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Solublity Enhancement Of Ibuprofen Using Different Techniques

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Abstract

The primary focus of this review is to address the challenges associated with the solubility and bioavailability of BCS Class-II drugs. These drugs are characterized by their low solubility and dissolution rates, making it essential to enhance their solubility to achieve the desired drug concentration in the systemic circulation and, subsequently, a pharmacological response.

Class-II drugs, commonly formulated in solid dosage forms like tablets and capsules, necessitate improvements in their solubility and dissolution rates. To tackle these issues, various methods and emerging technologies have been developed. These innovative approaches aim to increase the solubility and bioavailability of BCS Class-II drugs.

This article provides a comprehensive review of the current literature, focusing on the latest techniques and methods, as well as recent research in the development of formulations for Class-II drugs.

Keywords Chemical electric magnetic field, Coamorphous, Ibuprofen, Optical response curve, Paracetamol, Saturation solubility.

1. Introduction

Solubility and dissolution play crucial roles in the formulation of pharmaceuticals, affecting the oral bioavailability of poorly soluble drugs [1]. Various methods are employed to enhance the solubility of these drugs [2]. Amorphous forms of pharmacologically active materials are of particular interest due to their potential to enhance dissolution rates and bioavailability [3,4].

One promising approach to address solubility and stability issues in drug formulation is the use of Coamorphous (COAM) systems, which involve the combination of two different molecules to improve solubility, stability, and bioavailability. COAM systems are characterized by the combination of low-molecular-weight components, forming a homogeneous single-phase system. Various techniques are utilized for COAM preparation, including quenching, solvent evaporation, ball milling, spray drying, freeze-drying, fusion methods, hot-melt extrusion, and supercritical fluid methods [5-7].

Ibuprofen (IB), a widely used nonsteroidal anti-inflammatory drug, faces challenges due to its poor solubility and high permeability, categorizing it as a BCS Class II drug with limited bioavailability [8]. Additionally, its low glass transition temperature (Tg) makes the design of solid dosage forms difficult [9]. To address these issues, microwave techniques are employed to prepare COAM particles, which can enhance the physical stability of amorphous drugs [10]. However, many COAM products on the market suffer from stability issues and manufacturing challenges. Consequently, efforts are directed towards the development of stable COAM systems and feasible pharmaceutical formulations [11-13].

Recognizing the benefits of COAM combinations involving two drugs, this study aims to enhance the processability, solubility, in vitro dissolution, and amorphous state stability of IB by combining it with paracetamol (PA), a BCS Class III drug. Clinically relevant combinations of both drugs are available and are widely recommended for analgesic, antipyretic, and anti-inflammatory purposes. Five clinical dose combinations, including 500mg:200mg, 475mg:125mg, 325mg:400mg, 125mg:100mg, and 100mg:100mg of PA:IB, were prepared using microwave techniques for coamorphism.

Microwave irradiation is an eco-friendly and cost-effective technique for achieving molecular dispersion. Microwaves are electromagnetic waves with electric and magnetic field components [14-17]. Chemical electric magnetic (CEM) field microwave heating requires less reaction time and prevents drug degradation. It allows for the maintenance of a constant temperature throughout the reaction. Microwave technology is widely employed in the preparation of solid dispersions, tablet coating, granule drying, and semi-solid formulations. The heating process is based on the conversion of electromagnetic radiation into heat energy, ensuring rapid and uniform heating of the reaction mixture [18]. Consequently, this study focuses on the preparation of COAM systems and their assessment through solubility, Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and in vitro dissolution studies.

2. Factors Affecting solubilisation

The solubility of a substance is influenced by various factors, which can be categorized as follows:

Particle Size:

The size of solid particles significantly affects solubility.

Smaller particles have a higher surface area-to-volume ratio, promoting greater interaction with the solvent.

Temperature:

Solubility is temperature-dependent.

