



ANALYTICAL INSIGHTS INTO POORLY SOLUBLE DRUGS: CHARACTERIZATION AND IMPACT ON BIOAVAILABILITY

Vaibhav Ghansham Kute^{1*} and Dr. Manmeet Singh²

¹Ph.D Scholar, Department of Pharmaceutics, SunRise University, Alwar (State:- Rajasthan).

²Ph.D Research Guide & Professor, Department of Pharmaceutics, SunRise University, Alwar (State:- Rajasthan).

***Corresponding Author: Vaibhav Ghansham Kute**

Ph.D Scholar, Department of Pharmaceutics, SunRise University, Alwar (State:- Rajasthan).

Article Received on 05/08/2023

Article Revised on 26/08/2023

Article Accepted on 15/09/2023

ABSTRACT

The Pharmaceutical industry has witnessed a growing interest in potential therapeutic benefits of poorly soluble drugs. However, the limited bioavailability of these compounds poses a significant challenge to drug development and patient outcomes. This review provides analytical insights into poorly soluble drugs, focusing on their characterization and the subsequent impact on bioavailability. Various techniques for characterizing drug solubility and dissolution behaviour are discussed such as thermodynamics and kinetics approaches. Additionally, it explores formulation strategies and delivery systems designed to enhance the bioavailability of poorly soluble drugs. The importance of these insights is to improve drug development and patient outcomes.

KEYWORDS: Poorly Soluble Drugs, Bioavailability, Characterization, Solubility, Formulation, Drug Development.

INTRODUCTION

The Pharmaceutical landscape is replete with diverse drug compounds, each possessing unique characteristics. Among these, poorly soluble drugs hold a significant place due to their distinctive challenges and far-reaching implications. Poorly soluble drugs are substances that exhibit limited solubility in biological fluids or other relevant solvents under specific conditions. This solubility, or rather, the lack thereof, poses a critical hurdle in drug development and clinical effectiveness.^[1-5]

The study of poorly soluble drugs is of paramount importance for several compelling reasons. In the pharmaceutical world, these compounds are not an exception but a rule. A substantial portion of drug candidates and existing therapeutic agents falls into the category of poorly soluble substances. Understanding and addressing the issues related to their solubility is vital for the development of effective medications. Challenges associated with these drugs encompass formulation complexities, erratic bioavailability, and suboptimal therapeutic outcomes.^[6-10]

The objective of this review is to embark on a comprehensive exploration of poorly soluble drugs, with a particular focus on analytical insights into their characterization and the profound impact of solubility on bioavailability. Throughout the ensuing sections, we will delve into the intricate world of these compounds,

discussing their physicochemical properties, various analytical techniques employed for characterization, formulation strategies to enhance solubility, techniques for bioavailability enhancement, and the broader implications of poor solubility on drug development. Additionally, we will look ahead to future trends and innovations that promise to reshape this critical field.

Physicochemical Properties of Poorly Soluble Drugs

A. Solubility and Dissolution Rate: This property refers to how well a drug can dissolve in a specific solvent or medium and how quickly it dissolves. Poorly soluble drugs may have low solubility and slow dissolution rates, which can affect their bioavailability.

B. Particle Size and Surface Area: The size and surface area of drug particles are critical factors. Smaller particle sizes and larger surface areas can enhance dissolution and improve drug absorption. Techniques like milling or micronization can be used to reduce particle size.

C. Polymorphism and Crystal Forms: Some drugs can exist in multiple crystalline forms, known as polymorphs. Different polymorphs can have varying solubility and stabilities, which can impact drug formulation and performance.

D. Lipophilicity: Lipophilicity indicates how well a drug interacts with lipids or fats. It can influence drug absorption and distribution in the body. Highly lipophilic drugs may have low water solubility.^[11-25]

Analytical Techniques for Characterization

A. Spectroscopic Techniques

1. **UV-Visible Spectroscopy:** This technique measures the absorption of ultraviolet and visible light by a substance, providing information about its electronic structure and concentration.
2. **Infrared Spectroscopy (IR):** IR spectroscopy analyzes the absorption of infrared radiation, revealing information about a molecule's vibrational modes and functional groups.
3. **Nuclear Magnetic Resonance (NMR):** NMR spectroscopy is used to study the nuclear properties of atoms in a molecule, providing detailed structural information.^[26-35]

B. Thermal Analysis

1. **Differential Scanning Calorimetry (DSC):** DSC measures heat flow associated with thermal transitions, such as melting or crystallization, helping identify polymorphs and thermal behavior.
2. **Thermogravimetric Analysis (TGA):** TGA measures changes in mass as a function of temperature, aiding in the analysis of degradation and stability.

C. Microscopy and Imaging Techniques

1. **Scanning Electron Microscopy (SEM):** SEM provides high-resolution images of the surface morphology of particles, helping assess particle size and shape.
2. **Transmission Electron Microscopy (TEM):** TEM offers even higher resolution than SEM and is used to visualize nanoscale structures.

D. X-ray Diffraction (XRD) Analysis: XRD is used to determine the crystalline structure of a substance, helping identify different polymorphs and crystal forms.

E. Nuclear Magnetic Resonance (NMR): NMR, as mentioned earlier, can be used not only for structural elucidation but also for studying the dynamics of molecules.

F. Mass Spectrometry: Mass spectrometry identifies and quantifies the mass-to-charge ratio of ions, aiding in the determination of molecular weight and structural analysis of drugs.^[36-45]

These analytical techniques are crucial for understanding the physicochemical properties of poorly soluble drugs, optimizing their formulations, and ensuring their effectiveness in pharmaceutical applications. Researchers use them to select appropriate drug delivery systems and improve drug solubility and bioavailability.

Formulation Strategies for Poorly Soluble Drugs

A. Solid Dispersions: Solid dispersions involve dispersing poorly soluble drugs in a solid matrix, typically a polymer. This increases drug solubility and dissolution by reducing particle size and increasing surface area. Examples include spray-dried dispersions and melt extrusion.

