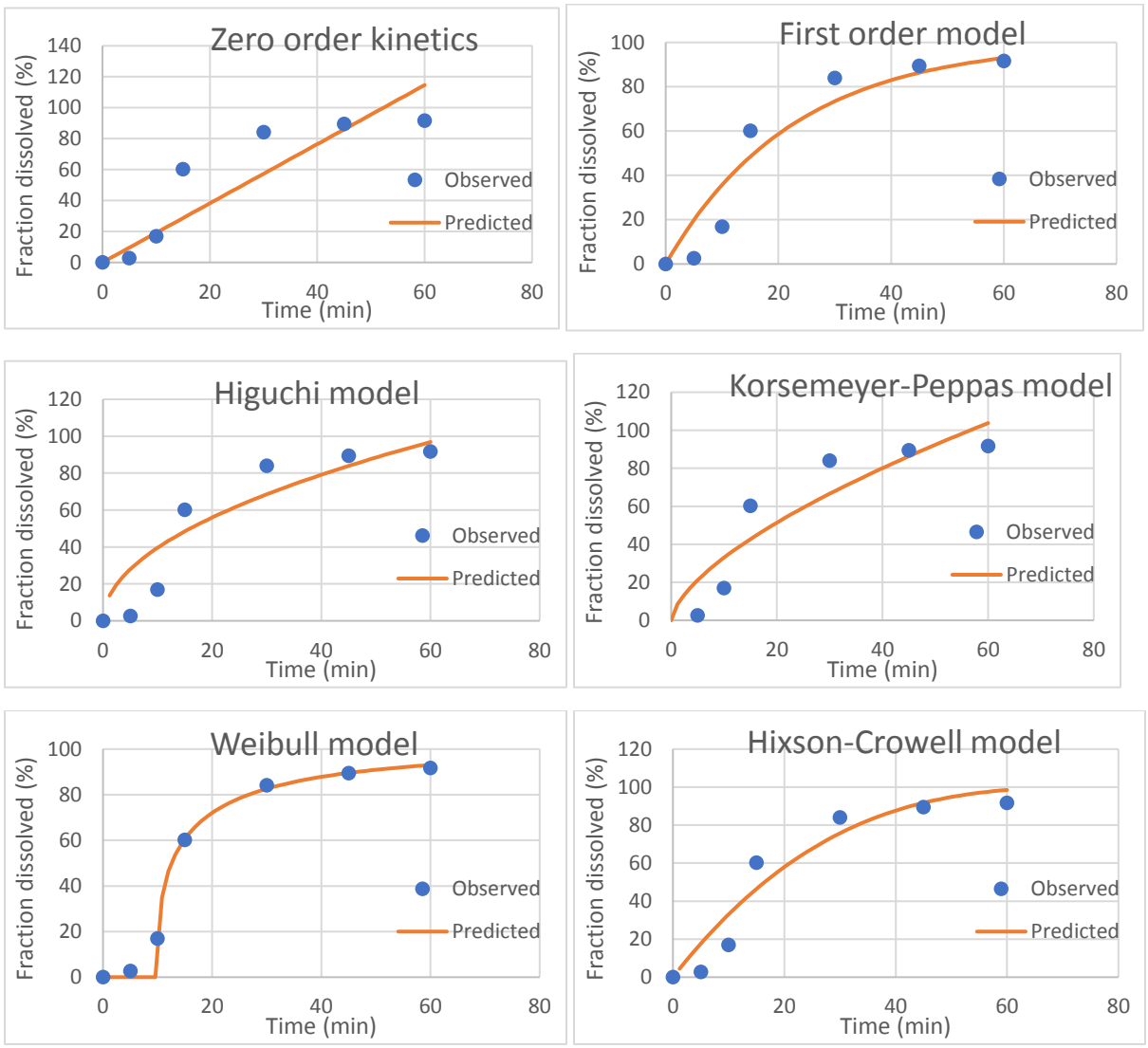


Table 8.11: Kinetic equations goodness of fit to equations (3.10-3.15) representing release of loperamide from formulation PM2 PVP.

Parameter	Zero order	First order	Higuchi model	Korsemeyer-Peppas	Weibull	Hixson-Crowell
R^2 adj	0.7784	0.9125	0.8470	0.7741	**0.9984**	0.9235