Review Article

Enhancement of Solubility and Dissolution Rate of BCS Class II Drugs

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ABSTRACT

The enhancement of solubility and dissolution rate is a critical aspect of pharmaceutical development, particularly for Biopharmaceutical Classification System (BCS) Class II drugs characterized by low solubility and high permeability. This review provides an extensive overview of techniques and strategies employed to address the challenges associated with these drugs, aiming to improve their bioavailability and therapeutic efficacy. The review begins by introducing the Biopharmaceutical Classification System (BCS) and its significance in drug formulation, emphasizing the importance of solubility and dissolution rate in determining oral bioavailability. Challenges associated with BCS Class II drugs are discussed, including formulation difficulties and variability in absorption along the gastrointestinal tract. Various techniques for solubility enhancement are examined, such as particle size reduction, salt formation, solubilization techniques (co-solvency, complexation, micellization), solid dispersion, cyclodextrin complexation, and nanoparticle formulation. Additionally, strategies for dissolution rate enhancement are explored, including nanocrystals, surfactants, spray drying, and porous carriers. Furthermore, the review highlights common assessment techniques for solubility and dissolution rate, both *in vitro* and *in vivo*, essential for evaluating the effectiveness of formulation strategies. The importance of these techniques in predicting drug behaviour and refining drug delivery mechanisms is emphasized. Overall, this comprehensive review underscores the significance of enhancing solubility and dissolution rate in pharmaceutical development, particularly for BCS Class II drugs, and provides valuable insights into the diverse strategies and methodologies employed to overcome formulation challenges and improve drug bioavailability and therapeutic outcomes.

Keywords: Hydrotropy, pelletization, Cyclodextrin complexation, Nanoparticle formulation, nanocrystals

INTRODUCTION

Background on biopharmaceutical classification system (BCS)

The biopharmaceutical classification system (bcs) is a framework designed to categorize drugs based on their solubility and permeability characteristics, which are critical in determining their absorption and availability when taken orally. This system was developed to offer a structured method for drug formulation and to forecast drug behaviour within the gastrointestinal tract. It comprises four classes:

Class i: high solubility and high permeability.

Class ii: low solubility but high permeability.

Class iii: high solubility but low permeability.

Class iv: low solubility and low permeability.

The BCS has played a pivotal role in the pharmaceutical sector, facilitating the improvement of more effective drug formulations and potentially reducing the need for bioequivalence testing for certain medications. For instance, drugs falling into class i, characterized by rapid dissolution and high solubility, are less likely to exhibit variations in bioavailability due to formulation differences, potentially obviating the necessity for bioequivalence testing[1].moreover, the BCS has been utilized to predict the solubility and permeability of various drug categories, such as fluoroquinolones[2]. and has spurred the creation of alternative drug delivery methods like self-micro emulsifying drug delivery systems (SMEDDS) for poorly soluble drugs and nanosuspensions for drugs with limited water solubility. Additionally, this classification system has been applied to categorize drugs on national essential medicine lists, furnishing valuable insights for drug development and refinement[3].

Significance of solubility and dissolution rate enhancement

Improving the ability of poorly water-soluble medications to dissolve and be absorbed more readily in the body is crucial for overcoming challenges that can restrict their effectiveness and absorption within the body. Various studies have illustrated the significance of improving these properties to enhance the bioavailability of such drugs. Techniques like solid dispersion and nanocrystalline suspensions have been proven effective in boosting dissolution rates and thereby improving the delivery and potential clinical outcomes of poorly soluble drugs [4,5,6]. These findings emphasize the pivotal role of solubility and dissolution rate enhancement in pharmaceutical advancement, especially concerning poorly water-soluble drugs, and underscore the promise of these approaches in addressing issues related to drug absorption.

Challenges associated with BCS class ii drugs

BCS class II drugs, pose challenges in formulation and delivery. A significant hurdle involves the development of

accurate in vivo dissolution models and establishing in vitro-in vivo correlations due to their varying absorption along the gastrointestinal tract, influenced by pH-dependent solubility [7]. Despite these challenges, lipid-based delivery systems such as liposomes, niosomes, and micelles have received FDA approval for effectively enhancing the solubility, permeability, and bioavailability of BCS class II and class IV drugs. Researchers have explored various formulation strategies such as solid dispersions, complexation, lipid-based systems, micronization, nanonization, co-crystals, and solubilization[8].