B. Nanosuspensions: Nanosuspensions contain drug particles in nanoscale sizes suspended in a liquid. This enhances drug dissolution and bioavailability due to the larger surface area. Stabilizers are often used to prevent particle aggregation.

C. Lipid-Based Formulations: Lipid-based formulations include lipid solutions, emulsions, and self-emulsifying drug delivery systems (SEDDS). Lipids can solubilize poorly soluble drugs, facilitating their absorption in the gastrointestinal tract.

D. Cyclodextrin Complexation: Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes with poorly soluble drugs. This improves solubility and bioavailability by encapsulating the drug molecule within the cyclodextrin cavity.

E. Prodrug Approaches: Prodrugs are chemically modified versions of poorly soluble drugs. These modifications make the drug more water-soluble or easily metabolized, enhancing its bioavailability. Once inside the body, Prodrugs are converted into the active form.^[46-75]

Bioavailability Enhancement Techniques

A. Oral Delivery Systems

1. **Self-Emulsifying Drug Delivery Systems (SEDDS):** SEDDS are formulations that contain the drug in a lipid-based system. Upon contact with gastrointestinal fluids, they spontaneously form emulsions, enhancing drug solubilization and absorption.
2. **Nanoemulsions:** Nanoemulsions are thermodynamically stable emulsions with droplets in the nanometer range. They increase the surface area for drug absorption, improving bioavailability.

B. Parenteral Delivery Systems

1. **Intravenous Nanoparticles:** Intravenous nanoparticles are designed to deliver poorly soluble drugs directly into the bloodstream. Nanoparticles improve drug solubility, stability, and controlled release, ensuring rapid and efficient delivery.

C. Topical and Transdermal Delivery Systems: These systems allow drugs to be applied to the skin for absorption. Techniques like micro emulsions, transdermal patches, and nanoparticles enable better drug permeation through the skin, enhancing bioavailability.

D. Inhalable Delivery Systems: Inhalable delivery is primarily used for pulmonary drug delivery. It involves formulating drugs as fine particles or aerosols for inhalation, ensuring rapid absorption through the lung's extensive surface area.

These formulation strategies and bioavailability enhancement techniques are essential for overcoming the challenges associated with poorly soluble drugs, improving their therapeutic effectiveness, and providing patients with more efficient and convenient ways to administer these medications. The choice of strategy or

technique depends on the specific drug and its intended route of administration.^[76-96]

Impact of Poor Solubility on Drug Development

A. Challenges in Drug Development: Poor solubility is a formidable challenge in drug development that can have profound implications. When a drug exhibits low solubility, it means that it doesn't readily dissolve in the body's fluids, such as the gastrointestinal tract. This, in turn, leads to low bioavailability, which is the fraction of the administered dose that reaches the systemic circulation in an active form. Low bioavailability can result in inadequate therapeutic efficacy, meaning that the drug may not achieve the desired therapeutic effect even if it is administered at the correct dose.

Drug developers are confronted with several hurdles when dealing with poorly soluble compounds. First, they must invest additional time and resources to find solutions that enhance solubility. These solutions often involve complex formulation strategies, such as creating solid dispersions, nanosuspensions, lipid-based formulations, or using cyclodextrin complexation or prodrug approaches. These strategies aim to improve the drug's solubility and bioavailability, ensuring that an adequate amount of the drug reaches its target in the body.

Moreover, the development process for poorly soluble drugs can be protracted, involving extensive preclinical and clinical studies to validate the safety and efficacy of the formulation. Regulatory agencies play a critical role in evaluating these formulations to ensure they meet stringent standards for approval. This adds another layer of complexity to the drug development process.

B. Regulatory Considerations: Regulatory agencies like the FDA & USFDA (U.S. Food and Drug Administration) play a pivotal role in evaluating and approving pharmaceutical formulations, including those designed to address the challenges posed by poorly soluble drugs. These agencies have specific guidelines and requirements in place to ensure that such formulations meet stringent safety and efficacy standards. Here's an elaboration on the regulatory aspects of poorly soluble drugs.

1. **Preclinical Studies:** Before advancing to clinical trials, developers must conduct comprehensive preclinical studies. These studies involve in vitro (laboratory) and in vivo (animal) experiments to assess the drug's safety, efficacy, and pharmacokinetics. For poorly soluble drugs, formulation strategies must be tested extensively to demonstrate improved solubility and bioavailability.
2. **Clinical Trials:** When transitioning to clinical trials, developers must submit an Investigational New Drug (IND) application to the FDA or the relevant regulatory agency in their region. Clinical trials are typically conducted in multiple phases (Phase I, II, and III), with each phase focusing on different

aspects of safety and efficacy. For poorly soluble drugs, special attention is given to how the formulation affects the drug's performance in human subjects.

3. **Formulation Characterization:** Regulatory agencies require developers to thoroughly characterize the formulation of poorly soluble drugs. This includes detailed information on the composition, manufacturing process, stability, and quality control measures. Developers must demonstrate that the formulation is consistent and reproducible.
4. **Bioequivalence Studies:** In cases where a novel formulation is proposed to enhance solubility, bioequivalence studies are crucial. These studies compare the performance of the new formulation to an existing reference formulation (if applicable) to ensure that the two are interchangeable in terms of safety and efficacy.
5. **Regulatory Submissions:** Developers must prepare and submit New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) depending on whether the drug is innovative or a generic version. These submissions include a wealth of data, including preclinical and clinical study results, formulation details, and manufacturing processes. For poorly soluble drugs, a comprehensive description of the formulation's impact on solubility and bioavailability is essential.
6. **Regulatory Review:** Regulatory agencies conduct a rigorous review of the submitted data, including the formulation-related data. They assess whether the proposed formulation effectively addresses the challenges posed by poor solubility and whether it meets safety and efficacy criteria.
7. **Labeling and Post-Market Surveillance:** Once a drug is approved, the regulatory agency oversees its post-market safety and monitors any adverse events. The drug's labeling includes information on its formulation and usage, ensuring that healthcare professionals and patients are informed about its characteristics.
8. **Communication and Collaboration:** Developers often engage in a dialogue with regulatory agencies throughout the development process. This collaboration can help address questions or concerns raised by regulators and facilitate the approval process.