Increasing temperature generally increases solubility for processes that absorb energy but decreases it for those that release energy.

Gaseous solutes tend to become less soluble in warmer solutions.

Pressure:

Solubility is largely unaffected by changes in pressure for solids and liquid solutes.

Gaseous solutes exhibit increased solubility with higher pressure and decreased solubility with lower pressure.

Nature of the Solute and Solvent:

The nature of the substances involved plays a crucial role in solubility.

Differences in the natures of solutes and solvents can result in significant variations in solubility.

Molecular Size:

Larger molecules with higher molecular weight and size tend to be less soluble.

Organic compounds may have increased solubility due to carbon branching, which reduces molecular size.

Polarity:

The polarity of both solute and solvent molecules affects solubility.

Like dissolves like, meaning polar solutes dissolve in polar solvents, and non-polar solutes dissolve in non-polar solvents.

Intermolecular forces such as dipole-dipole interactions and London dispersion forces play a role in solvation.

Polymorphs:

Different polymorphs of a substance may have varying solubilities.

These differences are often relatively small, typically within a 2-3 fold range, due to small variations in free energy.

Rate of Solution:

The rate at which a substance dissolves in a solvent is influenced by several factors, including:

(a) Size of the particles: Smaller particles dissolve more rapidly due to increased surface area.

(b) Temperature: Increasing temperature enhances the rate of dissolution for liquid and solid solutes.

© Amount of solute already dissolved: Dissolution is faster when there is less solute already in solution.

(d) Stirring: Agitating the mixture improves solubility by bringing fresh portions of the solvent in contact with the solute.

Understanding and manipulating these factors is crucial for controlling solubility in various applications, including pharmaceuticals and chemical processes.

3. TECHNIQUES FOR SOLUBILITY ENHANCEMENT

There are various techniques available to improve the Solubility of hydrophobic drugs. Some traditional and Novel approaches to improve the solubility are:

1. Particle Size Reduction
2. Solid Dispersion
3. Nanosuspension
4. Supercritical Fluid Technology
5. Floating Granules

Particle size reduction

is a critical factor affecting the solubility and bioavailability of pharmaceutical drugs. As particles become smaller, their surface area-to-volume ratio increases, facilitating greater interaction with solvents and thereby enhancing solubility.

Conventional methods for particle size reduction, like comminution and spray drying, rely on mechanical forces to break down the active compound. These techniques are well-established in the industry and offer efficient, reproducible, and cost-effective means of reducing particle size. However, the mechanical forces involved, such as milling and grinding, can impose significant physical stress on the drug product, potentially leading to degradation. Furthermore, the thermal stress generated during comminution and spray drying can be problematic, especially when dealing with thermosensitive or unstable active compounds. It's important to note that traditional

methods may not effectively reduce the particle size of nearly insoluble drugs (those with solubility below 0.1mg/mL).

Another conventional approach to particle size reduction is micronization. Micronization enhances the dissolution rate of drugs by increasing their surface area without affecting equilibrium solubility. Decreasing the particle size of these drugs results in a larger surface area, which, in turn, improves their dissolution rate. Micronization is typically accomplished through milling techniques involving equipment like jet mills and rotor-stator colloid mills. However, it's worth noting that micronization is not suitable for drugs with a high dose number since it does not alter the saturation solubility of the drug.

These techniques have been applied to various drugs, including griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate. In each case, micronization has proven effective in enhancing digestive absorption, leading to increased bioavailability and improved clinical efficacy.

Solid dispersions

are a pharmaceutical technique that can significantly enhance the dissolution, absorption, and therapeutic effectiveness of drugs within dosage forms. The concept of solid dispersions was initially introduced by Sekiguchi and Obi in the early 1960s when they explored the generation and dissolution performance of eutectic melts involving a sulfonamide drug and a water-soluble carrier.

