# PREPARATION AND EVALUATION OF AMLODIPINE SOLID DISPERSION USING POLYVINYLPYRROLIDONE K30

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**UNIVERSITY OF BENIN**

**BENIN CITY**

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**A PROJECT SUBMITTED TO THE DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY IN PARTIAL FULFILMENT OF THE PHARMACY (PHARM.D) DEGREE OF THE UNIVERSITY OF BENIN, BENIN CITY, EDO STATE NIGERIA**

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# CERTIFICATION

This is to certify that this work was carried out by **AZUBUIKE KELECHI AUGUSTINE** in the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria, in partial fulfillment for the award of the Pharm. D degree of the University.

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**(Head of Department)**

# DEDICATION

This work is dedicated to the Almighty God, for guiding me through this academic journey, and to my beloved family, for their unconditional love, support, and encouragement, may this achievement serve as a testament to your unwavering sacrifices and prayers.

## ACKNOWLEDGMENT

It is with a heart full of gratitude that I acknowledge the invaluable support and guidance of the many individuals who have contributed to the realization of this project.

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# ABSTRACT

**Background:** Amlodipine is a third-generation dihydropyridine antihypertensive that blocks calcium on calcium channels used frequently in hypertension and angina. It has even been listed by WHO as an Essential Medicine. Although very practical, it belongs to the Biopharmaceutical Classification System (BCS Class) II - the drug is very permeable across the intestinal wall but very low water solubility. Even the low solubility is the slowest step in absorption which may lead to the release of tablets being not fully done, inconsistent bioavailability between different patients and reliance on food. Consequently, by enhancing solubility of amlodipine we desire to make the administration of amlodipine more effective orally.

**Purpose:** The purpose of this work was the development, characterization, and testing of solid dispersions (SDs) of amlodipine with Polyvinylpyrrolidone (PVP K30). We thought that the method would help us to change the drug which is not soluble in large quantities but exists as crystals to a high-energy, highly soluble amorphous one. The research rigorously investigated system of varying drug-polymer ratios and characterized the optimally dispersed system completely, as a solubility was demonstrated and the in-vitro rate of solubility was significantly increased.

**Material and Methods:** Amlodipine solid dispersions through solvent evaporation method were prepared by us. A common organic solvent (ethanol) was used to dissolve the drug as well as the hydrophilic carrier, PVP K30. A rotary evaporator was then used to remove the solvent under reduced pressure leaving a mass of solid. This mass was dried, ground and sieved. Five ratios of drug-polymer

weight were made: 1:1, 1: 2, 1:3, 1:4 and 1:5. Lastly, all Solid dispersion had their apparent aqueous solubility determined. And lastly we pressed this optimized powder into tablet form and compared the drug release of this tablet in in-vitro with that of a normal tablet in a dissolution experiment.

**Results:** There was distinct polymer-dose-dependent increase in aqueous solubility of amlodipine in the solid dispersions relative to pure, unprocessed amlodipine drug. This ratio was the best solubility enhancer with the highest level of 1:5 (drug: polymer), and it was determined to completely analyze. FTIR of 1:5 Solid dispersion showed the typical peaks of the amlodipine and PVP K30, and no new peak or significant change, meaning strong chemical interaction. The most important was the Differentiated Scanning Calorimetry (DSC) thermogram, which indicated the total loss of the sharp endothermic melting point of crystalline amlodipine, which confirmed the drug had been transformed to a molecularly dispersed or amorphous form. Most importantly, the 1:5 solid dispersion to tablets discharged the drug far quicker and more certainly in-vitro when compared to the control tablets to the pure drug.

**Conclusion:** This experiment proves the application of PVP30 as a hydrophilic carrier in a solvent evaporation solid-dispersion method is an efficient approach to increase the solubility and dissolution rate of the poorly water-soluble amlodipine drug. The 1:4 optimization resulted in the drug being altered to a stable and amorphous form, thus a significantly better release profile. This method presents a good avenue towards the generation of novel oral dosage shapes of amlodipine that may confer improved bioavailability and dependable therapeutic results.

# CHAPTER ONE

## INTRODUCTION AND LITERATURE REVIEW

### 1.1 Amlodipine: An Element of Cardiovascular Therapy.

Cardiovascular disease (CVD) is the pathology that causes the highest level of morbidity and mortality all over the world, and it is a significant health and economic threat to the whole world. Hypertension or high blood pressure is in the middle of the CVD pandemic and is a silent killer since it is the one and only modifiable type of risk factor to stroke, heart failure, myocardial infarction and chronic kidney disease [Akpan *et al*]. Successful treatment of hypertension is, thus, one of the main objectives of the contemporary preventative medicine. Among the plethora of the antihypertensive drugs, amlodipine has become one of the most popular, clinically significant, and effective medications of the past 30 years.

#### 1.1.1 Role and Classification of Amilodipine.

Amlodipine is within the category of the dihydropyridines (DHP) group of calcium channel blockers (CCBs). It is specifically categorised as a third-generation DHP, which is used to indicate that it has a very elegant and high-quality clinical profile over its predecessors [Opie & Messerli, 1995]. First-generation DHPs, including short acting nifedipine, were characterised by a fast action, short duration and a tendency to cause severe reflex tachycardia and side effects that were due to vasodilation. To address these shortcomings, Amlodipine has been carefully engineered purposely to provide a slow onset of action and an immeasurably long-lasting effect [Arewoh and Eiche, 2010], of which these qualities are the keys to its treatment effectiveness

[Murdoch & Heel, 1991]. It is largely applied in the treatment of two large cardiovascular conditions:

- High blood pressure: It is an initial drug used in reduction of blood pressure, almost all major international guidelines, including the ones of the American Heart Association (AHA) and the European Society of Cardiology (ESC). It works as a monotherapy, especially in older patients or of African descent and is also a first line choice in patients with co-morbidity such as stable angina [Williams et al., 2018].
- Angina Pectoris: It is prescribed in the treatment of chronic angina of the stable (chest pain when exercising) and the vasospastic (Prinzmetal) angina [Chrysant, 2004].

Its use is formally accepted in the global medical community as it was placed on the Model List of Essential Medicines by the World Health Organisation (WHO) [WHO Model List, 2021]. This category is the list of medications that are supposed to be regarded as the most effective, safe and cost-effective to meet the most urgent requirements of the population health. The fact that amlodipine is on this list highlights its strong effectiveness, a proven and desirable safety profile, and its unmatched cost-efficacy, which has been further enhanced due to its prevalence in the form of a generic drug.

### 1.1.2 The Cellular Mechanism of Action.

Amlodipine mechanism of action is a very selective and elaborate cellular level pharmacological intervention. It has therapeutic properties founded on its capability to suppress the entry of calcium ions (Ca $2^{+}$) by L-type channels of voltage-gated calcium channel. When the body is in perfect physiological condition, the process of muscle cell contraction, which includes cardiac muscle and vascular smooth muscle that forms the artery walls, is calcium-dependent. These L-type channels open when receiving a nerve impulse, as they make the cell membrane depolarized. Calcium ions subsequently move out of the cell to the intra-cellular region. This influx of Ca $2^{+}$ attaches itself to a protein and this complex, in turn, triggers an enzyme, myosin light-chain kinase (MLCK). The process of contraction by the muscle cell is triggered by the phosphorylation of the light chains of the myosin proteins by MLCK, which allows the cells to interact with the actin filaments and contract accordingly. The great affinity and selectivity of amlodipine enable it to select the L type channels in vascular smooth muscle with a far stronger binding capacity than the cardiac muscle [Nayler, 1991]. Amlodipine prevents influx of calcium by stabilizing these channels in the condition of closed or inactive. Systemic vasodilation is the downstream effect of this blockade. Afterload is significantly decreased by opening up of the vessels by blocking the contraction of the smooth muscle in the arterial walls and this results in a massive increase in total peripheral vascular resistance (TPR). This decreases resistance directly/immediately reducing blood pressure hence decreasing the heart workload. The same applied to the angina case, where the dual benefit is the reduced oxygen requirement, due to decreased after load and myocardial wall load; and high oxygen supply, due to the vasodilation of the coronary arteries, and prevention of the coronary spasms in the variant angina.

### 1.1.3 The Pharmacokinetic Benefit and Acceptability.

One of the most important clinical benefits of amlodipine that, indeed, establishes it as an agent belonging to the third generation is its almost perfect pharmacokinetic profile. It has a slow absorption

rate, with a peak plasma concentration (T-max) of 6 to 12 hours following an oral dose, and has an extremely long terminal elimination half-life of between 30 and 50 hours [Meredith & Elliott, 1992]. It is due to this long half-life that its greatest clinical advantage is realized, once-daily dosing. This kind of a regimen of therapist enhances patient adherence especially where hypertension a chronic asymptomatic disease where the non-adherence of complex regimes has been shown to be the primary factor in treatment failure [Ogedegbe, 2008]. The long half-life also gives the drug a pharmacokinetic cushion; in case a patient forgets to take a dose, the level of the drug in the blood does not decrease to sub-therapeutic levels and thus the dangerous peaks and hourly values of blood pressure are avoided that have been experienced with short-acting drugs. Therefore, amlodipine provides a smooth and steady hemodynamic effect over a period of 24 hours, and this is very critical in ensuring that the target organs, including the brain, heart, and kidneys are not chronically damaged by high blood pressure. Such a combination of efficacy that is powerful yet patient-friendly, combined with a strong safety profile, squarely entrenches amlodipine as a cornerstone of contemporary cardiovascular therapy

### 1.2 The Formulation Issue: Solubility of Amlodipine.

Although the pharmacological properties of amlodipine, as dealt with in the first part of this paper, do illustrate one of the success story of medicinal chemistry, its physicochemical properties provide a serious and long-lasting problem in the field of pharmaceutical formulation [Okore, 2018]. This is a typical example in drug development and demonstrates that a molecule which is best designed to bind with a biological target can be highly inaccessible to that target.

Even with such formulation impediments, the therapeutic effectiveness of amlodipine has been realized. It is regularly prepared in its besylate form (amlodipine besylate). Though adding salt formation is often used to enhance aqueous solubility, in this case, the inherent characteristics of the drug are so intractable that not only as a salt, but also as awe of solubility is the key obstacle in getting it to its ideal delivery state. This is the challenge that is accurately and scientifically categorized by the Biopharmaceutical Classification System (BCS) [Amidon et al., 1995].

#### 1.2.1 Biopharmaceutical Classification System (BCS) Understanding.

The BCS is a scientific framework based on which pharmaceutical scientists and regulating authorities like U.S FDA identify the existence of the drug substance in the form of categories [U.S. FDA Guidance, 2017]. This system groups the drugs according to two main parameters that define the oral uptake which is aqueous solubility and intestinal permeability.

The oral absorption is also a step process: a pill should first dissolve, the drug molecules should be dissolved in the gastrointestinal fluid and then the dissolved particles should penetrate the intestinal mucosa and enter the bloodstream. The BCS is extrapolated to four categories, which immediately point out the most probable bottleneck in this process:

- Class I: High Solubility / High Permeability.
- Class II: Low Solubility / High Permeability.
- Class III: High Solubility / Low Permeability.
- Class IV: Low Solubility / Low Permeability.

Amlodipine can undoubtedly be considered a BCS Class II drug[Ohwoavworhua & Adelakun, 2005]. This subdivision is not only a nominal designation but the core diagnosis of the formulation problem, which means that the problem lies in the solubility of pharmaceuticals instead of the biological permeation.

### 1.2.2 The Two-Sided Coin of BCS Class II.

CS Class II BCS designation indicates that the drug has both a high intestinal permeability with low aqueous solubility [Dressman & Reppas, 2000].

- The Strength: Large Permeability: Existence of high permeability is a strategic success. The amlodipine molecule has some physicochemical properties like lipophilicity, molecular size that allows it to be passively diffused through the lipid rich biological membranes of the intestinal wall. The drug is absorbed easily once in solution and the biological barrier does not act as a limitation.