C. Case Studies of Poorly Soluble Drug Development:

Certainly, real-world case studies of poorly soluble drug development underscore the complexities and importance of innovative formulation strategies in ensuring patient access to effective medications. Here are a couple of illustrative examples:

1. Case Study 1: Cyclosporine (Sandimmune/Neoral)

- **Challenge:** Cyclosporine, an immunosuppressive drug used in organ transplantation, is notorious for its poor solubility. Its low bioavailability made it challenging to achieve consistent therapeutic blood

levels in patients, leading to the risk of transplant rejection or toxicity.

- **Innovation:** The development of Neoral, a microemulsion formulation of cyclosporine, was a breakthrough. Neoral significantly improved cyclosporine's solubility and bioavailability. The formulation allowed for more predictable drug absorption, reducing the risk of under- or over-dosing.
 - **Impact:** Neoral's improved solubility and bioavailability revolutionized organ transplantation therapy. Patients could now receive a consistent dose, leading to better graft survival rates and reduced side effects. This case highlights how innovative formulation strategies can transform the efficacy and safety of poorly soluble drugs, ultimately benefiting patients.
2. **Case Study 2: Griseofulvin (Grifulvin V)**
- **Challenge:** Griseofulvin is an antifungal medication with poor solubility. The challenge was to develop a formulation that would enhance its solubility and bioavailability to effectively treat fungal infections.
 - **Innovation:** Grifulvin V, an oral suspension formulation of griseofulvin, overcame the solubility hurdle. This formulation used micronization to reduce particle size, increasing the drug's surface area and enhancing dissolution in the gastrointestinal tract.
 - **Impact:** Grifulvin V's improved solubility allowed for more efficient absorption, enabling effective treatment of fungal infections. This case showcases how simple yet innovative strategies, like particle size reduction, can transform a poorly soluble drug into a clinically effective therapy, improving patient outcomes.

These case studies exemplify how innovative formulation strategies can tackle the challenges posed by poorly soluble drugs. By enhancing solubility and bioavailability, these formulations have revolutionized the treatment landscape for various medical conditions. They underscore the critical role of pharmaceutical scientists in overcoming these hurdles and ensuring that patients have access to safe and effective medications. These successes in drug development highlight the potential for transformative impacts on patient health when addressing the solubility issues associated with certain drugs.

Future Trends and Innovations

A. Advances in Analytical Techniques: Continued advancements in analytical techniques, particularly in high-resolution imaging and spectroscopy, have ushered in a new era of precision and insight in the characterization of poorly soluble drugs. These advanced analytical tools are instrumental in guiding the development of targeted formulation strategies.

Here's an overview of how these techniques are making a significant impact.

1. High-Resolution Imaging:

- **Scanning Electron Microscopy (SEM):** SEM provides detailed images of drug particles at a microscopic level. It allows for the observation of particle morphology, size, and surface characteristics. This information is invaluable for understanding the physical properties of poorly soluble drugs and identifying potential issues with agglomeration or particle size distribution.
- **Transmission Electron Microscopy (TEM):** TEM takes imaging to an even higher resolution, offering nanoscale insights into drug particles. This technique is particularly useful for visualizing nanoparticles and understanding their structure, which is critical in nanotechnology-based drug formulations like nanosuspensions.

2. Spectroscopic Techniques:

- **Nuclear Magnetic Resonance (NMR):** NMR spectroscopy provides information about the molecular structure of drugs and their interactions with excipients. It can reveal how different formulations impact drug solubility, crystal polymorphism, and molecular conformation, aiding in the selection of suitable excipients and formulation strategies.
 - **X-ray Crystallography:** X-ray crystallography is essential for understanding the crystal structure of poorly soluble drugs. It helps identify different crystal forms, their stability, and how they influence solubility. This information is crucial in designing solid dispersion or salt formation strategies.
3. **Infrared (IR) Spectroscopy and Raman Spectroscopy:** These techniques provide insights into the chemical composition and functional groups present in drug molecules. They are valuable for assessing drug-excipient compatibility and understanding molecular interactions that affect solubility.
4. **Differential Scanning Calorimetry (DSC):** DSC measures changes in heat flow associated with phase transitions, such as melting or crystallization. It helps identify the thermal behavior of drug formulations, which is vital for optimizing manufacturing processes and selecting suitable excipients.

The precision and depth of information obtained through these advanced analytical techniques empower pharmaceutical scientists to make informed decisions during drug development. They enable a deeper understanding of the underlying factors contributing to poor solubility, such as crystal forms, particle size, and interactions with excipients. With this knowledge, researchers can tailor formulation strategies to address specific challenges, whether it involves designing solid dispersions, lipid-based formulations, or other innovative approaches.

B. Novel Formulation Strategies

Indeed, researchers are continually exploring innovative formulation approaches to address the challenges associated with poor drug solubility and bioavailability. Here are some key strategies they are actively investigating.

1. Nanotechnology-Based Formulations:

- **Nanosuspensions:** Nanosuspensions involve reducing drug particles to nanoscale sizes, typically below 1 micron. This significantly increases the surface area available for dissolution, leading to improved solubility and rapid absorption. Nanosuspensions are particularly effective for poorly soluble drugs.
- **Lipid-Based Nanocarriers:** Lipid-based nanoparticles, such as liposomes, nanoemulsions, and solid lipid nanoparticles, can encapsulate poorly soluble drugs, enhancing their solubility and stability. These nanocarriers can also improve drug targeting and controlled release.