Purpose of solubility and dissolution rate enhancement

It is crucial in pharmaceuticals to boost the bioavailability of drugs with limited solubility and low oral bioavailability. Solid dispersion emerges as a novel approach aimed at improving solubility and dissolution rate. Its primary objective is to augment the solubility of poorly soluble drugs. Solid dispersions of drugs are formulated using various carriers and ratios through methods like solvent evaporation, kneading, and spray drying. The prepared solid dispersions undergo characterization employing diverse techniques such as fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and determination of drug content percentage. The efficacy of solid dispersion is assessed through solubility, FTIR, x-ray diffraction (XRD), DSC, micromeritics, and in vitro dissolution analysis[9,10,11].

BCS class II drug characteristics

Employing innovative super disintegrants: such as ocimum gratissimum mucilage, to create fast dissolving tablets of aceclofenac, thereby improving drug disintegration time and dissolution rate[12].

Solid dispersion techniques: like the use of peg 6000 and crospovidone in ternary solid dispersions of naproxen, have been effective in significantly boosting drug dissolution rate and oral bioavailability[13].

Adsorbents: like granulated fumed silica have been utilized to enhance ibuprofen solubility and dissolution characteristics, leading to increased drug solubility and dissolution rate[14].

Pegylation: of BCS class ii drugs such as raloxifene hydrochloride with high-molecular-weight polyethylene glycols has been found to enhance tablet dissolution rate and improve drug release characteristics[15].

lipid carriers: like niosomes, based on non-ionic surfactants, have shown promise in improving the solubility and bioavailability of BCS class ii drugs[16].

These strategies aim to address the limitations associated with BCS class ii drugs, ultimately improving their pharmacokinetic properties and therapeutic efficacy.

Definition and examples of BCS class ii drugs

Drugs classified under BCS class ii exhibit traits of limited solubility and high permeability, which may result in inconsistent and occasionally reduced bioavailability upon oral administration. Their absorption process relies predominantly on the rate at which they dissolve in the gastrointestinal tract, indicating a dependency on dissolution rate for entry into the bloodstream.

Example of bcs class ii drug includes

Ibuprofen, Naproxen, Diclofenac, Amlodipine, Verapamil, Diltiazem.

Formulation approaches are frequently needed to boost the solubility of such drugs. These may include employing solubilizing agents, employing complexation methods such as pharmaceutical co-crystals, or creating nano emulsions to improve their performance[17].

Properties affecting solubility and dissolution rate

Polymer type: the selection of the polymer used in extended-release systems can influence both the mechanism of release and the rate at which dissolution occurs.

Device type: the characteristics of the dosage form, like the shape and composition of tablets or pellets, can impact their adhesion properties and the manner in which they release their contents.

Stirring rate: the speed of stirring in the dissolution medium can impact the rate of dissolution, especially in hydrophilic matrix systems.

Dissolution media: the solubility and hydration duration of the polymer matrix, and consequently the release rate, can be impacted by the choice of solvent or dissolution medium utilized in the dissolution process[18].

Cooling methods: different approaches to cooling can impact the creation of various polymorphs as well as their rate of dissolution during recrystallization.

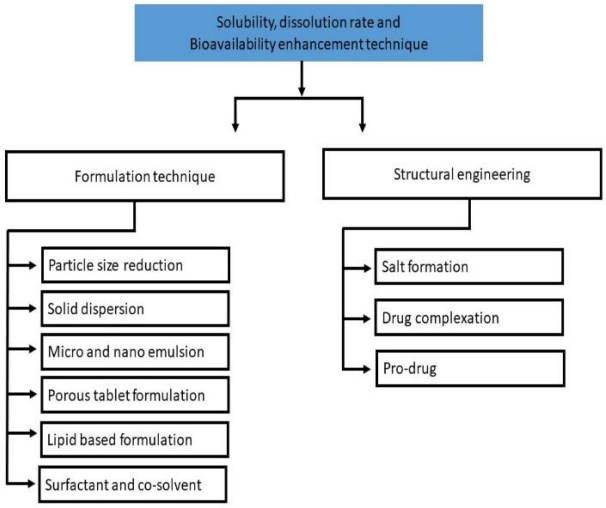
Particle size: reduced particle sizes typically result in accelerated rates of dissolution.