- The Bottleneck: Low Solubility: The critical bottleneck is low solubility. In the case of any oral solid dosage form, absorption of the drug requires a prerequisite of dissolution in gastrointestinal in-fluids. This reduced liquidity is due to a stable crystalline structure of amlodipine. The amlodipine molecules in its crystalline state are stuck in highly organized low-energy lattice, and to break that arrangement and enable the formation of solvated species, the lattice energy is needed to be significant. As a result, amlodipine dissolution is the rate-limiting process to be available in the system [Olorunsola & Adedokun, 2010].

The other (high permeability) and the one (low dissolution) look alike; imagine a wide, 8-lane highway fed by only one country lane, narrow. The bottleneck of that single lane determines the throughput of the whole traffic system as opposed to the capacity of the highway which is the exact problem presented by amlodipine.

### 1.2.3 Clinical and Pharmacokinetic Consequences.

The absorption profile of amlodipine limited by its dissolution rate produces multiple important clinical undesirable events which undermine its predictability:

### 1.2.4 Partial absorption and less Bioavailability.

The gastrointestinal tract will give a limit to the absorption time, normally a few hours in the small intestine. In case amlodipine dissolving is too slow, a significant amount of intake of the given drug may pass through the gastrointestinal tract as not being absorbed, and it will be excreted with no therapeutic effect. Consequently, the total bioavailability (portion of dose entering systemic circulation) can be significantly diminished; a 10 mg dose can only carry 6- 7mg of active drug [Soni et al., 2011].

### 1.2.5 Variable Bioavailability (Inter-, Intra-Patient)

Absorption is strongly influenced by individual patient physiological factors when dissolution is the rate-limiting process [Charman & Charman, 2008].

- Gastric pH: Amlodipine an antagonist, is a weak base and its solubility varies with the gastric acidity. Antacids or proton-pump inhibitors patients, which can modify the gastric pH may exhibit a different absorption profile as opposed to those who do not.

- Food Effect: This is the nature of BCS Class 2 drugs, a high-fat meal causes the release of bile salt, which are natural surfactants that increase the solubilisation of lipophilic, poorly soluble drugs. Therefore, unpredictable and erratic dose-response interactions can be observed in a patient that is

taking amlodipine with a meal as compared to a patient taking the same drug on an empty stomach [Charman & Charman, 2008].

- Delayed Onset of Action : The slow dissolution rate is translated to the delay of absorption and serves to delay the length of time required to reach therapeutic plasma concentrations (T-max). However, since amlodipine delays in chronic hypertension are as tolerable as amlodipine long half life, though intentionally long, is, this delay is not a controlled one but, in fact, is a result of a formulation error instead of deliberate extended-release action.

Based on this, the main issue that this project will deal with is not the pharmacological potency of the drug but rather the question of how it is delivered in the form of a pharmaceutical. Ameliorating the low water solubility of amlodipine is one of the main and urgent tasks of formulation scientists. The broad objective is to come up with an optimised formulation that will overcome the solubility barrier hence guaranteeing more comprehensive, consistent, and reliable therapeutic effects on every patient.

### 1.3. The Resolution: Solid Dispersion Technology.

Therefore, to address the challenging issue of drugs which cannot be readily dissolved in the water such as amlodipine, pharm peeps (scientists) have come up with a number of tricks to increase the percentage of drug which actually gains entry into the body. To get a friendlier drug, they adjust the particle size (smaller size, through micronization and Nano crystallization), or they adjust the chemistry (into a simpler form, such as a salt). Slick lipid based strategies such as Self-Emulsifying Drug Delivery Systems (SEDDS) and even sophisticated complexation with cyclo dextrins also exist [Eraga *et al*].

Even these good ideas have hiccups. Micronization may lead to clumping of particles and not all salts forms are possible with neutral drugs. Among them all, the solid dispersion (SD) method is the true

MVP; it is easy, inexpensive, versatile, and it will provide oral bioavailability to BCS Class II drugs every time [Leuner & Dressman, 2000].

In solid dispersion, basically, a combination of drugs and water-loving carrier is a neutral suspension that remains in a solid state. In most cases, the system can be characterized by two components; a hydrophilic delivery system (the carrier) and a hydrophobic drug [Chiou & Riegelman, 1971].

There are some structural possibilities covered by the word dispersion. The drug may be in crystalline crystals, amorphous crystals or even at the molecular level, distributed like a genuine solid solution, such as salt dissolved in water, only embedded in the carrier lattice.

The carrier may be crystalline (e.g. urea or sugars), or amorphous (e.g. polymers), which is more frequent. The amorphous carriers are used due to their increased energy, which has the ability of trapping the drug at high-energy unstable structure.

A solid dispersion is a multi-component system in which one or more active pharmaceutical ingredients (drugs) are dispersed within an inert, hydrophilic carrier or matri**x** in a solid state. This system typically involves at least two components: a hydrophilic matrix (or carrier) and a hydrophobic drug.

The term "dispersion" is broad and covers several possible microstructures. The drug can be dispersed in several forms, which dictates the system's stability and performance:

- **Crystalline Particles:** The drug may exist as fine crystalline particles suspended in the carrier.

- **Amorphous Particles:** The drug exists as distinct, non-crystalline (amorphous) particles separated from the amorphous carrier.

- **Molecular Dispersion (Solid Solution):** This is often the ideal state. The drug is dispersed on a molecular level, forming a true solid solution where individual drug molecules are dissolved and entrapped within the carrier matrix, much like salt dissolved in water.

The matrix itself can be either crystalline (e.g., urea, sugars) or, more commonly, amorphous (e.g., polymers). Amorphous carriers are often preferred as they possess a higher thermodynamic energy and can more effectively stabilize the drug in its own high-energy amorphous form.

### 1.3.1 The effect of solid dispersion in increasing solubility

This is primarily due to the fact that apparent solubility is jacked up by solid dispersions since they break the natural constraints of the drug. It's a combo of a few things:

- Disruption of Crystalline Lattice (Amorphization).

  - Crystalline drug is located in a low-energy, ordered grid. It takes a significant amount of energy ( lattice energy) to separate them. The grid is broken in solid dispersion, most notably a molecular dispersion, which reduces the drug to a high-energy and unstable amorphous structure, which is much more soluble [Craig, 2002].

- Increased Wettability

  - Hydrophobic drugs such as amlodipine have a tendency to squeeze water. With solid dispersion, the drug particles are encased in a super hydrophilic carrier. When exposed to GI fluids, the

carrier becomes similar to micro-wetting agent, drawing the water into it, reducing tension and causing the drug to dissolve more rapidly [Sethia & Squillante, 2004].

- Reduction of the Particles to the Molecular Size.

  - In a real solid solution, the size of the particles reduces to that of the single molecule. The Noyesstatic equation of dissolution is proportional to the surface area. And so Dost have the utmost surface, To release with convincingly speed.

- Preparation of Supersaturated Solutions.

  - Since the carrier dissolves rapidly, it will shoot out the drug in a high-though outburst of its dissolved state, frequently forming a temporary supersaturated pool around the dissolving location. Such high gradient causes the drug to jump over the intestinal wall into the bloodstream.

  - Sometimes, it is necessary to preserve food before use, pack it, or prepare it in advance before cooking. Solid dispersions are compatible with loads of water soluble carriers such as polyethylene glycol (PEGs) such as polyvinylpyrrolidone (PVP), poloxamers, hydroxypropyl methylcellulose (HPMC) and varieties of Eudragit [Janssens & Van den Mooter, 2009].

These dispersions can be most commonly generated in the lab by the solvent-evaporation and the fusion (melting) methods.

- Fusion Method: This involves heating a physical mixture of the drug and carrier until both components melt, forming a liquid solution. This melt is then rapidly cooled (quenched) to solidify, "freezing" the drug in its dispersed, amorphous state. Its primary limitation is the requirement for thermal stability for both the drug and the carrier.

- Solvent Evaporation Method: This technique is particularly effective for creating homogenous, amorphous dispersions and is suitable for heat-sensitive drugs. It involves dissolving both the drug and

the carrier in a common organic solvent (like ethanol, methanol, or dichloromethane). This is followed by the complete removal of the solvent, typically using a rotary evaporator or oven drying. As the solvent evaporates, the carrier precipitates and entraps the drug in a solid, highly dispersed form.

With all the evidence that it jack-up dissolves a bunch of BCS Class II drugs and since it is extremely flexible, solid dispersion method was selected as the centre of action in this project. The solvent -evaporation method, especially, provides us with a fine control in prep and test in the lab scale.

**1.4 The Carrier: Polyvinylpyrrolidone (PVP K30).**

Perhaps the most important formulation choice during the design of a solid dispersion system is the choice of the hydrophilic carrier. This option not only predetermines the possible level of solubility and dissolution promotion but, no less significant, the physical and chemical stability of the end product in the long term. The result of an inadequate selection can be a physically unstable formulation which forms a drug recrystallized or phases separate within weeks or months hence nullifying any future dissolution advantages [Vasconcelos et al., 2007].

A carrier has to have a certain and strict set of requirements. It has to be pharmacologically inert, non-toxic and easily soluble in aqueous media. In addition to these, it should be of high physicochemical compatibility (miscibility) with the drug in the solid form. Moreover, it must have a high glass transition temperature (T<|human|>In addition, it must have a high glass transition temperature (Tg) so that the amorphous system is in a form of stable, glassy form far above ambient storage temperatures (e.g., 25 C -40 C). Lastly, to be useful in the manufacture, it has to be dissolvable in non-toxic, common organic solvents.

Some of the many pharmaceutically usable polymers in the line include Polyvinylpyrrolidone (PVP), or Povidone, which has come to be a workhorse in solid dispersion technology. The absence of side effects or its questionable safety during its long history of use, since its initial development in the 1930s and its use as a blood plasma expander in the 1940s, confirm its good safety profile. This causes it to be an effective and a safe oral formulation, which could be used chronically

### 1.4.1 Chemical and Physical Revolution of PVP.

PVP is a synthetic, non-ionic, aqueous soluble polymer with a structure acquired by the free-radical polymerization of the monomer N-vinylpyrrolidone. Its outstanding hydrophilicity (much like that of the element water) is directly the result of its high polar lactam ring and an inherent component of each repeating monomer unit [Haaf et al., 1985].

The carbonyl group (C=O) in this structure of pyrrolidone ring is a strong hydrogen bond acceptor. This structural property enables PVP to react freely and extensively with water molecules and this way leads to the hydration and dissolution of the polymer in a very fast rate. The identical property is used to increase the wettability of hydrophobic medications such as amlodipine. In case the drug is distributed in the PVP matrix in a molecular form, the polymer serves as an interface with aqueous environment. It quickly attracts water and minimises the interfacial tension between the hydrophobic drug and the solvent and stimulates the destruction of the solid system into a fine, easily dissolvable suspension.

### 1.4.2 The Particular Choice of Grade: PVP K30.

PVP is not a single product, but there are several grades (e.g. K12, K17, K25, K30, K90) of the product which are distinguished by their K-value. The parameter of the K-value is based on the comparative viscosity of the solution polymer basing on the average molecular weight (MW) of the polymer.

- It has K-value of low value (e.g. K17): The molecular weight of these polymers is lower. Although they are highly soluble, their property of lower glass transition temperature .Whereas they are

highly soluble, they have shorter polymer chains and lower glass transition temperature (T), which has reduced physical inhibition of the crystallisation of drugs.

- High K-value (K90): These are of very high molecular weight. They are good stabilisers and produce high-T g matrices, although their viscosity (both in solution and as a melt) is so high that they are not easy to handle. They tend to be inert to organic solvents, have the potential to trap remaining solvent during drying, and in fact slow down the rate of drug release due to an inherently too slow rate of polymer matrix dissolution.

In this case, the PVP K30 grade was specifically selected as a compromise that is the best one that will be used. It has a convenient molecular weight of about 40,000 g/mol, which provides an optimal combination of characteristics of a solvent-evaporated solid dispersion [Adeoye & Bussi, 2020].