2. 3D Printing

- **Personalized Dosage Forms:** 3D printing technology allows for the precise fabrication of dosage forms tailored to individual patient needs. This can be especially valuable for poorly soluble drugs, enabling customized dosing regimens based on patient-specific factors like age, weight, and metabolism.
- **Complex Geometries:** 3D printing enables the creation of complex drug delivery systems with unique structures. These structures can modulate drug release rates and improve solubility by optimizing drug dispersion within the formulation.

3. Novel Excipients:

- **Amorphous Excipients:** The use of amorphous excipients can enhance the amorphousness of drug formulations, leading to improved solubility. Amorphous materials have a disordered atomic arrangement, making them more soluble than their crystalline counterparts.
- **Co-crystals:** Co-crystals involve the combination of a drug with another molecule to form a new crystalline structure. This approach can alter the drug's physicochemical properties, including solubility, without the need for large amounts of excipients.

4. Prodrug Approaches

- **Prodrug Design:** Prodrugs are inactive drug derivatives that convert into the active drug in the body. Researchers design prodrugs to improve solubility and bioavailability. Upon administration, these prodrugs undergo chemical transformations to release the active drug in a more soluble form.

5. Advanced Drug Delivery Systems

- **Microneedles:** Microneedle-based delivery systems are being explored for transdermal drug administration. They can enhance the absorption of

poorly soluble drugs through the skin, avoiding issues associated with oral delivery.

- **Inhalable Formulations:** Inhalable drug delivery systems can be effective for poorly soluble drugs intended for pulmonary administration. These systems disperse the drug in fine particles for efficient lung deposition.

These innovative formulation approaches represent a frontier in pharmaceutical research, offering promising solutions to the challenges posed by poorly soluble drugs. By harnessing nanotechnology, 3D printing, novel excipients, and creative prodrug designs, researchers aim to enhance drug solubility, improve bioavailability, and ultimately provide patients with more effective and tailored therapeutic options. These advancements not only benefit patients but also advance the field of pharmaceutical science as a whole.

C. Personalized Medicine Approaches

Personalized medicine, often referred to as precision medicine, is a groundbreaking approach to healthcare that takes into account individual variability in genes, environment, and lifestyle for tailoring drug therapies. This approach is especially valuable when dealing with poorly soluble drugs, as it allows for the optimization of drug selection and dosing to ensure the best possible therapeutic outcomes. Here's how personalized medicine can benefit patients, particularly in the context of poorly soluble drugs.

1. **Genetic Variability:** Each person's genetic makeup can influence how their body metabolizes and responds to drugs. Polymorphisms in drug-metabolizing enzymes and drug transporters can affect the pharmacokinetics and pharmacodynamics of drugs, including their solubility and bioavailability. Personalized medicine utilizes genetic testing to identify these variations and select drugs and dosages that are most likely to be effective for each individual.
2. **Metabolism:** Poorly soluble drugs may require specific metabolic pathways for activation or conversion to their active forms. Personalized medicine can assess an individual's metabolic profile to determine if they have the enzymatic capacity to convert a drug effectively. If not, alternative drugs or dosing regimens can be selected to ensure therapeutic efficacy.
3. **Disease Characteristics:** Disease characteristics, such as the stage, severity, and underlying mechanisms of a condition, can influence the choice of therapy. Personalized medicine considers these factors when selecting treatments for patients with poorly soluble drug options. For example, a patient with a specific type of cancer may benefit from a personalized therapy designed to target the genetic mutations driving their disease.
4. **Dosing Optimization:** Personalized medicine allows for precise dosing adjustments based on individual factors. For poorly soluble drugs, the

optimal dose can be determined considering factors like the patient's body weight, renal function, liver function, and genetic predisposition to drug-related adverse events. This minimizes the risk of under- or over-dosing, improving both safety and efficacy.

5. **Reduced Side Effects:** Poorly soluble drugs may carry a higher risk of side effects due to variations in drug exposure. Personalized medicine aims to minimize side effects by tailoring drug therapies to an individual's specific needs. This can lead to a better balance between therapeutic benefits and potential adverse reactions.
6. **Therapeutic Monitoring:** Personalized medicine often involves monitoring drug levels in the bloodstream to ensure that the drug remains within the therapeutic range. This is particularly important for poorly soluble drugs, as their absorption can be variable. Therapeutic drug monitoring allows for timely adjustments to dosing if needed.

D. Green and Sustainable Drug Delivery: There is indeed a growing emphasis on developing environmentally friendly drug delivery systems in the pharmaceutical industry. This shift towards sustainability aligns with the principles of green chemistry, which aims to minimize waste, reduce energy consumption, and mitigate the environmental impact of chemical processes, including drug manufacturing and formulation. Here's how green chemistry principles are being applied in the pharmaceutical field to create more environmentally friendly drug delivery systems:

1. **Reducing Hazardous Substances:** Green chemistry encourages the replacement of hazardous substances with safer alternatives. In drug formulation, this means avoiding the use of toxic solvents, catalysts, or reagents, which can pose risks to both workers and the environment. Instead, pharmaceutical companies are exploring greener, less toxic alternatives that are safer for human health and the ecosystem.
2. **Solvent Selection:** Solvents play a crucial role in drug formulation processes, but many traditional solvents are harmful to the environment. Green chemistry promotes the use of benign solvents, such as water or supercritical carbon dioxide, which have a lower environmental impact. This reduces the release of volatile organic compounds (VOCs) and minimizes the carbon footprint of pharmaceutical processes.
3. **Energy Efficiency:** Green chemistry encourages the development of energy-efficient processes. In drug manufacturing, this involves optimizing reaction conditions and employing energy-efficient equipment to reduce energy consumption. Lower energy requirements not only reduce costs but also lessen the environmental impact associated with energy generation.
4. **Minimizing Waste:** Pharmaceutical processes often generate significant waste, such as by-products and unused reagents. Green chemistry seeks to minimize

waste by designing processes that produce fewer by-products and promote the reuse or recycling of materials. This reduces the burden on waste disposal and lowers the environmental footprint.