Shape of crystals: the dissolution rate can be influenced by the crystalline structure, where needle-shaped crystals tend to exhibit superior dissolution characteristics.

Excipients: in co-crystallization, the inclusion of excipients such as co-formers can boost both solubility and the rate of dissolution[20].

Polymer coating systems: the release profiles of sustained-release drug pellets can be influenced by the solubility of the drug within the polymer solution and the amount of coating applied[21].

Tabel 1: Techniques for solubility enhancement



Particle size reduction

It is commonly utilized to improve the solubility of pharmaceuticals and enhance their bioavailability. Various techniques are employed for this purpose, including milling, liquid anti-solvent crystallization, spray drying, high-pressure homogenization, spray freeze-drying, micronization, pulsed laser ablation, and combined methods[22]. Studies have shown that high-pressure homogenization followed by bead milling, consistently achieve superior decreases in particle size when compared to alternative techniques[23]. Furthermore, strategies such as solid dispersion, nanonization, pH adjustment, co-solvency, complexation, hydrotropy, and the use of vitamin E TPGS-based microemulsions are Utilized to improve the solubility of drugs that have low water solubility[24].

Salt formation

Improving solubility is a crucial aspect, and various methodologies have been explored for this purpose. These include strategies such as reducing particle size, forming salts, creating solid dispersions, generating complexes, utilizing cosolvent techniques, employing surfactants, undergoing physical and chemical modifications, and adjusting ph through buffering agents[25]. Among these approaches, salt formation stands out as a promising avenue for enhancing both solubility and dissolution rates of active pharmaceutical ingredients[26]. Additionally, hot-melt extrusion (HME) emerges as a scalable and industrially viable technique, which has demonstrated effectiveness in improving the solubility[27].

Solubilization techniques (cosolvency, complexation, micellization)

These approaches are employed to aid in the formulation and delivery of drugs, by enhancing their solubility for improved efficacy.

Cosolvency: is a method that entails utilizing an additional solvent, known as a cosolvent, to enhance a drug's solubility in water. Ethanol, propylene glycol, and polyethylene glycol are typical examples of cosolvents. This approach enables the solubilization of both ionized and non-ionized forms of the drug.

Complexation: involves the solubilization of drugs through the creation of complexes with substances like cyclodextrins or other complexing agents. For instance, hydroxypropyl beta-cyclodextrin (hpbetacd) and sulfobutyl ether beta-cyclodextrin (sbebetacd) are examples of cyclodextrins capable of forming inclusion complexes with drugs that are either nonpolar or possess slight polarity, thereby enhancing their solubility.

Micellization: is a method that utilizes surfactants to create micelles, which have the ability to dissolve drugs within their hydrophobic center. This process is highly efficient for dissolving nonpolar medications. Polysorbate 20 and polysorbate 80 are frequently employed surfactants in this technique[28,29].

Solid dispersion

Improve solubility of drugs with low water solubility can be achieved using different methods of solid dispersion.

Hydrotropy and mixed hydrotropy-based solid dispersion techniques: aim to improve drug solubility in water and its dissolution rate by utilizing a combination of different hydrotropic agents during the creation of solid dispersions using solvent evaporation techniques[30].

Dispersion in an inert hydrophilic carrier: the process of dispersing slightly water-soluble drug molecules into an inert hydrophilic carrier is employed in solid dispersions to enhance their dissolution characteristics and increase bioavailability[31].

Solid dispersion and pelletization methods: encompass the creation of solid dispersions through solvent evaporation and the application of drug coating onto nonpareil sugar beads to form pellets. A variety of polymers and solubility enhancers are employed to enhance the solubility[33].