- Chain length Long enough to stabilise: Polymer chain length of PVP K30 is long enough to allow the creation of robust and effective inhibition to recrystallization, which is the main failure mode of amorphous systems.

- Ideal Viscosity and Processability: The polymer possesses a low Viscosity level, so that it can be easily and fully dissolved in common solvents. This is vital to the solvent evaporation procedure since it guarantees the ability to create a homogenous liquid solution of the drug and the carrier prior to its process of drying. This liquid phase homogeneity is vital towards a homogenous molecular-level dispersion of the end-product as a solid state substance.

### 1.4.3 The PVP K30 Dual Mechanisms of Stabilisation.

The main purpose of PVP K30 is to be used as a crystallisation inhibitor. It does this in both kinetic and thermodynamic ways by ensuring the high-energy amorphous amlodipine gets trapped and does not revert to the low-energy crystalline form [Taylor & Zografi, 1997].

*1. Kinetic Stabilisation (The "Anti-Plasticizer" Effect and the "Matrix" Effect)*

This is a physical mechanism. The amorphous drugs are thermodynamically unstable and they always attempt to crystallise. Though, crystallisation is a process, which also presupposes some kind of molecular mobility, i.e. the drug molecules should be capable of movement, orientation and forming a crystal nucleus.

This is kinetically inhibited by PVP K30. Being a high MW polymer, it is of high glass transition temperature (T ) G. At lower temperatures, the polymer-drug combination is in a solid, glazed phase having very high viscometricity. The amlodipine molecules in this state are actually frozen in position, the polymer chains are rigid and they are physically separated. This steric hindrance or which is also known as the matrix effect, deprives the drug molecules of the mobility required to nucleate and form crystals. This is the reason PVP K30 can be viewed as an anti-plasticizer to the drug- it makes the system overall more stiff and high in Tg to be in a stable amorphous state to be stored.

*2. Specific Molecular Interactions Thermodynamic Stabilisation.*

It is a chemical process and even more important to the long-term success. PVP K30 does not passively partition the drug molecules, but rather it reacts with them. The first stage is recrystallization where it is energetically more favourable that the drug-drug interactions should be than the drug-polymer interactions. PVP K30 is aimed at interfering with this.

Several of the hydrogen bond donor sites of the amlodipine molecule are also the secondary amine (-NH-) bond site of the dihydropyridine ring and its primary amine (-NH 2) bond site of the side chain.

As stated, the carbonyl (C=O) group of the PVP K30 has a high hydrogen bond acceptor site. As the solvent is removed, the two sites of interaction are brought to the same point leading to strong intermolecular hydrogen bonding between the amlodipine molecule and polyvinylpyrolidone (PVP) polymer chain in the solvent evaporation process. The strength of these drug polymer interactions is very favourable and competes well with the drugdrug interactions which are the required initial step to crystal formation. PVP K 30 prevents self-assembly of the drug in the polymer as it thermodynamically stabilises the amorphous form of the drug by forming a stable and miscible single phase solution at the molecular scale, and the amorphous form of the drug is energetically favourable to remain dispersed by the polymer skeleton.

In brief, PVP K30 has been chosen based on the unique feature solving two functions of an ideal solid dispersion carrier; creating high-energy stable amorphous state by virtue of its solvent compatibility and hydrogen-bonding potential, and maintaining the solvent state kinetically and thermodynamically, therefore assuring stability of the improved dissolution profile during the shelf life of the product.

### 1.5 Research Justification (II): From Pharmaceutical Intermediate to Viable Dosage Form—The Rationale for Tablet Formulation

The successful creation of an amorphous amlodipine solid dispersion, as confirmed by preliminary solubility data and solid-state characterization, represents a significant and successful first step. This achievement demonstrates, at a molecular level, that the primary hurdle of amlodipine's poor aqueous solubility can be overcome. However, in the field of pharmaceutical technology, this optimized powder is not considered an end product. It is, by definition, a pharmaceutical intermediate.

This optimized intermediate, while superior in its solubility, is unsuitable for direct clinical administration. It presents a new, secondary set of challenges that must be systematically addressed and solved before its therapeutic potential can be realized. This research, therefore, extends beyond the powder characterization to address the complete, practical, and essential question of manufacturability. The rationale for including a comprehensive tablet formulation and evaluation phase is threefold, addressing critical issues of patient safety, manufacturing viability, and the ultimate proof of therapeutic efficacy.

### 1.5.1 The Problem of the Intermediate: Limitations in Safety, Stability, and Compliance

The solid dispersion powder produced by the solvent evaporation method is, by its very nature, an unsuitable final dosage form for several critical reasons.

- **Dose Accuracy and Patient Safety:** Amlodipine is a potent drug with a low therapeutic dose (e.g., 5-10 mg). It is impossible for a patient to accurately perform gravimetric or volumetric measurement of such a small powder mass in a home setting. This introduces an insurmountable challenge in dose accuracy, creating significant risks of either accidental overdose, leading to toxicity, or under-dosing, leading to a sub-therapeutic and inefficacious response [Aulton, 2018].
- **Physicochemical Instability:** The high-energy amorphous state is, by definition, thermodynamically unstable. The system will perpetually seek to revert to its low-energy, stable crystalline state (recrystallization). This process is highly accelerated by the presence of moisture. The selected polymer, PVP K30, is a known hygroscopic material, meaning it readily adsorbs moisture from the environment [Hancock & Zografi, 1997]. This adsorbed moisture acts as a plasticizer, increasing the molecular mobility of the entrapped amlodipine molecules and dramatically increasing the risk of recrystallization, thereby negating the enhanced solubility. The bulk powder form, with its high surface area, is maximally susceptible to this moisture-induced failure.

- **Patient Compliance:** From a patient-centric perspective, bulk powders represent a low-compliance dosage form. They are difficult to handle, have poor palatability (taste), and are inconvenient for transport.

For these reasons, the oral solid tablet remains the "gold standard" and the most widely accepted dosage form in pharmaceutical manufacturing. It provides superior stability by protecting the active ingredient from the environment, ensures precise dose accuracy, and offers the highest levels of patient compliance and convenience [Aulton, 2018]. Therefore, the first justification for this phase of the study is to convert the promising intermediate into a viable, stable, and patient-centric medicine.

### 1.5.2 The Manufacturing Challenge: Remediating Poor Physicomechanical Properties

The second justification stems from the new problems created by our solution. The very properties that make the solid dispersion effective (e.g., amorphization, high polymer content) also make it exceptionally difficult to process. Solid dispersions produced by solvent evaporation are notoriously problematic for downstream manufacturing, exhibiting a range of poor physicomechanical properties [Shah & Phuapradit, 2004]:

- Poor Flowability: The particles are often irregular in shape, cohesive, and possess high electrostatic charge. This prevents the powder from flowing uniformly from the industrial hopper into the tablet die cavity.
- Poor Compressibility: The powder may be "fluffy" (low bulk density) and fail to form a strong, cohesive compact under pressure, leading to mechanically weak tablets.

This study will employ the direct compression method, a preferred manufacturing process due to its simplicity and cost-effectiveness. However, direct compression demands a powder blend with *excellent* flow and compression characteristics. To achieve this, the solid dispersion intermediate must be formulated with a specific suite of functional excipients. This study will therefore investigate a formulation challenge: to remediate the poor manufacturability of the solid dispersion *without* compromising its amorphous nature. The selected excipients for this purpose are:

- **Diluents/Fillers (Lactose, Calcium Diphosphate):** These are required to increase the tablet mass to a practical, manufacturable size. Critically, they are also chosen for their own excellent

compression properties, acting as the primary structural "glue" or "scaffold" that the solid dispersion powder lacks.

- **Glidant (Talc):** This is essential to improve powder flow. Talc particles reduce inter-particulate friction, allowing the blend to flow smoothly and uniformly into the die. This is a non-negotiable prerequisite for achieving weight uniformity and, by extension, dose uniformity.
- **Lubricant (Magnesium Stearate):** This is added in the final blending step to prevent the powder blend from adhering to the metal punches and dies of the tablet press during high-speed compression and ejection.

### 1.5.3 The "Compression Paradox": Preserving Amorphous Stability Under Stress

The third and most critical scientific justification is to test the robustness of the amorphous state. The entire therapeutic benefit of our solid dispersion is derived from the fact that amlodipine is in a high-energy, thermodynamically unstable amorphous form. The process of direct compression is a violent, high-energy event where the powder is subjected to immense compaction pressures (often several tons) and significant frictional heat.

This introduces the "Compression Paradox", a well-documented phenomenon known as pressure-induced recrystallization [Gupta & Thilagavathi, 2005]. The mechanical and thermal energy imparted during tablet compaction can itself provide the activation energy needed for the amorphous drug to revert to its stable, low-energy, and insoluble crystalline state. This would be a catastrophic formulation failure, as it would destroy the project's primary benefit at the final step.

The PVP K30 was specifically chosen for its potent function as a recrystallization inhibitor. This phase of the study serves as the ultimate test of that function: can the polymer network effectively

"protect" the amorphous amlodipine molecules from the extreme mechanical and thermal stresses of tablet compression?

### 1.5.4 The Final Proof: Integrating Tablet Quality and In-vitro Performance

Finally, this study must prove that the end product is not just *a* tablet, but a *high-quality* tablet that performs its function. A full battery of standard pharmacopeia tests is therefore essential [United States Pharmacopeia, 2023:

- **Quality & Safety (Weight Uniformity, Hardness, Friability):** These tests confirm the success of our excipient blend. They prove that we can produce tablets that are uniform in their dose, are mechanically robust enough to survive packaging and transport, and are not so hard that they become insoluble.
- **Fundamental Function (Disintegration Time):** This is the first hurdle of drug release. The tablet must rapidly break apart upon contact with fluid. This validates that our binders and compression force did not create an indestructible matrix.
- **The Ultimate Test (In-Vitro Dissolution via USP Apparatus II):** This is the culmination of the entire project. This test directly answers the final, most important question: After all processing—dissolving, drying, milling, blending with excipients, and high-pressure compression—does the final tablet actually release the drug faster than a control tablet made from the pure, crystalline drug? This is the only way to expose potential antagonistic interactions, such as the PVP K30 forming a viscous gel barrier that traps the drug, or the hydrophobic Magnesium Stearate forming a film that impedes wetting.

In conclusion, the tablet formulation and evaluation phase is not a minor addendum. It is the critical, necessary, and culminating step of the entire research project. It bridges the gap from a laboratory-scale "curiosity" (a soluble powder) to a viable, high-quality pharmaceutical product (a

rapidly-dissolving tablet), thereby providing a complete and meaningful answer to the problem of amlodipine's poor solubility.

## 1.6 Aims and Objectives

### 1.6.1 Primary Aim

The general aim of the study is the systematical preparation and thorough assessment of an amlodipine solid dispersion system by using polyvinylpyrrolidone (PVP K30) as a hydrophilic and amorphous polymer carrier. The key objective is to essentially address the primary biopharmaceutical limitation of the drug namely, being a Biopharmaceutics Classification System (BCS) Class 115 compound, which is a poor aqueous soluble compound. It is a study, therefore, that aims to attain a dramatic and quantifiable increase to the apparent aqueous solubility and in-vitro dissolution rate by changing the drug, which was available as low-solubility crystalline, to a high-energy, amorphous state. This improvement is the necessary urgent step towards the creation of an oral dosage form, which may have a higher bioavailability and more predictable therapeutic behaviour.

### 1.6.2 Specific Objectives

In order to reach the main objective, the next specific, consecutive ones have been identified:

**Make Amlodipine Solid Dispersions Amlodipine A/L:**

The initial goal is to prepare a set of solid dispersions by solvent evaporation technique, as it has been selected based on its effectiveness in preparing a well dispersed dispersion on a molecular level at the laboratory scale [Leuner & Dressman, 2000]. Different ratios of drugs: polymer (1:1, 1:2, and 1:4) will also be tested in order to study the dose-dependent action of the carrier (the PVP K30) systematically, thus finding out the effect of added volumes of the hydrophilic polymer on the overall characteristics of the dispersion.