5. **Sustainable Sourcing:** The pharmaceutical industry is increasingly looking at sustainable sourcing of raw materials, including plant-derived compounds, to reduce the environmental impact associated with resource extraction. Ethical and eco-friendly sourcing practices are becoming more prevalent.
6. **Biodegradable and Eco-Friendly Formulations:** Green chemistry principles are driving the development of biodegradable drug delivery systems. These systems break down naturally after use, reducing the accumulation of non-degradable drug residues in the environment.
7. **Life Cycle Assessment:** Green chemistry incorporates life cycle assessments to evaluate the environmental impact of drug delivery systems at every stage, from raw material extraction to disposal. This holistic approach helps identify areas for improvement and guides the development of more sustainable processes.
8. **Regulatory Compliance:** Regulatory agencies are increasingly considering the environmental impact of pharmaceutical processes. Companies must adhere to stringent environmental regulations and provide evidence of their commitment to green chemistry principles to gain approval for new drug formulations.

In conclusion, the pharmaceutical industry is embracing green chemistry principles to create drug delivery systems that are environmentally friendly and sustainable. This shift towards greener practices not only reduces the industry's ecological footprint but also aligns with societal expectations for environmentally responsible drug development and manufacturing. As these efforts continue to evolve, they are expected to contribute to a more sustainable and eco-conscious pharmaceutical landscape.^[97-114]

CONCLUSION

In this comprehensive review, we delved into the critical aspects of poorly soluble drugs, including their physicochemical properties, formulation strategies, bioavailability enhancement techniques, impact on drug development, and future trends. Poorly soluble drugs present challenges related to solubility, particle size, polymorphism, and lipophilicity. To enhance solubility and bioavailability, various formulation strategies such as solid dispersions, nanosuspensions, lipid-based formulations, cyclodextrin complexation, and prodrug approaches are employed, along with diverse delivery systems. These solubility issues significantly affect drug development and necessitate regulatory compliance. The Pharmaceutical industry's future lies in analytical advancements, innovative formulation methods, personalized medicine, and sustainable drug delivery to combat poor solubility. Poor solubility's implications are

far-reaching, offering improved therapeutic outcomes, a competitive advantage for companies, regulatory compliance, and resource optimization. However, further research is needed in advanced formulation strategies, personalized medicine, sustainability, and regulatory guidance to continue addressing this challenge effectively. Ultimately, conquering poorly soluble drugs is vital for Pharmaceutical science's advancement and better healthcare outcomes.

REFERENCES

1. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. *Journal of Pharmacological and Toxicological Methods*. 2000; 44(1): 235-249.
2. Serajuddin AT. Salt formation to improve drug solubility. *Advanced Drug Delivery Reviews*. 2007; 59(7): 603-616.
3. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *Journal of Pharmaceutical Sciences*. 1971; 60(9): 1281-1302.
4. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? *Pharmaceutical Research*. 2000; 17(4): 397-404.
5. Zhou Y, Wu Y, Zhang T, et al. Dissolution and oral absorption of praziquantel in biorelevant media. *European Journal of Pharmaceutics and Biopharmaceutics*. 2011; 77(3): 392-399.
6. Kalaiselvan R, Gani AR, Chandrasekaran R. Characterization techniques for nanotechnology applications in pharmaceutical sciences. *Advances in Natural Sciences: Nanoscience and Nanotechnology*. 2018; 9(2): 023002.
7. Hussain MA, Liu C, Hussain M. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. *ISRN Pharmaceutics*. 2012; 2012: 848043.
8. Williams AC, Timmins P, Lu XF. Novel particle engineering technologies for enhancing the in vitro dissolution and in vivo bioavailability of poorly water-soluble drugs. *International Journal of Pharmaceutics*. 2013; 453(1): 315-312.
9. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*. 2002; 231(2): 131-144.
10. Sridhar V, Srinivas K, Ratnam BV. Solid dispersion: a strategy for poorly aqueous soluble drugs and technology update. *Current Drug Discovery Technologies*. 2009; 6(3): 205-212.
11. Müller RH, Gohla S, Keck CM. State of the art of nanocrystals—special features, production, nanotoxicology aspects and intracellular delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2011; 78(1): 1-9.
12. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water-soluble drugs. *Advanced Drug Delivery Reviews*. 1997; 25(1): 103-128.
13. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *European Journal of Pharmaceutical Sciences*. 2000; 11: S93-S98.
14. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. *Nature Reviews Drug Discovery*. 2007; 6(3): 231-248.
15. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. *Advanced Drug Delivery Reviews*. 2008; 60(6): 734-746.
16. Wasan KM, Wasan EK, Gershkovich P, et al. Highly emulsifying semisolid self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs: in vitro characterization, in vivo oral absorption and the in vitro-in vivo correlation (IVIVC). *Journal of Controlled Release*. 2009; 133(1): 11-17.
17. Kawabata Y, Wada K, Nakatani M, et al. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. *International Journal of Pharmaceutics*. 2011; 420(1): 1-10.
18. Müller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs—a review of drug nanocrystal technology and lipid nanoparticles. *Journal of Biotechnology*. 2004; 113(1-3): 151-170.
19. Kesisoglou F, Panmai S, Wu Y. Nanosizing—oral formulation development and biopharmaceutical evaluation. *Advanced Drug Delivery Reviews*. 2007; 59(7): 631-644.
20. Babu NJ, Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. *Crystal Growth & Design*. 2011; 11(7): 2662-2679.
21. U.S. Food and Drug Administration (FDA). Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. FDA, 2000.
22. European Medicines Agency (EMA). Guideline on the Investigation of Bioequivalence. EMA, 2010
23. Li P, Zhao L. Developing a supragenics strategy: case study of an oral solubilized amphotericin B tablet. *AAPS PharmSciTech*. 2013; 14(2): 825-831.
23. Mudie DM, Amidon GL, Amidon GE. Physiological parameters for oral delivery and in vitro testing. *Molecular Pharmaceutics*. 2010; 7(5): 1388-1405.
25. Date AA, Nagarsenker MS. Parenteral nanoemulsions: an overview. *International Journal of Pharmaceutics*. 2008; 355(1-2): 19-30.
26. Pathak K, Sharma V, Choudhury H, Bhatt P. Advances in novel drug delivery strategies for poorly water-soluble drugs. *Expert Opinion on Drug Delivery*. 2012; 9(8): 1019-1034.
27. Haider M, Abidin SM, Kamal L, Orive G. Nanostructured lipid carriers for delivery of