These methods provide efficient means to boost the solubility of drugs with limited water solubility, consequently enhancing their bioavailability and dissolution characteristics.

Cyclodextrin complexation

The enhancement of solubility through cyclodextrin complexation relies on creating inclusion complexes between cyclodextrins and drugs with limited solubility. This strategy has undergone thorough investigation for its ability to boost the solubility and dissolution rates of drugs. Commonly utilized techniques for cyclodextrin complexation include forming inclusion complexes.

Physical blending

Kneading

Co-evaporation

Co-lyophilization

Various methods have been demonstrated to enhance drug solubility and dissolution rates by partially incorporating the drug into the cyclodextrin cavity while diminishing drug crystallinity in the complex preparation process. Cyclodextrins, including α-, β-, and γ-cyclodextrins, are commonly employed for complexation, with β-cyclodextrin being preferred due to its size and hydrophilic nature. Additionally, modified cyclodextrins like sulfobutyl ether β-cyclodextrin (captisol) are utilized to enhance solubility and dissolution. The selection of complexation method relies on factors such as drug solubility, drug-cyclodextrin compatibility, and desired complex properties. Characterization of these complexes typically involves techniques such as DSC, infrared spectroscopy, x-ray diffractometry, and near infrared spectroscopy[34,35,36].

Nanoparticle formulation

Ionic gelation: involves the utilization of polymers such as chitosan and tripolyphosphate to produce nanoparticles. This technique was employed in formulating olmesartan medoxomil nanoparticles, resulting in a notable threefold enhancement in the dissolution rate in vitro compared to the existing marketed formulation[37].

Nano emulsion: is a method where a drug is dispersed within an amalgamation of oil, co-surfactant, surfactant and yielding a stable, transparent, and homogeneous system. This approach has proven effective in improving the solubility and dissolution of celecoxib, achieving a solubility of 228.24 mg/ml and 99.9% dissolution[38].

Spray pyrolysis: entails creating nanoparticles by spraying a solution comprising the drug and a polymer into a heated chamber. Here, the solvent evaporates, resulting in the formation of drug-polymer nanoparticles. This approach was applied in developing α-mangostin-chitosan nanoparticles, demonstrating a sustained release mechanism and heightened cytotoxicity against breast cancer cells[39].

Homogenization: utilizes high-energy equipment such as high-pressure homogenizers to decrease the particle size of drug nanoparticles, leading to potential improvements in solubility and dissolution rates.

The solid intermediate method: entails creating solid drug nanoparticles through the utilization of a solid intermediate, such as amorphous solid dispersions or solid lipid nanoparticles. This technique has the potential to enhance the solubility and dissolution of poorly soluble drugs[40].

These methodologies have demonstrated effectiveness in enhancing the solubility of drugs with poor solubility, resulting in increased bioavailability and therapeutic effectiveness.

Techniques for dissolution rate enhancement

Nanocrystals

Nanocrystals represent a potentially effective method for boost solubility of poorly soluble drugs, particularly those falling under BCS class ii. These crystals are crafted by downsizing drug particles to the nanoscale, thereby amplifying their surface area and subsequently enhancing their solubility and dissolution kinetics.

Anti-solvent precipitation: involves initially dispersing the drug within a solvent, after which an anti-solvent is introduced, inducing the drug to precipitate as nanocrystals.

High-pressure homogenization: utilizes elevated pressure to disperse the drug within a liquid medium, ultimately generating nanocrystals.

Ultrasonication: employs ultrasound waves to disperse the drug in a liquid medium, thereby facilitating nanocrystal formation.

The advantage of nanocrystals includes

Enhance solubility and dissolution rate

Improve bioavailability

Presents an opportunity for targeted drug delivery

Decreased particle size may further enhance absorption and mitigate adverse effects.

Yet, nanocrystals come with their own set of drawbacks. One such limitation is the potential compromise of their stability, often requiring the use of stabilizing agents to uphold their characteristics. Moreover, the intricacies and costs associated with the manufacturing process may pose restrictions on their broad application[41,42].