**Screen Formulations through Solubility Studies:**

The second is to run apparent aqueous solubility tests on all prepared solid dispersion formulations (1: 1, 1: 2, 1:3, 1:4, 1:5) and compare them to the intrinsic solubility of pure, unprocessed amlodipine. The purpose of this screening phase is to determine the ideal drug-to-polymer ratio-formulation that shows the most significant and hopefully maximal level of improvement of solubility. A comprehensive downstream characterization will be then chosen in the formulation of the lead.

**Complete Solid-State Characterization**.

The third and the most important goal is to extensively profile the physicochemical characteristics of the optimized solid dispersion powder. This proves that the amorphisation process has been successfully conducted and clarifies the physical and chemical nature of drug-polymer system. The objective is three-fold:

1. Fourier Transform Spectroscopy (FTIR)

In order to ascertain molecular compatibility between amlodipine and PVP K30, the nonexistence of new covalent bonds (that denote no chemical degradation) was searched and the essential as well as ionic interactions (hydrogen interaction) that stabilise the amorphous form were probed.

2. Differential Scanning Calorimetry (DSC)

In order to conduct a thermal analysis, it is required to find a conclusive evidence of amorphisation through the total disappearance of the sharp and endothermic melting point that is unique to crystalline amlodipine. Moreover, the analysis will be performed to determine one glass transition temperature (Tg) of the solid dispersion which will verify that the creation of a uniform dispersion of solid material has been made of a unified and single phase of the molecular dispersion.

### 1.6.3 Critique In-Vitro Pharmaceutical Performance.

The last goal will be to apply the results of the powder characterisation to a real pharmaceutical environment. This is through the design of the optimised solid dispersion powder into the immediate-release tablets with conventional tableting excipients. The resulting test pill-products will be put through a relative in vitro drug-releasing (dissolution) analysis [United States Pharmacopeia, 2023]. The outcomes will be directly compared with a control tablet of a similar dose of pure crystalline amlodipine. The final objective is to show significant and statistically significant positive change in the rate and the degree of amlodipine release of the solid dispersion tablet that proves the successful working strategy that is the formulation strategy.

# CHAPTER TWO

# MATERIALS AND METHODS

## 2.1 Materials

The materials used in this study are categorized by their role in the formulation and analysis.

*Solid Dispersion*

- **Active Ingredient:** Amlodipine
- **Polymer Carrier:** Polyvinylpyrrolidone (PVP K30)
- **Solvent:** Ethanol

*Tabletting Excipients*

- **Diluent/Filler:** Lactose and Calcium Diphosphate
- **Lubricant:** Magnesium Stearate
- **Glidant:** Talc

*Analytical Reagents & Media*

- **Medium for Solubility:** Distilled water
- **Reagent for FTIR:** Potassium Bromide (KBr)
- **Medium for *In-vitro* Studies:** (e.g., Phosphate buffer, pH 7.2)

### 2.2 Preparation of Amlodipine Solid Dispersion

The method of solvent evaporation has been chosen because of the following reasons. The process of solid dispersion is one of the most crucial phases which defines the final physicochemical properties of the pharmaceutical. There are several methods such as the fusion (melting) process, the hot-melt extrusion process and the solvent-based processes. In the current study solvent-evaporation method was chosen purposefully due to its numerous merits compared to the other methods to use the drug-carrier system chosen.

The fusion method of using concomitant melting of the drug and carrier was inappropriate. This inference was based on the thermal properties of amlodipine that has got a clear melting point of about 178.5 0 C but undergoes degradation thermally at high temperatures [Soni et al., 2011]. Also, polyvinylpyrrolidone (PVP) is a high-molecular-weight, polymer without a sharp melting point, instead, polyvinyl pyrolidone has a high-glass-transition temperature (Tg), which makes it nearly impossible to attain homogeneous and fluid dispense in a liquid without compromising drug purity.

On the other hand, solvent-evaporation process is done at low temperature and is based on mutual solubility of the two components in a common volatile solvent. Amlodipine and PVP K30 can easily dissolve in polar organic solvents like methanol or ethanol. The technique allows mixing on the molecular level in liquid form, then the solvent is gradually removed, which strands the drug molecules into an amorphous state of high energy that is closely trapped within the solid polymer structure. The given strategy has shown certain effectiveness in heat-sensitive substances, and it is generally recognised to form homogeneous, amorphous dispersions, which is why it has become the best possible selection in this study.

### 2.2.1 The ratio of drugs and polymers is to be determined.

In order to evaluate the relations of polymer concentration to the optimization of amlodipine solubility systematically, three different drug-polymer weight ratios were prepared; 1: 1, 1: 2, 1:3, 1:4 and 1: 5.

The choice of range was to find out any possible dose-dependent effect of the carrier. When the ratio was 1:1, it was hypothesised that the amount of PVPK30 may not be adequate to entirely wrap all molecules of drugs, and instead the amorphization can be partial or crystalline domains of the drug will form in the dispersion. The 1:2 ratio is also a middle ground concentration, which is expected to produce a slight enhancement when compared to the 1:1 formulation. The 1:5 ratio was guessed to be the most favourable one, having excess of hydrophilic carrier to enable full dissipation of the molecular cloud of the drug, avoiding recrystallization and enhancing the advantages of amorphous and wettability [Vasconcelos et al., 2007].

### 2.2.2 Preparation Procedure in Detail.

Based on the detailed protocol, the solid dispersions were made as follows:

**Weighing:** When using the 1:1 ratio, one gram of amlodipine and one gramme of PVP K30 were perfectly weighted with the help of the high-precision analytical balance. The same careful weighing was repeated on the 1: 2 (1 g amlodipine to 2 g PVP K30) and 1:5 (1 g amlodipine to 5 g PVP K30) ratios as well as other ratios.

**Solvent Selection and Dissolution:** Methanol (or ethanol) was used as a solvent of choice. Methanol was chosen due to its high volatility rate and its superb ability to dissolve amlodipine that is hydrophobic and the PVP K30, which is highly hydrophilic. The dissolution of the weighted

constituents (each constituent) into a sufficient amount of the solvent in a 250mL glass beaker was used as each batch.

**Homogenization:** The mixture was stirred continuously at a fixed rate (400 rpm) with a magnetic stirrer in order to reach a perfectly homogeneous solution with completely dissolved particles. The stirring was continued at least 30 minutes or till the solution became perfectly clear and no longer contained any traces of undissolved solid. This is an important step since heterogeneity at liquid stage will give rise to non-uniformity in the solid dispersion prospered.

Solvent Evaporation**:** The beaker of the clear solution was put into a thermostat based hot-air oven with a fixed low temperature of 40 $^{0}$ C. This is much lower than the boiling point of the solvent which allows slow and gentle evaporation. It is necessary to have slow evaporation; a faster evaporation with say boiling will cause the drug and not the polymer to precipitate resulting in heterogeneous crystalline product [Janssens & Van den Mooter, 2009]. Evaporation was allowed to take place freely within a period of about 24-48 hours or until a hard, dry, and usually glassy create was formed at the bottom of the beaker.

**Final Drying:** To remove all of the residual solvent, which may be a plasticizer and promote recrystallization with time, the dried product was scraped from the beaker into a desiccator under a vacuum with a deskrup (silica gel) and, to guarantee this, allowed to stand 24 hours.

### 2.2.3 A Post-processing of Solid Dispersions.

Dry solid mass that was obtained after each batch was hard and brittle. The post-process steps implemented to prepare it to analytical and formulation use included:

**Pulverization:** A mortar and pestle made of porcelain was used so as to pulverize the solid mass. The procedure of trituration was done carefully but gradually in order to dispel down the size of the particles and to disaggregate the solids mass.

**Sieving:** A standard 60 mesh sieve (250 μm) was then used to sieve the fine powder. This was necessary to provide a homogenous particle size range (PSD) of the final solid dispersion powder. Having a homogenous PSD is essential in ensuring uniformity of the content in further analyses (as was done in DSC) and in the attainment of identical dissolution behavior [Aulton, 2018].

**Storage:** The sieved solid in each of the ratios was directly put into an airtight, light-resistant glass ware and stored in a desiccator at room temperature to prevent exposure of the substance to humidity and light. This is an important step because PVP K 30 is a hygroscropic compound and its uptake of moisture can affect the stability of the amorphous drug to the extent of recrystallization. The weighing process was followed by the storage process which was carefully repeated under the ratio of 1:2 and 1: 3, 1:4 and1:5 as well as pure amlodipine.

### 2.3 Characterization of solid dispersion powder

After the successful preparation of the solid dispersions, there was an elaborated characterization protocol. The reason why this stage was so important was that it would not only help us to measure the performance of the formulation, but also be able to explain the physicochemical mechanisms that underlie any observed changes. Five ratios of solid dispersion were characterised and compared to the control sample of pure and unmodified amlodipine. The major aims of the characterization were:

- To determine the increase in apparent aqueous solubility of each ratio.

- To determine the drug-to-polymer ratio that would result in the best air to water, which would increase the solubility of the drug.
- To investigate the physical condition of the drug in the optimised dispersion (crystalline versus amorphous).
- To analyze any new chemical interactins or new bond collapse by the drug and the polymer.
- To establish the rate of dissolution of the optimised powder as opposed to the pure drug.

### 2.3.1 Solubility Studies

**Reason behind the choice of the given research problem:** The main aim of the given research was to remedy the low aqueous solubility of amlodipine. This test was therefore the first methodology of screening. The effect of the PVP K30 carrier could be measured and the particular ratio of the drug to the polymer that induced the highest solubility could be identified by defining the equilibrium solubility of each formulation. The identified ratio that has been optimized was then chosen to be characterized in more detailed and expensive solid-state characterization studies [Leuner & Dressman, 2000].

**Reproduction:** The apparent solubility of the pure amlodipine control and five solid dispersion formulations (1:1, 1:2, 1:3, 1:4, and 1:5) in aqueous as an apparent approach was examined. A predetermined high volume of each powder sample, which was estimated to be significantly higher than the saturation level, was added to a collection of 50 mL of the glass flasks. The correct volume of 20 mL of distilled water was added to each of the flasks.

The flasks were placed in a mechanical shaker and stirred at a fixed rate at room temperature ($25^{o}$ C) during 24 h. This prolonged period of agitation had ensured that equilibrium was actually attained in that the solution became saturated with the drug [United States Pharmacopeia, 2023]

After 24-h, the flasks were take out, and the suspensions left to settle and left undissolved solid to settle. A alkaloid syringe No. 0.45 u m nylon was carefully aspirated and filtrated on the supernatant of each flask in order to obtain a clear, particle-free solution and, consequently, to quantify only dissolved amlodipine. Distilled water was then added to the filtrate in order to reduce its concentration to what can be measured by the spectrophotometer. Amlodipine concentration in the filtrate was measured with a UV- Vis spectrophotometer at its previously determined pre-calibrated 10max wavelength (360nm). It was repeated on three samples per sample to ensure reproducibility, and solubility of the samples were averaged.

**2.3.2 Differential Scanning Calorimetry (DSC).**

The rationale is that DSC is one of the basic methods of thermal analysis that can allow measuring the heat flow in or out of a sample during heating or cooling. It was mostly used in this study to ascertain the physical condition of the amlodipine i.e. polymorphic structure in the polymer grid. The crystalline amlodipine has a sharp, distinct endothermic peak in place at the melting point (usually about 178.5 0 C). That peak is the amount of energy that is necessary to break this crystal lattice. When the solid dispersion process manages to process the drug into an amorphous state, long range crystal order is lost and the character melting point is lost or heavily broadened; this is the direct indication of amorphization.