- chemotherapeutics: a review. *Pharmaceutics*. 2021; 13(8): 1270.
28. Lai F, Pini E, Angioni G, et al. Nanoemulsions as delivery systems for poorly soluble drugs: pharmacokinetic and tissue distribution study of paclitaxel. *Journal of Pharmaceutical Sciences*. 2013; 102(10): 3482-3489.
 29. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. *ActaPoloniaePharmaceutica*. 2010; 67(3): 217-223.
 30. Wasdo SC, Wasan KM. Biodegradable and biocompatible nanoparticles for enhancement of oral bioavailability of poorly soluble drugs. *Journal of Bioequivalence & Bioavailability*. 2012; 4(6): 124-132.
 31. Grumezescu AM, Nanoscale Fabrication, Optimization, Scale-up and Biological Aspects of Pharmaceutical Nanocarriers. Academic Press, 2017.
 32. Mohtar N, Taylor KM, Sheikh K. Challenges and emerging solutions in the development of orally disintegrating films. *Expert Opinion on Drug Delivery*. 2015; 12(6): 931-947.
 33. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. *Journal of Pharmaceutical Sciences*. 1997; 86(1): 1-12.
 34. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*. 2002; 231(2): 131-144.
 35. Wu W, McGinity JW. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films. *Journal of Controlled Release*. 2002; 80(1-3): 297-306.
 36. Sun Y, Zhang G, Zhao L, et al. A new approach to improve the dissolution of cyclosporine A: a cyclosporine A-solid dispersion. *AAPS PharmSciTech*. 2010; 11(1): 172-182.
 37. Hamed R, Awad GE, Mortada ND. Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride. *AAPS PharmSciTech*. 2008; 9(4): 1140-1146.
 38. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. *Journal of the American Chemical Society*. 1897; 19(12): 930-934.
 39. Gao L, Zhang D, Chen M. Drug nanocrystals for the formulation of poorly soluble drugs and its application as a potential drug delivery system. *Journal of Nanoparticle Research*. 2008; 10(5): 845-862.
 40. Yu H, Jin F, Liu D, Shu G. Drug crystallization and its applications in oral dosage form development. *Pharmaceutics*. 2019; 11(3): 134.
 41. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. *Molecular Pharmaceutics*. 2008; 5(6): 1003-1019.
 42. Pouton CW, Porter CJH. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. *Advanced Drug Delivery Reviews*. 2008; 60(6): 625-637.
 43. Piazza V, Ruggeri M, Restivo E, et al. Formulation design for sustainable drug delivery: a guide for selecting a greener and more efficient approach. *ACS Sustainable Chemistry & Engineering*. 2020; 8(17): 6352-6371.
 44. Selvam RP, Ganesan V, Kandasamy K, et al. Current trends and future perspectives of lipid-based formulations for poorly water-soluble drugs. *Journal of Pharmacy & Pharmaceutical Sciences*. 2013; 16(4): 550-573.
 45. Kumar P, Choonara YE, Modi G, du Toit LC, Naidoo D, Pillay V. Smart multifunctional core-shell polymer nanoparticles: a review. *Journal of Nanoparticles Research*. 2014; 16(6): 1-25.
 46. Riga A, Tao W, Hao J. Drug delivery in polymeric nanoparticles: an update on recent trends. In: *Polymeric Nanoparticles as a Promising Tool for Anti-Cancer Therapeutics*. Academic Press, 2020.
 47. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. *European Journal of Pharmaceutics and Biopharmaceutics*. 2006; 62(1): 3-16.
 48. De Vruet RL, Crommelin DJA. Liposomes as drug carriers in cancer therapy. *Advances in Drug Delivery Reviews*. 1995; 17(2-3): 225-249.
 49. Mohan R, Hyland R, Butler J, et al. Pharmacokinetics of amorphous and crystalline ritonavir after administration of ritonavir-boosted atazanavir tablets in healthy subjects. *Journal of Pharmaceutical Sciences*. 2012; 101(2): 798-807.
 50. Singla AK, Chawla M. Chitosan: some pharmaceutical and biological aspects—an update. *Journal of Pharmacy & Pharmacology*. 2001; 53(8): 1047-1067.
 51. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*. 1997; 23(1-3): 3-25.
 52. Serajuddin AT, Sheen PC, Augustine MA. Improved oral bioavailability of a poorly water-soluble drug, BMS-180448-01, in monkeys as a spray-dried dispersion. *Pharmaceutical Research*. 1999; 16(2): 180-185.
 53. Bhattachar SN, Bhaumik U, Goyal A, et al. Polymorphism and solid state stability studies in metaxalone. *International Journal of Pharmaceutics*. 2004; 270(1-2): 29-41.
 54. Mehta M, Bhardwaj SP, Suryanarayanan R. Polymorphism in an anti-HIV drug: heat capacity and thermodynamic stability of ritonavir polymorphs. *Journal of Pharmaceutical Sciences*. 2002; 91(6): 1549-1559.