Use of surfactants

Utilizing surfactants represents a strategy aimed at augmenting the dissolution rate of poorly soluble medications, which frequently suffer from inadequate and inconsistent oral absorption due to their limited solubility in water. These compounds work by diminishing the surface tension existing between the drug and its surrounding medium, thereby promoting the drug's release into the dissolution medium. Surfactants, characterized by their amphiphilic nature with both hydrophilic and hydrophobic regions, can create micelles in aqueous solutions. These micelles serve to enhance the solubility of hydrophobic drugs by effectively solubilizing them. Moreover, surfactants can be employed in conjunction with other methods such as solid dispersions to further enhance drug solubility and dissolution.

Use of salt forms.

Polymorphs.

Micronization.

Self-emulsifying micro and nano dispersion systems.

Cyclodextrin complexation.

Prodrugs.

Solid dispersions in water-soluble and dispersible carriers.

Microemulsion.

These methodologies hold significant relevance for drugs classified BCS as class II, characterized by their combination of Limited solubility but extensive permeability[43,44,45].

Spray drying

Spray drying stands out as a method employed to improve drug dissolution rates, particularly through the creation of amorphous solid dispersions (ASDS), which in turn enhance solubility. This technique involves the incorporation of polymers to aid in maintaining solubility, ultimately leading to enhanced bioavailability. Apart from spray drying, there exist alternative approaches to augment dissolution rates, including methods like milling, high-pressure homogenization, and micronization processes utilizing supercritical carbon dioxide (scco2). Another effective strategy involves employing β-cyclodextrin inclusion complexation through various means such as spray drying, solvent evaporation, and the kneading method, all aimed at improving the rate at which poorly soluble drugs dissolve[46,47].

Porous carriers

Porous carriers play a pivotal role in improving the dissolution of poorly water-soluble medications by augmenting surface area and pore volume, thereby facilitating enhanced drug loading and dissolution rates. Utilizing techniques like combined spray drying and template removal, porous lactose and mannitol carriers exhibited notably accelerated dissolution rates for indomethacin, releasing over 80% of the loaded drug within 10 minutes[48]. Similarly, mesoporous silica nanoparticles loaded with repaglinide showcased a remarkable 96.5% drug release, surpassing that of the pure drug and commercially available formulations, owing to their amplified surface area. Moreover, solid dispersion systems based on phosphatidylcholine, solidified with adsorbent carriers like neusilin® us2, demonstrated augmented apparent the solubility of celecoxib in water and its dissolution[49].

Techniques for dissolution rate enhancement

Assessing the solubility and dissolution rate of drugs typically requires employing a blend of characterization methods and in vitro experiments to gauge the efficacy of different approaches aimed at improving these properties. Common assessment techniques encompass a variety of methodologies.

Conducting solubility studies: involves assessing the solubility of a drug across various solvents or mediums to identify the most suitable solvent for formulating the drug.

Particle size analysis: is employed to measure the dimensions of drug particles or nanoparticles, which can impact their dissolution rate.

Polydispersity index (PDI): is utilized to evaluate the uniformity of particle size distribution.

Zeta potential: measurements determine the surface charge of particles, which plays a role in their stability and dissolution behavior.

Differential scanning calorimetry (DSC): is utilized to investigate the thermal characteristics of the drug and its formulations, aiding in the detection of any incompatibilities or alterations in crystallinity.

Fourier transform infrared spectroscopy (FTIR): is employed to examine the chemical composition and potential interactions between the drug and excipients.

Powder x-ray diffraction (PXRD): is utilized to analyze the crystalline structure of the drug and its formulations, aiding in the identification of changes in crystallinity.

scanning electron microscopy (SEM): is utilized to observe the morphology of drug particles or cocrystals.

Drug content estimation: involves determining the quantity of drug present in the formulation.

In vitro drug release profiling: is conducted to evaluate the dissolution rate of the drug from the formulation under controlled conditions, often utilizing a dissolution apparatus.