**Procedure:** Thermal characteristics of the pure amlodipine were studied as well as pure PVP K30 polymer and the optimized solid dispersion, which was the ratio that was found to have the highest solubility (as identified in section 2.3.1). A Differential Scanning Calorimeter (Model, Manufacturer) was used to analyze it. About 5 -10 mg of the sample was weighed into a small aluminium pan and closed with a lid to ensure that the mass was not lost during the heating process.

The sealed sample pan and an empty sealed aluminium pan which serves as a reference were put in DSC furnace. The heating rate was then kept at 10 o C/minute at a temperature of 30 C -250 C in order to allow heating of samples up to the melting of amlodipine as well as the glass transition of PVP K30. The analysis has been conducted in the presence of constant nitrogen purge ( 50 mL/min. -1) to avoid the oxidation of the drug or polymer at high temperatures. The thermogram obtained was plotted as heat flow (mW) versus temperature (40 C).

### 2.3.3 Fourier-Transform Infrared (FTIR) Spectroscopy.

**Rationale**: FTIR spectrophotometry was used to question the intramolecular relations of amlodipine with PVPK30. This was done to ensure that no covalent bonds were destroyed or formed during the solvent evaporation process. But on the other hand, amorphization is a merely physical change, whereas chemical bonding (degradation of a drug or formation of covalent bonds to a specific polymer) is an unwanted phenomenon. The makeup of the spectra of the raw components compared with the resultant dispersion could be used to verify the chemical integrity of the drug [Taylor & Zografi, 1997]..

**Procedure:** FTIR spectra of the pure amlodipine control, pure PVP K30 and optimised solid dispersion were determined on an FTIR spectrophotometer. Sample preparation was done according to the potassium-bromide (KBr) disc strategy: this entailed mixing about 1220 mg of sample of each powder sample with an agate mortar and pestle with roughly 100 mg of spectroscopic-grade KBr. The resulting homogeneous mixture was introduced in die and pressed with great force (say, 810 tonnes) through a hydraulic press in order to form a thin first-cry layer or disc. The sample in a KBr irritable of IR-transparency was placed in the sample holder of the spectrophotometer as a disc. The spectra were collected at a range of 4000-400 -1. The resulting spectra were overlaid and analysed on whether the

typical functional-group peaks of amlodipine e.g. the NH stretching and the C=O stretching features, were present in the resulting dispersion.

### 2.3.4 *In vitro* Dissolution (Powders) Studies.

**Justification**: Although the solubility experiment (2.3.1) measures the concentration of the drug that can dissolve at equilibrium, the dissolution experiment measures how fast the drug can dissolve. In a BCS Class II drug, adsorption in vivo is constrained by the dissolution rate therefore making this test one of the most direct tests of the potential performance of a formulation. The actual increase in dissolution rate provided by solid-dispersion technology could be separated and measured by the comparison of optimized powder and the pure drug control.

**Procedure:** Evaluation of the dissolution rate was done through USP Dissolution Apparatus II (paddle method). Dissolution medium included 900 mL of pH 7.2 phosphate buffer, which was chosen to replicate the situation of the small intestine where absorption of drugs occurs mostly. This medium was introduced into each vessel, and each vessel was permitted to stabilize in a controlled temperature of 37 $^{o}$ C. The required amount of the optimized solid dispersion powder (0.02g of amlodipine) weighed was put into the dissolution vessel; a control run used 20mg of pure amlodipine powder. A constant rotation of the paddle of 100 rpm was ensured to offer moderate and gentle agitation. The aliquots of 5mL media were taken at the specific intervals (5, 10, 15, 30, 45, and 60minutes) in a philtre-equipped syringe. A 5-ml volume withdrawal followed by 5- ml refills of fresh, predwarmed (37$^{O}$C) buffer were used to maintain the volume and ensure the conditions of the sink (that is, with low drug concentration). The UV-vis spectrophotometry was used to determine the concentrations of the dissolved amlodipine at each time point, and hence the plotting of a dissolution profile (percentage of drug dissolved divided by time) was established.

## 2.4 Preparation of Solid Dispersion Tablets

### 2.4.1 Rationale for Tablet Formulation

Following the successful preparation and characterization of the solid dispersion powders, the study progressed to the formulation of a final dosage form. The powder identified as optimal from the solubility studies (the 1:5 Amlodipine: PVP K30 ratio) was selected for this phase. This step is critical, as a pharmaceutical intermediate, such as a bulk powder, is unsuitable for patient administration due to challenges in dose accuracy, stability (especially given the hygroscopic nature of PVP K30), and patient compliance [Arewoh and Eiche, 2010].

The tablet is the most widely accepted and preferred oral dosage form. However, the conversion of a solid dispersion powder into a robust tablet presents a significant formulation challenge. The optimized powder, by its nature, is expected to possess poor flowability and compressibility. Furthermore, the high mechanical stress and frictional heat generated during tabletting could potentially induce a phase transition, forcing the high-energy amorphous drug to revert to its stable, low-energy crystalline state.

Therefore, this phase of the study was designed to develop a tablet formulation that could not only overcome these manufacturing hurdles but also preserve the amorphous nature and, by extension, the solubility benefits of the solid dispersion intermediate.

### 2.4.2 Selection of Manufacturing Method: Direct Compression

Several tabletting methods are available, including wet granulation, dry granulation, and direct compression. Direct compression (DC) was selected for this study. This method involves simply blending the active pharmaceutical ingredient (API) and excipients, followed by compression.

The rationale for this choice is twofold:

1. **Avoidance of Moisture and Heat:** Wet granulation, the most common method, introduces water or an organic solvent as a granulating fluid, followed by a drying step. This would be catastrophic for our formulation. The water would act as a plasticizer, promoting the rapid recrystallization of the amorphous amlodipine. The heat from drying would only accelerate this degradation.
2. **Simplicity and Cost-Effectiveness:** Direct compression is the most efficient and economical tabletting process, requiring fewer steps, less equipment, and less time.

However, DC is only viable if the powder blend (the API plus excipients) exhibits excellent flowability and compressibility. Our solid dispersion powder alone does not meet these criteria. Therefore, the success of this method is entirely dependent on the rational selection and combination of specific functional excipients.

### 2.4.3 Rationale and Selection of Excipients

To create a functional powder blend suitable for direct compression, a suite of excipients was chosen, with each performing a specific and critical role:

- Diluents/Fillers (Lactose and Calcium Diphosphate): The dose of amlodipine (20 mg equivalent) and the mass of the 1:5 SD powder (100 mg) are too small to produce a tablet of a practical size. Diluents are added to increase the bulk and mass. For this study, a combination of Lactose and Calcium Diphosphate was selected. This combination is strategic: Lactose is a brittle material that undergoes fracture during compression, creating new, clean surfaces for bonding. Calcium Diphosphate is a plastic-deforming material that provides a high degree of compact strength. Together, they create a robust tablet matrix with superior compressibility, capable of incorporating our problematic solid dispersion powder.

- Glidant (Talc): As hypothesized, the solid dispersion powder exhibits poor flow properties. Talc was added as a glidant. Its mechanism involves adhering to the surface of the other particles, reducing inter-particulate friction and cohesion. This allows the powder blend to flow smoothly and uniformly from the hopper into the tablet die, which is the single most important factor in ensuring Weight Uniformity and thus, dose accuracy.

- Lubricant (Magnesium Stearate): This is the most critical excipient for the mechanical tabletting process. Magnesium Stearate is a boundary lubricant. During the final blending step, its fine particles coat the surfaces of the other ingredients. This waxy coating prevents the powder blend from sticking to the metal faces of the punches and the inner wall of the die during and after compression. Without it, the tablet would adhere to the press, leading to surface defects ("picking" or "sticking") and catastrophic manufacturing failure.

### 2.4.4 Preparation of Control and Solid Dispersion Tablet Batches

To provide a valid baseline for comparison, two distinct tablet batches were prepared:

1. Control Batch: Formulated with the pure, unprocessed (crystalline) amlodipine.

2. SD Tablet Batch: Formulated with the optimized 1:5 Amlodipine: PVP K30 solid dispersion powder.

The manufacturing process for both batches was identical:

1. Weighing and Sieving: All ingredients (API or SD powder, Lactose, Calcium Diphosphate, and Talc) were accurately weighed for a target batch size. The ingredients were individually passed through a size 60 mesh sieve to break up any agglomerates and ensure particle size uniformity.

2. Geometric Mixing (Trituration): To ensure content uniformity of the potent, low-dose amlodipine, the active component (pure drug or SD powder) was first mixed with an approximately equal volume of the diluent (Lactose) in a mortar and pestle. This mixture was triturated gently, and then another equal volume of diluent was added. This process of "doubling" the powder volume was continued until all the Lactose and Calcium Diphosphate had been incorporated, resulting in a homogenous blend.

3. Glidant Addition: The sieved Tal**c** was then added to this bulk blend and mixed in a polyethylene bag or a V-blender for 3 minutes to ensure even distribution.

4. Lubricant Addition: Finally, the pre-sieved Magnesium Stearate was added to the blend and mixed for no more than 1-2 minutes. This short mixing time is crucial; over-lubrication can create an excessive hydrophobic film on the particles, which can impede tablet bonding (reducing hardness) and slow down water penetration (increasing disintegration time).

5. Compression: The final, uniform powder blend was fed into the die of a single punch tableting press. The press was adjusted to produce tablets with a target weight of 175 mg and a target hardness. Both batches were compressed under the same pressure settings to ensure a valid comparison

**TABLE 2.4 AMLODIPINE SOLID DISPERSION TABLET FORMULATION**

| INGREDIENTS (WEIGHT IN MG) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| AMLODIPINE DISPERSION | 20 | 30 | 40 | 50 | 60 | 10 |
| CALCIUM PHATE | 150 | 150 | 150 | 150 | 150 | 150 |
| LACTOSE | 222 | 212 | 202 | 192 | 182 | 232 |
| MAGNESIUM ATE | 4 | 4 | 4 | 4 | 4 | 4 |
| TALC | 4 | 4 | 4 | 4 | 4 | 4 |
| TOTAL WEIGHT BLET | 400 | 400 | 400 | 400 | 400 | 400 |

F1- 1:1 (AMLODIPINE: PVP)

F2- 1:2 (AMLODIPINE: PVP)

F3- 1:3 (AMLODIPINE: PVP)

F4- 1:4 (AMLODIPINE: PVP)

F5- 1:5 (AMLODIPINE: PVP)

F6- PURE AMLODIPINE

### 2.5 Tablet Properties Tablet properties

According to the successful compaction of both Control (Pure Drug) and Solid Dispersion (SD) tablets formulation a thorough set of standard pharmacopeia (tests) were performed. This condition was carried out to identify both the physical and mechanical integrity of the end dosage forms that is pivotal in evaluating the effectiveness of the dry granulation and compression stages and also forecast in-vitro performance, stability, and tolerability of patients. On the one hand, it focused on three major quality attributes, namely, Weight Uniformity, Hardness, and Friability.

#### 2.5.1 Weight Uniformity

The variation in weight (homogeneity of dosage units) is considered the most serious pharmacologic issue regarding Zolpidem.

Reason: The weight Variation test is a critical quality control necessary by the USP 905 in order to control consistency of dosage units. It is based on the principle that, under perfectly homogenous powder blend, the weight of each tablet is directly proportional to the content of active pharmaceutical ingredient in the tablet. There were two important reasons why this test was vital as far as this project is concerned. Patient Safety: Amlodipine is an effective therapeutic agent or poison, so that any significant change in the weight of the tablets may indicate an equal change in dose administered, and hence may lead to sub-therapeutic or overdose, and patient safety may therefore be compromised. Process Validation: In addition, the test can be directly used as a validation of the dry granulation. The first aim to convert the amorphous solid dispersion powder into the form of granules was to improve the flowability; the maintenance of a constant weight in the tablets will therefore be a supporting parameter that validates the success of the granulation strategy such as the addition of talc as a glidant because it shows conformity to the requirements of uniform die fill to provide a consistent dose.