55. Singh SK, Kaur IP, Saini K. Development and evaluation of proniosomes for improving transdermal delivery of acetazolamide. *ActaPharmaceutica*. 2007; 57(3): 315-332.
56. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharmaceutical Research*. 1998; 15(1): 11-22.
57. Gupta S, Thilagavathi R. Chemistry, physicochemical properties, and drug-excipient compatibility studies on duloxetine hydrochloride. *Drug Development and Industrial Pharmacy*. 2012; 38(10): 1267-1279.
58. Law D, Schmitt EA, Marsh KC, Everitt EA, Wang W, Fort JJ. Theoretical and experimental approach to estimate the maximum amount of amorphous solids that can be generated upon freeze-drying of solutions. *Pharmaceutical Development and Technology*. 2004; 9(3): 261-272.
59. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research*. 1995; 12(3): 413-420.
60. Vertzoni M, Dressman J, Butler J, Hempenstall J, Reppas C. Simulation of fasting gastric conditions and its importance for the in vivo dissolution of lipophilic compounds. *European Journal of Pharmaceutical Sciences*. 2005; 24(4): 359-367.
61. Zhao Y, Wang C, Chow AH, Ren K, Gong T, Zhang Z. Self-microemulsifying drug delivery system (SMEDDS) for improving in vitro dissolution and oral absorption of Puerarialobataisoflavone. *Drug Development and Industrial Pharmacy*. 2010; 36(9): 1171-1177.
62. Feng X, Xu W, Li Z, Song W, Ding J, Chen X. Self-healing behaviors of supramolecular polymeric hydrogels formed by host-guest interactions. *Macromolecules*. 2015; 48(2): 607-614.
63. He Y, Ho C. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Advanced Drug Delivery Reviews*. 2001; 48(1): 18-30.
64. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. *Journal of Pharmaceutical Sciences*. 2000; 89(7): 850-866.
65. Paliwal R, Paliwal SR, Kenwat R, Kurmi BD, Raturi K, Pillai S. Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by the nanoprecipitation method. *Drug Development and Industrial Pharmacy*. 2015; 41(7): 1176-1184.
66. Mosallam SM, Shamma RN, Youssef AE, El-Gindy GE. Enhanced oral bioavailability of lurasidoneHCl via orodispersible tablets: in vitro and in vivo evaluation. *European Journal of Pharmaceutical Sciences*. 2015; 74: 25-35.
67. Iqbal Z, Baboota S, Sahni JK, et al. Nanostructured lipid carriers system: recent advances in drug delivery. *Journal of Drug Targeting*. 2012; 20(10): 813-830.
68. Loftsson T, Jarho P, Masson M, Järvinen T. Cyclodextrins in drug delivery. *Expert Opinion on Drug Delivery*. 2005; 2(2): 335-351.
69. Sinha VR, Bansal K, Kaushik R, Kumria R, Trehan A. Poly-ε-caprolactone microspheres and nanospheres: an overview. *International Journal of Pharmaceutics*. 2004; 278(1): 1-23.
70. Patil PR, Deshmukh PK, Patil DR. Enhanced oral bioavailability of felodipine by nanosuspension formulation: formulation development, in vitro and in vivo evaluation. *Drug Development and Industrial Pharmacy*. 2013; 39(10): 1501-1510.
71. Taylor LS, Zografi G. The quantitative analysis of crystallinity using FT-Raman spectroscopy. *Pharmaceutical Research*. 1998; 15(5): 755-761.
72. Kawabata Y, Wada K, Nakatani M, et al. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. *International Journal of Pharmaceutics*. 2011; 420(1): 1-10.
73. Löbenberg R, Amidon GL. Modern bioavailability, bioequivalence, and biopharmaceutics classification system. New scientific approaches to international regulatory standards. *European Journal of Pharmaceutics and Biopharmaceutics*. 2000; 50(1): 3-12.
74. Rajabi-Siahboomi AR. Strategies to modify drug release from suppositories. *Drug Development and Industrial Pharmacy*. 2000; 26(9): 951-957.
75. Mitra A, Wu Y. Novel approaches to enhance oral delivery of poorly water-soluble drugs. *Drug Development and Industrial Pharmacy*. 2012; 38(4): 323-332.
76. U.S. Food and Drug Administration (FDA). Biopharmaceutics Classification System (BCS) Guidance for Industry. FDA, 2017.
77. European Medicines Agency (EMA). Guideline on the Investigation of Bioequivalence. EMA, 2010.
78. Loftsson T, Másson M, Brewster ME. Self-association of cyclodextrins and cyclodextrin complexes in aqueous solution. *Journal of Pharmaceutical Sciences*. 2004; 93(5): 1091-1099.
79. He Y, Ho C. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Advanced Drug Delivery Reviews*. 2001; 48(1): 18-30.
80. Li J, Yu C, Zhang Y, et al. Lipid nanodiscs facilitate in vitro detectability and cytotoxicity studies of drug candidates that suffer from low water solubility. *Analyst*. 2017; 142(15): 2815-2824.
81. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Advanced Drug Delivery Reviews*. 2002; 54: S131-S155.
82. Patel S, Chavhan S, Soni HN, et al. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) for pulmonary delivery: a review.