Solid dispersions, as the term suggests, consist of solid products comprising at least two different components, typically a hydrophilic matrix and a hydrophobic drug. Hydrophilic carriers commonly employed in the formation of solid dispersions include polyvinylpyrrolidone, polyethylene glycols, and Plasdone-S630. In some cases, surfactants such as Tween-80, Docusate sodium, Myrj-52, Pluronic-F68, and Sodium Lauryl Sulphate are also used in the creation of solid dispersions.

One of the notable advantages of solid dispersions is their ability to enhance the solubility of specific drugs like celecoxib, halofantrine, and ritonavir by utilizing suitable hydrophilic carriers. Various techniques are available for preparing solid dispersions of hydrophobic drugs, which, in turn, contribute to an improved aqueous solubility. This approach offers a valuable method for addressing solubility challenges and increasing the effectiveness of pharmaceutical drugs in various dosage forms.

Nanosuspension

technology has emerged as a promising solution for the efficient delivery of hydrophobic drugs, particularly those with poor solubility that are insoluble in both water and oils.

Pharmaceutical nanosuspensions are biphasic systems, comprising nano-sized drug particles stabilized by surfactants. These nanosuspensions find applications in both oral and topical use and parenteral and pulmonary administration. Notably, the particle size distribution of solid particles in nanosuspensions is typically less than one micron, with an average particle size falling within the range of 200 to 600 nm.

To create nanosuspensions, various methods are available, including:

Media Milling (Nanocrystals)

High-Pressure Homogenization in water (Dissocubes)

High-Pressure Homogenization in nonaqueous media (Nanopure)

A combination of Precipitation and High-Pressure Homogenization (Nanoedge)These methods offer effective ways to address the delivery challenges posed by hydrophobic drugs with poor solubility, enhancing their solubility and enabling their efficient use in pharmaceutical applications

Supercritical Fluid (SCF) Process

has become a notable nanosizing and solubilization technology in recent years. These processes involve reducing particle size using supercritical fluids, which are fluids that exist at temperatures and pressures greater than their critical temperature (Tc) and critical pressure (Tp). In this state, they exhibit properties of both a liquid and a gas. Near their critical temperature, supercritical fluids are highly compressible, and even slight changes in pressure can significantly affect density and mass transport characteristics, which are key factors in their solvent power.

Once drug particles are solubilized within a supercritical fluid, they can be recrystallized to achieve substantially reduced particle sizes. SCF processes offer a remarkable degree of flexibility and precision, enabling the micronization of drug particles within narrow size ranges, often down to sub-micron levels. Present SCF methods have demonstrated the capability to create nanoparticulate suspensions with particle sizes ranging from 5 to 2,000 nanometers in diameter.

Several pharmaceutical companies, including Nektar Therapeutics and Lavipharm, are specializing in particle engineering through SCF technologies to achieve particle size reduction and enhance solubility.

To address various challenges and shortcomings, several methods of SCF processing have been developed, including:

Precipitation with Compressed Antisolvents Process (PCA)

Solution Enhanced Dispersion by SCF (SEDS)

Supercritical Antisolvents Processes (SAS)

Rapid Expansion of Supercritical Solutions (RESS)

Gas Anti-Solvent Recrystallization (GAS)

Aerosol Supercritical Extraction System (ASES)

These methods offer unique approaches to harness the benefits of supercritical fluids for enhancing solubility and reducing particle size in pharmaceutical applications.

Floating Granules

Rajanikant Patel and colleagues utilized an innovative approach to enhance the dissolution of ibuprofen by creating a floating formulation. Ibuprofen, a weakly acidic, non-steroidal anti-inflammatory drug, possesses high permeability through the stomach, mainly because it remains 99.9% un-ionized in the stomach (with a pKa of Ibuprofen at 4.43 and a gastric fluid pH of 1.2). Although Ibuprofen can readily pass through the stomach, its limited solubility prevents it from entering the systemic circulation. Furthermore, the gastric emptying time is relatively short, ranging from 30 minutes to 2 hours. After this period, ibuprofen moves into the small intestine, where it can be solubilized but struggles to permeate through the intestinal membrane due to its pH-dependent solubility and permeability characteristics.