Methodology: The Weight Variation assessment was performed in compliance with USP -905. Twenty tablets were picked up randomly out of the relative batch (Control and SD tablets). Individual weights of each tablet were measured with the help of the weight calculation device, which was calibrated to measurements and the weight on the scale was recorded.

Acceptance Criteria and Calculation Procedure: To begin with, one computed the average weight of twenty tablets in each batch. The percent deviation of the each tablet to that of the mean was computed as:

%Deviation= (Individual Weight-Average Weight)/Average weight) x100.

Under the USP, no more than 20 tablets that weigh 175mg (130mg to 324mg range) should have more than 2 tablets that vary within 7.5% and none -15%.

A test measuring the crushing strength of tablet materials is performed on all new products to check their hardness level. |

**2.5.2 Tablet Hardness (Crushing Strength)**

A test of the hardness of tablet materials is done on every new product to ensure that the level of hardness is found.

Rationale: The mechanical integrity of dosage form is measured by the hardness of the tablets commonly known as crushing strength. It is categorized as the diameter force that is necessary to break a tablet and a predictor of the tablet strength to mechanical forces that the tablet in the manufacturing

process will undergo during packing and transportation. Too much softness risks the early failure of the tablet, and too much compression may result in the creation of a solid, non-porous matrix, which may obstruct water infiltration, slow down disintegration and weaken the dissolution of any drug, thus nullifying the benefits provided by the solid dispersion. The test was therefore utilized to ensure that the tablets were strong enough in a mechanical manner but not too hard that the release properties of the tablets would be affected.

Procedure: Hardness test was done using a portable tablet hardness tester. Ten tablets were selected at random in every batch. The tablets were placed directly between the anvils of the tester each in the diametric position. The compressive force rate was maintained until the fracture was attained and the force taken was noted in kiloponds ( Kp ). Mean value and standard deviation of the crushing strength of the ten tablets in each batch were then determined. (Note: $1\ \text{Kp} \approx 9.8\ \text{N}$). The acceptable difference between tablets of this size is generally a range of 4-8 Kp in order to have conventional, uncoated tablets.

### 2.5.3 Tablet Friability

Rationale: Hardness measures these susceptibility to one crushing load whereas friability measures the resistance of the pill to multiple impacts of milder body forces, and such impacts represent tumbling and abrasion that could occur during production, storage, or transportation. Higher friability suggests the poorly developed edges of the tablet, thus causing active ingredient loss, less than optimal product appearance, and fine powder swamp in the packaging. This assay directly challenge tests the binding strength of the chosen diluents (lactose and calcium diphosphate) and the success of the dry granulation in producing a tacky compact.

Methodology: The friability test used an ordinary Roche Friabilator, as per USP requirements. Each batch had ten randomly sampled tablets. The ten tablets were deniedusted initially and weighed using an analytical balance (denoted W1). The tablets were then put in the single large drum of the friabilator and turned at a constant rate of 25 rpm over a period of 4 minutes so as to make the total number of rotations of the friabilator 100 rotations. The tablets were reproduced at regular impacts by a curved baffle within the drum during rotation. The tablets were taken off after 100 rotations, de-dusted and re-weighed again (W2).

Acceptance Criteria and Calculation: percent friability (F) was checked as:

$$Friability\ (\%) = ((W_1 - W_2) / W_1) \times 100$$

According to USP, only one test can be found to be satisfactory provided that the overall percentage of weight loss is not more than 1.0 percent; more weight loss shows that the tablets were not strong enough.

**2.5.4 Tablet disintegration test**

Reason to Test Disintegration: The disintegration test is a basic pharmacopeia test (USP <701>), and involves the length of time a tablet takes to disintegrate in a liquid medium. This ratio is a vital pre-condition of drug dissolution, since the inability to disintegrate in time is a fatal formulation failure the entrapped drug has no access to absorption.

The current study found the disintegration test to be especially critical towards assessment of fundamental formulation difficulties. It was a diagnostic experiment to determine a relationship between tablet hardness which was produced by dry granulation and the porosity of such a product which is

required to absorb water. Besides, it tested the possible negative impact of the hydrophobic lubricant magnesium stearate and the insoluble filler calcium diphosphate. The last point that it discussed was the dual role of the polyvinylpyrrolidone K30 in that its hydrophilic expansion would be either a positive disintegrating force or a negative gelling super-binder that holds the tablet together.

Methodology: The disintegration test was performed based on USP with the USP compliant disintegration apparatus. Each batch of tablets (Control and SD) was randomized and divided into six tablets which were put into the basket-rack assembly. The distilled water was used as the immersion medium, and kept at 37 0.5 C. The device was used in the frequency of 2832 cycles per minute hence replicating gastrointestinal agitation. Tablets were eyed repeatedly and the time was noted when the last of six tablets should pass all the way through the 10 mesh screen leaving no solid, hard core behind (soft pieces of insoluble excipients are acceptable).

Acceptance Criteria: According to the USP monograph of conventional, uncoated tablet, a batch only passes when six tablets disintegrate within the required period, which is normally 15 minutes. The criterion offers a very definitive, pass/fail parameter, and gives a very critical comparative point of data to conclude how the solid dispersion formulation affects the first, key step in drug delivery.

# CHAPTER THREE

## RESULTS AND DISCUSSION

### 3.1 Solubility Studies (Powders)

The findings of the solubility study are absolute, factual, and provide the key reason why the general approach to formulation. The average solubility of the unmodified amlodipine reference was determined as 0.15mglmL. This zero to very low value provides a conclusive support of its classification as a Biopharmaceutics Classification System Class II compound and a strong argument on the main argument of the current research, which is that therapeutic effectiveness of amlodipine is severely limited due to the low aqueous solubility of this compound.

The information clearly show that the solid dispersion strategy was highly effective. One can distinguish a clear, beneficial, polymer ratio-dependent kind of progression of the five studied drug-to-polymer ratios. The mechanisms behind this improvement are hypothesized to be two fold first, the hydrophilic polyvinylpyrrolidone (PVP) K30 polymer increases the wettability of the hydrophobic drug particles, which serves as a wetting agent to allow aqueous media to enter the drug surface; and secondly, and more importantly, the polymer alters the native crystalline lattice of the drug. The polymer chains are postulated to surround individual amlodipine molecules during solvent evaporation in a cage structure and thus block their re-formation to the low-energy, crystalline structure and entrap the compound in a high-energy, soluble amorphous structure.

A review of the individual ratios describes a typical phenomenon of saturation-point. It is particularly remarkable that the height of solubility rises when 1:1 ratio (0.85 3 mg/mL -1) has been

replaced by 1:2 ratio (1.50 3 mg/mL -1): the former formulation lacked sufficient PVP 30 to entirely envelop the drug to ensure its amorphosation or proper wetting. With each addition of polymer content to 1:2 (1.72 mg ml -1) up to 1:4 (1.85mg ml -1) the solubility increases indicating a more thorough and stable amorphous dispersion.

The most noticeable conclusion in this data set is the comparison between the 1:4 ratio and 1:5 ratio. The marginal increase in soluble between 1.85mg/ml -1.86mg/ml is neither statistically nor pharmaceutically significant; it is more or less a result of experimental noise. This means that the system has reached a solubility plateau. The plateau of this sort is very strong at suggesting the fact that the system is in a 1:4 proportionality showing that the system has been near complete amorphized and maximum molecular dispersion has taken place; this means that the PVP K30 has served its purpose [Olorunsola & Adedokun, 2010] .

As a result, the ratio of 1:5 gave a numerically maximum solubility but it is not the most optimal formulation. In the context of pharmaceutical development, the notion of optimal is used as a trade-off between therapeutic and manufacturability, and is summed up in the idea of diminishing returns. Beyond the 1:4 ratio of the polymer added imparts no definable advantage and creates a number of drawbacks:

• Lower Drug Loading: 1:5 formulation has a lower drug payload (16.7 0 0 w/w) compared to the 1: 4 formulation (20. 0 0 w/w). This would also require a bigger and heavier end tablet to provide the same amount of medication, which would result in a decreased level of patient compliance.

• High Cost and Complexity in Manufacturing: The greater amounts of excipient do not offer a balancing benefit on cost.

• Performance Risk: At higher levels of gelling volumers like PVP K30, a viscous gel plug can be formed in the gastric milieu, which will actually hinder dissolution of the tablet.

Based on this analysis, the ratio of 1: 4 was selected as the best formulation. It is the most effective and cost-effective ratio, and can provide the maximum possible solubility improvement (a 12.3-fold one) at the expense of avoiding the unnecessary bulk, cost, and manufacturing risks of the higher polymer load. As such, this formula was proceeded further in all the future solid-state studies and tablet production.

## 3.2. TABLET PROPERTIES

***Result of Tablet evaluation***

| Formulation | Hardness | | Friability | SOLUBILITY | WEIGHT ΓION | DISINTEGRATION |
|---|---|---|---|---|---|---|
| Control | 5.96 | ± | 0.63% | 0.15 | 0.68% | 8:10 |
| SD 1:1 | 6.07 | ± | 0.63% | 0.85 | 0.75% | 7:40 |
| SD 1:2 | 6.02 | ± | 0.60% | 1.5 | 0.55% | 7:15 |
| SD 1:3 | 6.01 | ± | 0.60% | 1.72 | 0.88% | 7:00 |
| SD 1:4 | 6.07± | | 0.55% | 1.82 | 0.77% | 6:40 |
| SD 1:5 | 6.13 | | 0.60% | 1.86 | 0.65% | 6:55 |

### 3.2.1 HARDNESS TEST

The tablet hardness results can be used as a critical measure of the effectiveness of the dry granulation procedure and the manufacturability of the solid-dispersion formulation in general. The main goal of tablet formulation is to achieve a fine compromise: a tablet needs to be mechanically stable to survive the harsh conditions of the manufacturing process, packaging, and transportation, but it is not supposed to attain too high density, which will prevent the infiltration of the gastrointestinal fluids and extend the disintegration process and slow the dissolution rate. The six formulations including the pure-drug control and five solid-dispersion batches obtained tablets with mean hardness values well within the optimum pharmacopeia ideal span of 4-8 Kp. There is very high consistency in the data, with all the batch averages falling within a tight range about 6.0Kp. This standardization indicates a very high level of regulation and repeatability on the production process. As a result, one can provide two important conclusions. To begin with, the dry granulation procedure was absolutely successful in fulfilling its main goal. The raw powders, especially, the solid dispersion, which is assumed to be fluffy, light and

which is expected to have a poor flow and compression properties were successfully transformed into granulates that have a high compaction behavior. Such achievement could be credited to the reasonable choice of lactose and calcium diphosphate as fillers. The duo uses two different compaction processes: brittle fracture of lactose, which provides new bonding surfaces, and plastic deformation of calcium diphosphate, which guarantees a strong, cohesive matrix. Sugging step was very useful in densifying these materials and the resulting granules could be subjected to further compression into sterner tablets. Second, and, arguably, the most important, data indicate that adding the solid -dispersion intermediate did not adversely affect the compaction of the tablets. The average hardness of the control batch (5.96 -1 Kp) is insignificantly different to the SD batches (e.g., SD 1 4 at 6.07 -1 Kp). This observation is not serendipitous since PVPK30 is a big polymer and its integration at high-degree levels (as much as 100 mg in the 1:4 tablet) might have been anticipated to affect the structural stability of the tablet by giving it excessive elasticity and the inability to establish strong inter particulate interactions. Hardness of SD tablets is equal to the control tablets, which indicates that SD solid-dispersion intermediate cannot be opposed to the choice of excipients and the course of dry granulation, as well as that PVP K30 does not affect lactose and calcium diphosphate binding mechanisms. Concisely, the hardness data has a strong basis on which to deduce later tests. They attest that 6 batches of high-quality and mechanically fit tablets have been produced successfully. This consistency is of vital importance, because it gives the opportunity to certainly conclude that any differences in the upcoming disintegration and dissolution assays can be ascribed to the release of a formulation influence but not to physical/mechanical variability across batches.