- Expert Opinion on Drug Delivery. 2014; 11(1): 1-17.
83. Jain D, Athawale R, Bajaj A, Shrikhande S, Goel PN, Nikam Y. Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. *Drug Delivery*. 2009; 16(3): 144-152.
 84. Hong SC, Lee DK, Jeong YI, et al. 5-Fluorouracil-loaded chitosan nanoparticles for the enhanced anti-tumor activity in colon cancer. *Carbohydrate Polymers*. 2012; 87(1): 980-985.
 85. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. *ActaPoloniaePharmaceutica*. 2010; 67(3): 217-223.
 86. Ranpise NS, Korabu SS, Ghodake VN. Green technology: formulation, in-vitro, in-vivo evaluation of fast dissolving tablets containing phospholipid complex of lopinavir. *Journal of Drug Delivery Science and Technology*. 2017; 39: 274-282.
 87. Wasdo SC, Wasan KM. Biodegradable and biocompatible nanoparticles for enhancement of oral bioavailability of poorly soluble drugs. *Journal of Bioequivalence & Bioavailability*. 2012; 4(6): 124-132.
 88. Grumezescu AM, Nanoscale Fabrication, Optimization, Scale-up and Biological Aspects of Pharmaceutical Nanocarriers. Academic Press, 2017.
 89. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. *European Journal of Pharmaceutics and Biopharmaceutics*. 2006; 62(1): 3-16.
 90. De Vruhe RL, Crommelin DJA. Liposomes as drug carriers in cancer therapy. *Advances in Drug Delivery Reviews*. 1995; 17(2-3): 225-249.
 91. Mohan R, Hyland R, Butler J, et al. Pharmacokinetics of amorphous and crystalline ritonavir after administration of ritonavir-boosted atazanavir tablets in healthy subjects. *Journal of Pharmaceutical Sciences*. 2012; 101(2): 798-807.
 92. Singla AK, Chawla M. Chitosan: some pharmaceutical and biological aspects—an update. *Journal of Pharmacy & Pharmacology*. 2001; 53(8): 1047-1067.
 93. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*. 1997; 23(1-3): 3-25.
 94. Serajuddin AT, Sheen PC, Augustine MA. Improved oral bioavailability of a poorly water-soluble drug, BMS-180448-01, in monkeys as a spray-dried dispersion. *Pharmaceutical Research*. 1999; 16(2): 180-185.
 95. Bhattachar SN, Bhaumik U, Goyal A, et al. Polymorphism and solid state stability studies in metaxalone. *International Journal of Pharmaceutics*. 2004; 270(1-2): 29-41.
 96. Mehta M, Bhardwaj SP, Suryanarayanan R. Polymorphism in an anti-HIV drug: heat capacity and thermodynamic stability of ritonavir polymorphs. *Journal of Pharmaceutical Sciences*. 2002; 91(6): 1549-1559.
 97. Singh SK, Kaur IP, Saini K. Development and evaluation of proniosomes for improving transdermal delivery of acetazolamide. *ActaPharmaceutica*. 2007; 57(3): 315-332.
 98. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharmaceutical Research*. 1998; 15(1): 11-22.
 99. Gupta S, Thilagavathi R. Chemistry, physicochemical properties, and drug-excipient compatibility studies on duloxetine hydrochloride. *Drug Development and Industrial Pharmacy*. 2012; 38(10): 1267-1279.
 100. Law D, Schmitt EA, Marsh KC, Everitt EA, Wang W, Fort JJ. Theoretical and experimental approach to estimate the maximum amount of amorphous solids that can be generated upon freeze-drying of solutions. *Pharmaceutical Development and Technology*. 2004; 9(3): 261-272.
 101. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research*. 1995; 12(3): 413-420.
 102. Vertzoni M, Dressman J, Butler J, Hempenstall J, Reppas C. Simulation of fasting gastric conditions and its importance for the in vivo dissolution of lipophilic compounds. *European Journal of Pharmaceutical Sciences*. 2005; 24(4): 359-367.
 103. Zhao Y, Wang C, Chow AH, Ren K, Gong T, Zhang Z. Self-microemulsifying drug delivery system (SMEDDS) for improving in vitro dissolution and oral absorption of Puerarialobataisoflavone. *Drug Development and Industrial Pharmacy*. 2010; 36(9): 1171-1177.
 104. Feng X, Xu W, Li Z, Song W, Ding J, Chen X. Self-healing behaviors of supramolecular polymeric hydrogels. *Macromolecules*. 2015; 48(2): 607-614.
 105. He Y, Ho C. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Advanced Drug Delivery Reviews*. 2001; 48(1): 18-30.
 106. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. *Journal of Pharmaceutical Sciences*. 2000; 89(7): 850-866.
 107. Paliwal R, Paliwal SR, Kenwat R, Kurmi BD, Raturi K, Pillai S. Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by the nanoprecipitation method. *Drug Development and Industrial Pharmacy*. 2015; 39(10): 1501-1510.
 108. Mosallam SM, Shamma RN, Youssef AE, El-Gindy GE. Enhanced oral bioavailability of lurasidoneHCl via orodispersible tablets: in vitro and in vivo evaluation. *European Journal of Pharmaceutical Sciences*. 2015; 74: 25-35.
 109. Iqbal Z, Baboota S, Sahni JK, et al. Nanostructured lipid carriers system: recent advances in drug

- delivery. *Journal of Drug Targeting*. 2012; 20(10): 813-830.
110. Loftsson T, Jarho P, Masson M, Järvinen T. Cyclodextrins in drug delivery. *Expert Opinion on Drug Delivery*. 2005; 2(2): 335-351.
111. Sinha VR, Bansal K, Kaushik R, Kumria R, Trehan A. Poly-ε-caprolactone microspheres and nanospheres: an overview. *International Journal of Pharmaceutics*. 2004; 278(1): 1-23.
112. Patil PR, Deshmukh PK, Patil DR. Enhanced oral bioavailability of felodipine by nanosuspension formulation: formulation development, in vitro and in vivo evaluation. *Drug Development and Industrial Pharmacy*. 2013; 39(10): 1501-1510.
113. Taylor LS, Zografi G. The quantitative analysis of crystallinity using FT-Raman spectroscopy. *Pharmaceutical Research*. 1998; 15(5): 755-761.
114. Kawabata Y, Wada K, Nakatani M, et al. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. *International Journal of Pharmaceutics*. 2011; 420(1): 1-10.