The logical solution was to design ”ormu’ations that would remain in the stomach for more than 2 hours, allowing the drug to dissolve completely within the stomach region. This objective was achieved by creating a floating dosage form.

To create floating ibuprofen granules, a fusion method was employed. The process involved dividing 200 mg of ibuprofen into two portions: 50 mg and 150 mg. Additionally, 350 mg of gelucire 44/14 was melted, and 50 mg of ibuprofen was incorporated into the formulation.

4. Materials and Methods

Materials:

Macrogol 6000 and Macrogol 4000 were procured from Unichem Chemical Reagents.

Ibuprofen was obtained as a gift sample from ACI Pharmaceuticals Ltd, Dhaka, Bangladesh.

All other components used in the study were of analytical grade and were sourced from the local market.

Preparation of Solid Dispersions:

Solid dispersions (SDs) were prepared using the fusion method with macrogol 4000 and macrogol 6000 as the carriers.

The SDs were produced at weight ratios of 1:0.5, 1:1, and 1:1.5 (drug:carrier).

These were coded as follows:

For macrogol 4000: SD(M4)1/0.5, SD(M4)1/1, and SD(M4)1/1.5.

For macrogol 6000: SD(M6)1/0.5, SD(M6)1/1, and SD(M6)1/1.5.

The required quantities of the carrier and ibuprofen were melted in a beaker on a water bath maintained at 80ºC.

The mixture was stirred thoroughly for 5 minutes and then rapidly cooled by placing the beaker in an ice bath for 5 minutes to solidify.

The solidified mixture was powdered using a mortar, sieved through a 30-mesh screen, and stored in screw-cap vials at room temperature in desiccators for future use.

Preparation of Physical Mixtures:

Physical mixtures (PMs) were prepared in the same weight ratios as the SDs.

Appropriate quantities of ibuprofen and the carrier were mixed thoroughly for 10 minutes in a mortar.

The mixtures were coded as follows:

For macrogol 4000: PM(M4)1/0.5, PM(M4)1/1, and PM(M4)1/1.5.

For macrogol 6000: PM(M6)1/0.5, PM(M6)1/1, and PM(M6)1/1.5.

The mixtures were sieved through a 30-mesh sieve and stored in screw-cap vials at room temperature for further analysis.

Assay of Samples:

To assess the uniformity of drug mixing in the solid dispersions, ibuprofen standard samples and equivalent solid dispersions were dissolved separately in methanol.

Methanol was chosen as the dilution solvent due to ibuprofen's high solubility in methanol.

The standard and sample solutions were diluted appropriately with methanol, and the absorbance was measured using a UV spectrophotometer (UV mini 1240, Shimadzu) at 221 nm.

The assay was performed three times, and standard deviation was calculated to assess uniformity.

Solubility Studies:

Solubility studies of pure ibuprofen and solid dispersions were conducted in three different media: 0.1 N HCl solution, phosphate buffer (pH 7.2), and distilled water.

Standard ibuprofen and powder samples of solid dispersions, equivalent to 100 mg of pure ibuprofen, were taken in 15 ml screw-cap test tubes containing 10 ml of the respective medium.

The solutions were shaken and left undisturbed for 24 hours with continuous stirring.

After 24 hours, the sample solutions were filtered through Whatman filter no. 1, and 1 ml of the solution was diluted to a suitable concentration with the respective medium.

The absorbance of the prepared dilutions was measured at 221 nm using a UV-Visible spectrophotometer.

Characterization of Drug Release Rate:

To characterize the drug release rate in different experimental conditions, Mean Dissolution Time (MDT), T50%, and T80% Dssolution Efficiency (DE) were calculated from dissolution data using specific equations.