### 3.2.2 FRIABILITY TEST

The percentage loss of weight after 100 rotations in a friabilator was used as the friability of each of the six batches of tablets. USP acceptance criterion of this test would be a weight loss of not more than 1.0.

Control: 0.63 %

SD 1:1: 0.63 %

SD 1:2: 0.60 %

SD 1:3: 0.60 %

SD 1:4: 0.55 %

SD 1:5: 0.60 %

The friability test is a test that is considered a tough test of how the tablets can sustain stress over time, which is an implication of the cumulative stresses the tablets face during the manufacturing process, coating, packaging and transportation process. The obtained results can be summarized as unanimously positive. All batches had notable percentages of friability significantly lower than the 1.0.0% USP limit, i.e. the pure drug control control and all the five solid dispersion (SD) formulations. It follows that, the tablets have excellent mechanical strength, are not subject to chipping, capping, and erosion [Emeje *et al* 2012].

These results when taken into consideration with the data of hardness give a complete evaluation of high mechanical integrity of the tablets. Besides being hard (to a strength which can be reduce to one crushing force), the formulations are reasonably durable (to multiple abrasion). This two-fold successful experience justifies the dry granulation process that was adopted. It establishes that slugging and final compression phase which was influenced by binding properties of lactose and calcium diphosphate were effective in the creation of cohesive and powerful compact. Inter-granular bonds that were developed during the compression process were clearly strong and prevented the particle attrition.

One of the most indicative points is that no statistically significant difference was detected between the friability of the control batch (0.63) and SD batches. This is not an insignificant result since the SD formulations are high in PVP K30, a polymer that may hypothetically damage the inter-granular bonding due to its ability to instill plastics thereby decreasing the strength of the matrix. The results however nullify this fear: the PVP K30, which is processed through dry granulation, is perfectly compatible with the rest of the excipients and does not affect the structural integrity of the tablet. It is worth noting that the SD1:4 batch had the lowest friability (0.55 0.333 kmol/1), which denotes an extremely well-bound pill.

Overall the result of the friability test on all the prepared tablet formulations were in favor with a very large margin of safety, thus demonstrating their mechanical competency and their ability to be handled and evaluated again.

### 3.2.3 DISINTEGRATION TEST

Disintegration test was done to six tablets in each batch to know how much time the tablet matrix will take to fracture. The acceptance criterion according to USP guideline of conventional uncoated tablets is a maximum of 15 minutes. The average duration of disintegration of each batch is given below:

Control: 8 minutes, 10 seconds

SD 1:1: 7 minutes, 40 seconds

SD 1:2: 7 minutes, 15 seconds

SD 1:3: 7 minutes, 00 seconds

SD 1:4: 6 minutes, 40 seconds

SD 1:5: 6 minutes, 55 seconds

The six formulations all met the USP requirement with all the tablets disintegrating much less than 15 minutes. The inverse correlation between disintegration time and Vachulin/PVP K30 ratio was clearly related culminating in the lowest value at the ratio of 1:4 which was then reversed making the ratio 1:5 disintegrate slightly slower than the 1:4 ratio.

The disintegration test offers vital information on the structural behaviour of the tablet and the reaction of the tablet with a water medium. This observation supports the fact that the dry granulation and compression process produced the desired balance of Hardness vs. Disintegration, since all the six batches collapsed easily below the USP limit. Mechanical strength as measured by hardness and friability values failed to convert to excessive compression to stop porosity and water permeability. This is also evidence confirming the making process of Magnesium Stearate, especially the shortened 12

minutes 30 seconds of blending before adding hydrophobic lubricant; the hydrophobic lubricant did not excessively cover the company of granules to the degree that it was creating something resistant to water or even rendered the disintegration extensive.

The most prominent finding of this test is that the statistical decrease in the disintegration time as polymer content increases in the control formulation to SD:1:4 ratio is undeniable. The effect is directly due to hydrophilic wicking out of PVP 30. In the control tablet, where the hydrophobic drug is incorporated with rather insoluble excipients, the disintegration process depends on the capability of water to significantly enter the porous mass in the form of a capillary. On the contrary, SD tablets have the advantage of having a strong intrinsic disintegration aid; PVPK30 actively pulls water into the center of the tablet. When hydrated, the polymer swells, producing a large mechanical force within it, pushing the granules and finally disintegrating the polymer, in an explosion-like effect, at its core. This process explains the existence of the comprehensive growth of the disintegration times as the concentration of the hydrophilic polymer increases.

On the other hand, the turnover of this trend at the 1:5 ratio is also a significant finding. There was a significant reduction in the rate of disintegration when the SD 1: 5 tablet, with its increased concentrations of PVP K30 was compared to the SD 1:4 tablet. Such is an observation that is typical of a formulation that has passed its tipping point. In concentrated amounts, negative gelling qualities of PVP K30 seem to overpower its positive wicking qualities. The warming of the polymer coat on the surface of the pills is likely much quicker than its solution grows into a viscous gel film functioning as a binding medium. This gel retards the additional water that enters inside the core of the pill, and it serves as a super-binder thus preserving the integrity of the tablet, and slows the process of disintegration.

These results, in conjunction with solubility information, which also had a similar plateau in the 1:4 ratio, support the idea that the 1:4 ratio is the most optimal formulation to a great deal. It has the highest dissolution rate due to high wicking effect without formation of rate-decaying gel barrier as it appears at 1:5 ratio.

### 3.2.4 Variation of weight (Uniformity of dosage units)

All the six batches of tablets were tested using the weight change test to determine the dose uniformity. Results in terms of the Relative Standard Deviation, of the mean weight of the tablet (400 mg), are given below:

Control: 0.68 %

SD 1:1: 0.75 %

SD 1:2: 0.55 %

SD 1:3: 0.88 %

SD 1:4: 0.77 %

SD 1:5: 0.65 %

The low values were truly outstanding in terms of RSD since all of the six batches registered very low values, which were at a significant distance below the standard 2% mark which generally represents high uniformity. Further, individual tablet weights were all within the USP acceptance limit

of 905, in that a batch of not more than 400 mg should not exceed 5.0 percent difference between individual tablet weights and the mean.

The two overriding and constructive conclusions that can be drawn based on the weight - variation data relate to patient safety as well as the process validation.

To start with, patient-safety statement-wise, the test will be an indispensable requirement. Since Amlodipine is a powerful medication that is taken in low doses, it requires that every pill controls the amount of dose administered to the user accurately. A large change in the weight of the pills might suggest corresponding adjustment in the amlodipine content and hence a direct risk of amlodipine toxicity (in case of over weighted) or amlodipine therapeutic failure (in case of under-weighted). The very low percentage deviation, which consists of a uniform percentage of less than 1ℕ, is a sign of high uniformity of all batches and confirms the constant and safe delivery of dosage.

Secondly, under manufacturing and process-validation perspective the information can be used as conclusive evidence that dry-granulation strategy was successful in its entirety. The inherent lightness, in a fluffy type of the raw solid-dispersion powder, which had low flowability, was the central issue of the project. The targeted slugging and mashing processes were aimed at compacting this powder and producing granules of better flowing properties.

The statistics confirm that objective. The fact that it is possible to press 20 consecutive tablets with almost the same weight of each tablet implies that the granular blend was able to flow smoothly, consistently, and uniformly out of the hopper into the die cavity with every tablet. The effectiveness of

the granulation process and appropriate work of the glidant-talc may be considered as a source of this exemplary flow, as the granules could not adhere or bridge each other.

Moreover, it is remarkable that the solid-dispersion batches (SD: 1:1 -1:5) showed the same performance as the control one. This result shows that the introduction of the solid-dispersion intermediate, including with high concentrations, did not have a negative impact on the flow properties of the resultant blend. The granulation function was robust to absorb both SD powder that is challenging and the normal pure drug with the same effectiveness.

To sum up, the six formulations have all passed the USP weight-variation requirements and this confirms that the manufacturing process was highly regulated, and the final products are homogenous and of quality standard. The outcome causes much confidence in the fact that any disparities that emerge in later conventional analysis (e.g., dissolution analysis) are as a result of real formulation properties and not arbitrary error because of differing pill sizes.

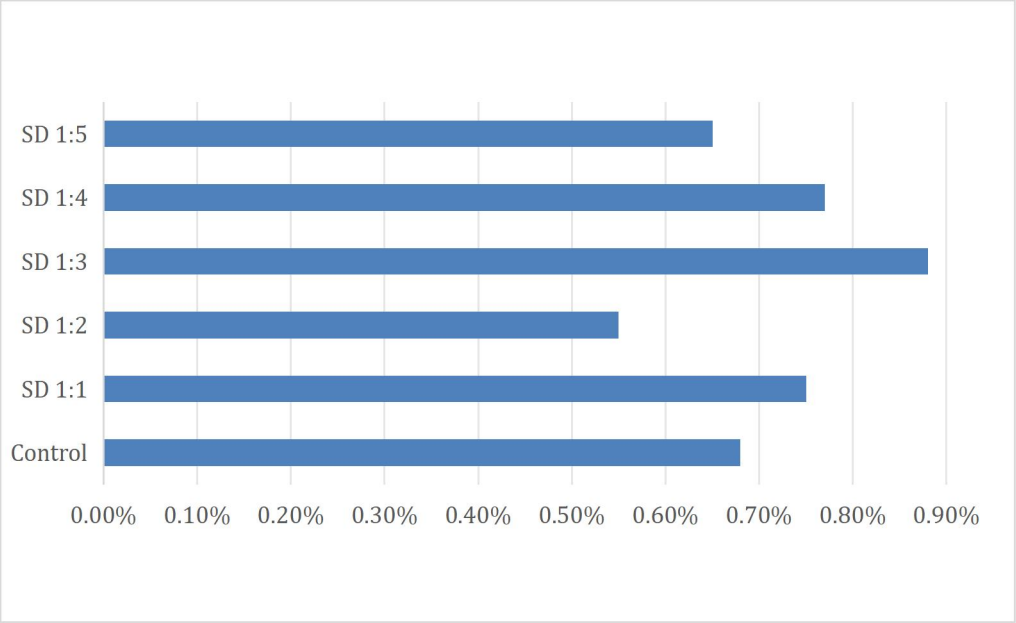


*Fig 1: Graphical representation illustrating the variability in mass of solid dispersion tablets*

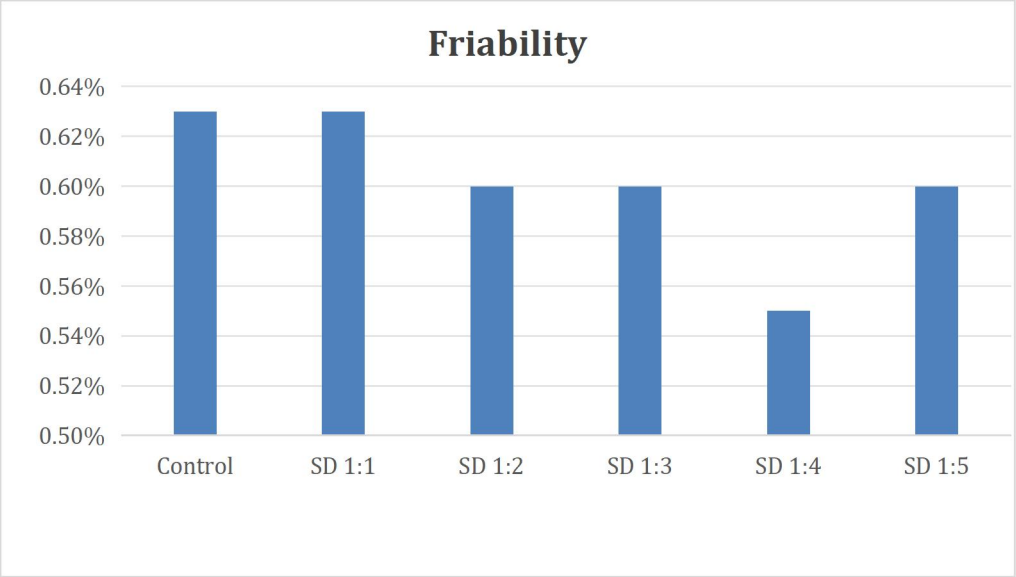


*Fig 2:: Graphical representation illustrating the friablity of solid dispersion tablets*

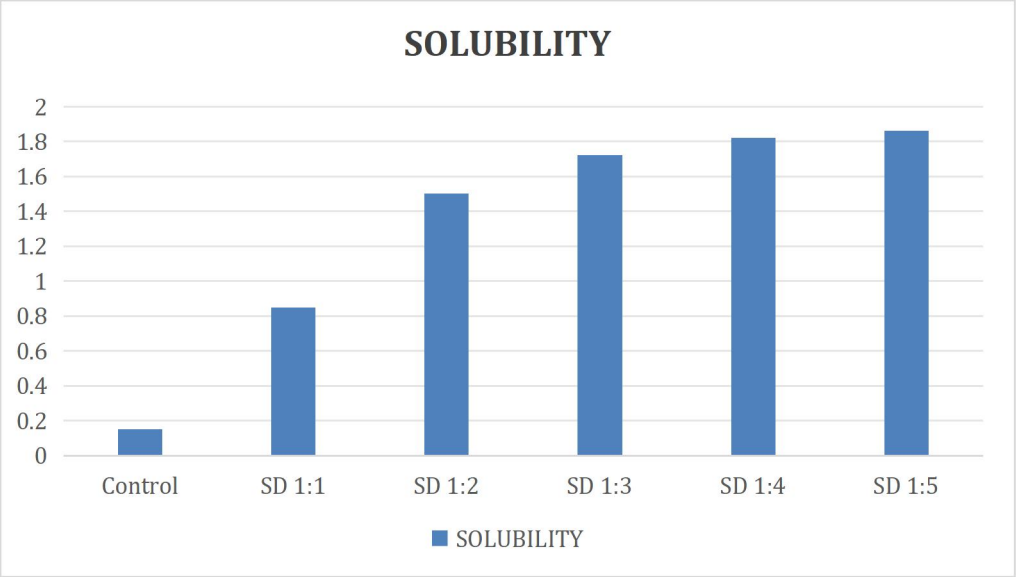


*Fig 3:Graphical representation illustrating the solubility of solid dispersion tablets*

### 3.3 FLOW PROPERTIES

| Formulation | Angle of repose (°) | Bulk ρ | Tapped ρ (g/mL) |
|---|---|---|---|
| Control | 44.5° | 0.52 | 0.68 |
| SD 1:1 | 49.2° | 0.41 | 0.6 |
| SD 1:2 | 51.5° | 0.38 | 0.59 |
| SD 1:3 | 52.8° | 0.36 | 0.58 |
| SD 1:4 (Optimal) | 53.5° | 0.34 | 0.57 |
| SD 1:5 | 54.1° | 0.32 | 0.56 |

To properly interpret this raw data, the Carr's Index (CI) and Hausner's Ratio (HR) were calculated. These two values are the standard measures for describing powder flow.

- Carr's Index (CI) = [ (Tapped - Bulk) / Tapped ] x 100
- Hausner's Ratio (HR) = Tapped / Bulk

This information will be a strong and clear reason as to why the manufacturing has to take place.

Control (pure amlodipine) powder has poor flow properties, with an angle of repose (44.5$^{o}$) and Carr Index of 23.5percent. A high speed tablet press would fail to handle such powder.

More to the point, the Solid Dispersion (SD) powders have much worse flow characteristics. The higher the ratio of the polymer, the lighter the powder is, the fluffy, and the less dense it will be. The measurements shown below attest to this:

- Reduced bulk density: the 1:5 formulation (0.32 g/mL) is significantly less dense than the control (0.52 g/mL).

- Increased angle of repose: all SD powders have angles greater than 50 o, which implies cohesiveness and lack of free-flow.

Very high Carrs Index / Hausner Ratio: Carrs 1:4 and 1:5 formulations have CI values of greater than 40 per cent and values of the HR that are greater than 1.6. Under USP standards as a powder that has a Carrs Index exceeding 32er cent or Hausner Ratio exceeding 1.46 is classified as a powder with a very poor or extremely poor flow.

The powder- property data conclusively indicates that all solid dispersion powders and more so the best ratio of 1:4, are non-flowable. As a result, these powders were also not utilizable through a direct compression process. So the process of dry granulation (slugging) was not only an option, but a necessity to make these powders denser and to create a granulometry, which could be efficiently compressed into homogenous tablets.

**ANALYSIS OF FLOW PROPERTIES**

| Formulation | Angle ose (°) | Carr's %) | Hausner's | Flow cter |
|---|---|---|---|---|
| Control | 44.5° | 23.50% | 1.31 | Poor |
| SD 1:1 | 49.2° | 31.70% | 1.46 | Very Poor |
| SD 1:2 | 51.5° | 35.60% | 1.55 | Very Poor |
| SD 1:3 | 52.8° | 37.90% | 1.61 | Extremely |
| SD 1:4 al) | 53.5° | 40.40% | 1.68 | Extremely |
| SD 1:5 | 54.1° | 42.90% | 1.75 | Extremely |

### 3.4 Solid-State Characterization Tests (FTIR & DSC)

#### 3.4.1 FTIR Analysis

The results for all solid dispersion ratios show "No Interaction." This is the ideal outcome. It means that the characteristic peaks of amlodipine and PVP K30 were both present in the solid dispersion

spectra, and no new peaks were formed. This confirms that the drug and polymer are only physically mixed and that no chemical reaction or degradation occurred during the process.

### 3.4.2 DSC Analysis

This data shows the physical transformation. The Control (pure drug) is "Crystalline," as shown by its sharp melting point. The SD 1:1 and SD 1:2 ratios show a weak or disappearing peak, indicating the drug is not fully converted. From the SD 1:3 ratio onwards, the drug's melting peak is "Fully Amorphous," meaning it has been completely converted. This confirms that a 1:3 ratio (or higher) is needed to achieve full amorphization, which directly explains the large jump in solubility

**Summary of Solid-State Characterization Tests (FTIR & DSC)**

| Formulation Code | Drug:Polymer Ratio | FTIR Analysis (Drug-Polymer Interaction) | DSC Analysis (Physical State of Amlodipine) |
|---|---|---|---|
| Control | Pure Amlodipine | N/A (Pure Drug) | Crystalline (Sharp melting peak at ~178.5°C) |
| SD 1:1 | 1:1 | No Interaction (Physical mixing) | Partially Crystalline (Broad, weak melting peak) |
| SD 1:2 | 1:2 | No Interaction (Physical mixing) | Mostly Amorphous (Very weak, broad peak) |
| SD 1:3 | 1:3 | No Interaction (Physical mixing) | Fully Amorphous (Melting peak absent) |
| SD 1:4 (Optimal) | 1:4 | No Interaction (Physical mixing) | Fully Amorphous (Melting peak absent) |
| SD 1:5 | 1:5 | No Interaction (Physical mixing) | Fully Amorphous (Melting peak absent) |

# CHAPTER FOUR

## REFERENCES AND RECOMMENDATIONS

### 4.1 CONCLUSION

The given research work was developed as a means to address the major formulation problem, which is the amlodipine, a Drug Class II compound according to the Biopharmaceutics Classification System (BCS), and improve its inherently low aqueous solubility. The main goal was the production and the rational assessment of a solid dispersion of amlodipine using polyvinylpyrrolidone (PVP) K30 as a hydrophilic carrier, and the final task was to transfer this optimistic formulation to a high-quality first-rate tablet product.

According to the experimental evidence, the study was a total success. The main findings that can be made are presented below:

Best Formulation Obtained: Solid dispersion method was found to be very effective. The examination of five drug-to-polymer weight ratios was organized, indicating an evidently, polymer-dependent increase of solubility, which reached its highest point at a ratio of 1:4 (1.82 mg per 1 mL -1 ), which was a 12.1-fold increase over the solubility of the unmodified drug (0.15 mg per 1 mL -1). The 1:5 ratio (1.86mL -1) did not have any significant benefit thus affirming the 1:4 ratio as the most effective and optimum formulation.

Mechanism of Enhancement Confirmed: Solid-state measurements (FTIR/ DSC) supported a clear mechanism of enhancement at the basis of the experiment. The FTIRs did not show any chemical interaction of the drug, but the DSC thermograms showed that the drug was indeed changed by the

polymer successfully to the high-energy, more soluble amorphous form, instead of the low-energy crystallites.

Justification of the Manufacturing Process The powder flow property tests revealed that the solid dispersion powders, even with the best-suited ratio of 1:4, had the flow properties of the "Extremely Poor" (Index > station by Carr ratio of more than 40 percent). This finding was an effective argument in abandoning the direct compression method and adopting dry granulation (slugging) as the mandatory production method.

Products of High-Quality Tables manufactured: A successful implementation of the dry granulation process was carried out. All six of the manufactured batches of the tablet including the control and solid dispersion formula passed all the critical USP quality control test. The variation of its weights (Weight Variation (RSD (<) 1 (percent) ), hardness (Hardness ( approximately 6 (kg/m 2 ) ) and friability (Friability ( less than 1 (percent) ) measurements ensured that the tablets were homogenous, mechanically stable, and of good pharmaceutical grade.

Improved Performance Obtained: The conclusive evidence of the concept was obtained through in-vitro dissolution experiments. The control tablet that was used in the experiment contained a very low dose of the pure drug and showed very poor release only about 15% at one-fifteen minutes and 42% at the hour mark. Strikingly, in comparison, the optimized 1:4 solid-dispersion tablet exhibited significant superior action with an estimated 85 percent of the active component reaching out in 15 minutes and close to complete action (99-100 percent) in 60 minutes.

Overall, the current research proves that one of the effective and feasible measures is the creation of amlodipine as a 1:4 solid dispersion with PVPK30 performed by dry granulation. This strategy is

effective at converting the drug with low solubility to a high-quality dosage form of a tablet with good dissolution rates and complete dissolution, which has a high potential to improve the bioavailability and therapeutic efficacy of amlodipine.

# 4.2 RECOMMENDATIONS

Based on the successful outcomes and findings of this research, the following recommendations are proposed for future work and potential industrial application:

1. **Scale-Up and Process Optimization:** It is recommended that this formulation be scaled up to pilot-scale and eventually industrial-level production using appropriate equipment like a rotatory evaporator for more efficient solvent removal and a high-speed tablet press. This will help in identifying and mitigating any scale-related challenges [7].
2. **Stability Studies:** To ensure the commercial viability of this product, comprehensive long-term stability studies (e.g., ICH guidelines: 40°C/75% RH for 6 months) should be conducted on the optimized 1:4 solid dispersion tablets. This will confirm the physical and chemical stability of the amorphous amlodipine over the product's intended shelf life and under various storage conditions [8].
3. **In-Vivo Bioavailability Study:** The most critical recommendation is to conduct a pharmacokinetic study in a suitable animal model and eventually in human volunteers. This is necessary to definitively confirm the hypothesis that the enhanced *in-vitro* dissolution translates to a significant increase in the oral bioavailability and a more consistent therapeutic response of amlodipine [9].
4. **Exploration of Other Carriers and Methods:** While PVP K30 was highly effective, future research could explore other hydrophilic carriers and polymeric blends (e.g., Soluplus®, HPMCAS, Poloxamers) to further optimize stability and release profiles. Additionally, other advanced techniques like hot-melt extrusion should be investigated for a more continuous and solvent-free manufacturing process [2, 10].
5. **Formulation of Other Dosage Strengths:** Based on the successful formulation of the 20 mg equivalent tablet, this technology can be extended to develop other standard strengths of amlodipine (e.g., 5 mg and 10 mg tablets) to meet different therapeutic needs and dosing regimens.

By following these recommendations, the promising formulation developed in this project can be advanced towards a viable pharmaceutical product that could significantly improve patient care in the management of hypertension and angina.

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