MDT, T50%, and T80% were determined to provide insight into the drug release behavior.

Drug-Polymer Interactions Study:

FT-IR spectra were recorded using an IR-Prestige 21 spectrophotometer from Shimadzu, Japan.

Spectra were obtained by scanning samples in potassium bromide (KBr) discs.

Before taking the sample's spectrum, a blank spectrum of air background was recorded.

Spectra of pure drug, pure polymers, and the solid dispersions containing both the drug and polymer were scanned over the frequency range of 2000 cm-1 to 450 cm-1.

The IR spectra of solid dispersions were compared with standard IR spectra of pure ibuprofen and the respective carrier.

5. Results and Discussion

Objective of the Study:

The study aimed to enhance the dissolution rate of ibuprofen, a drug known for its poor water solubility. This was achieved by preparing solid dispersions (SDs) and physical mixtures (PMs) using macrogol 4000 and macrogol 6000 in various ratios.

Characteristics of Solid Dispersions:

All solid dispersions created via the melting method exhibited desirable characteristics, being granular, fine, and free-flowing. The assay results indicated that the solid dispersions contained 98% to 102% of the theoretically expected ibuprofen content.

Solubility Enhancement:

Table 1 presents the saturated solubility of ibuprofen and solid dispersions in different media: 0.1 N HCl solution, phosphate buffer at pH 7.2, and distilled water. The solubility study revealed the effectiveness of solid dispersions prepared with macrogol 4000 and macrogol 6000 in enhancing solubility in all three media. The solubility of ibuprofen was increased by up to 8% in 0.1 N HCl, 17% in phosphate buffer (pH 7.2), and a remarkable 70% in aqueous medium compared to pure ibuprofen. In Vitro Drug Release in Phosphate Buffer (pH 7.2):

Figures 1 and 2 depict the in vitro drug release in phosphate buffer (pH 7.2) from solid dispersions and physical mixtures prepared with macrogol 4000 and macrogol 6000. Solid dispersions exhibited significantly higher drug release (up to 76.7% within 5 minutes) compared to pure drug samples (48.3% within 5 minutes) from the

beginning of the dissolution study. This increase in drug release from solid dispersions can be attributed to the presence of molecular dispersion and the amorphous form of the drug. In contrast, the initial lower drug release from physical mixtures may result from the soluble carrier in these mixtures.

In Vitro Drug Release in 0.1 N HCl:

In 0.1 N HCl, drug release was initially low due to the inherent insolubility of ibuprofen in this medium (as indicated in Table 1). Only 5.89% of ibuprofen dissolved within 1 hour from the pure drug sample. However, solid dispersions prepared using macrogol 4000 and macrogol 6000 released 14.8% to 16.4% and 9.8% to 15.1%, respectively, after 1 hour. In comparison, physical mixtures of the same carrier released 7.6% to 8.4% and 8.1% to 9.3% of ibuprofen after 1 hour. These findings suggest that both solid dispersions and physical mixtures can enhance ibuprofen release in acidic media.

Characterization of Drug Release:

Mean Dissolution Time (MDT), T50% (Time for 50% drug release), T80% (Time for 80% drug release), and dissolution efficiency (% DE) were calculated from the dissolution data and are presented in Table 2. The MDT was influenced by carrier loading, with a lower MDT indicating a faster dissolution rate. Higher % DE values indicated a greater extent of drug release from the solid dispersions. In summary, solid dispersions notably increased both the rate and extent of drug release.

Drug-Polymer Interactions:

Figures 5-9 present the IR spectra of pure ibuprofen, the carrier, and the solid dispersions. The IR spectrum of pure ibuprofen (Figure 5) was identical to that of the solid dispersions (Figures 8 and 9). This suggests that there was no interaction between ibuprofen and the carriers in the prepared solid dispersions. Furthermore, no degradation of the drug or carrier due to the high temperatures during manufacturing was observed in the IR spectra.

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