These methodologies aid researchers in comprehending how formulation strategies influence solubility and dissolution rate, both critical determinants of drug bioavailability and therapeutic effectiveness[50,51,52].

In vitro techniques

In the realm of pharmaceutical development and formulation, in vitro methodologies play a vital role in gauging the drug solubility and dissolution rate of compounds. These techniques are instrumental in forecasting the behavior within living organisms and refining drug delivery mechanisms. Various customary in vitro approaches exist for appraising solubility and dissolution rate, aiding in the optimization of pharmaceutical formulations.

Solubility determination

Shake flask technique: is a commonly employed approach wherein an abundance of the drug is introduced into a solvent, followed by agitation for a designated duration. Subsequently, the saturated solution undergoes filtration, and the drug concentration within the solvent is assessed utilizing analytical methodologies such as UV-vis spectroscopy, HPLC, or LC-MS.

Solubility screening: entails employing a solubility screening kit comprising a selection of solvents with diverse polarities. The drug is introduced into each solvent,

and the solubility is assessed through visual examination or analytical methods.

Dissolution testing

The USP apparatus 1: Known as the basket method entails immersing the medication into a dissolution vessel with a defined volume of dissolution medium. Subsequently, the basket housing the medication is rotated consistently, and samples are retrieved at predetermined intervals for subsequent analysis.

The USP apparatus 2: Also referred to as the paddle method, operates akin to the basket method, albeit with a variation in apparatus. In this method, the medication is positioned within a cylindrical vessel featuring a paddle that maintains a constant rotation speed. Subsequent to this, samples are extracted at predetermined intervals for subsequent analysis.

The flow-through cell method: Entails a continual passage of dissolution medium through a cell housing the medication. Samples are gathered at the cell's outlet for subsequent analysis.

Dialysis sac method: The medication is enclosed within a dialysis sac submerged in a dissolution medium. This sac permits the passage of dissolved drug while retaining the undissolved portion. Samples are then retrieved from the dissolution medium for analytical purposes.

Enhancements to these techniques can involve the utilization of biorelevant media and adjustments in ph, temperature, and agitation speed to closely resemble physiological conditions. Moreover, there are ongoing advancements such as high-throughput dissolution testing and microfluidic devices aimed at enhancing the precision and efficacy of these assessments.

However, it's important to acknowledge that while in vitro methods offer valuable insights, they might not entirely mirror in vivo responses. Consequently, in vivo investigations are frequently essential to validate findings derived from in vitro experiments.

***In vivo* techniques**

The assessment of in-vivo pharmacokinetics (pk) is pivotal in gauging the effectiveness of drug formulations that boast enhanced solubility and dissolution characteristics. These evaluations are instrumental in deciphering how these improvements manifest in terms of heightened bioavailability and therapeutic effectiveness in living organisms. Numerous methodologies have been devised to scrutinize the pk profile of such formulations, encompassing a range of approaches and techniques.

In-vitro to in-vivo correlation (IVIVC): The concept of in-vitro to in-vivo correlation entails employing an in vitro model that accurately replicates the conditions within a living organism to forecast the performance of a drug formulation in either animal subjects or humans. IVIVC facilitates the estimation of in vivo dissolution rates based on in vitro data, thereby aiding in the refinement of dosage forms and minimizing reliance on animal experimentation.

Animal models: Utilizing animal models continues to be a prevalent method for investigating the impacts of improving solubility and dissolution on drug absorption. This approach typically involves studying various species such as rodents (e.g., mice, rats) and larger mammals (e.g., dogs, pigs).

Human studies: Particularly clinical trials employing human participants, are widely regarded as the most reliable method for assessing the safety and effectiveness of new medications. Nevertheless, conducting such trials may not always be viable due to financial constraints, time limitations, and ethical concerns. Consequently, alternative approaches like microdosing are being investigated to obtain data on the pharmacokinetic profiles of innovative formulations without subjecting individuals to undue risks.

Pharmacometrics modelling: Involves the integration of quantitative biomedical information with mathematical and statistical approaches to enhance comprehension of drug mechanisms across different domains such as drug distribution and response. Through pharmacometric modeling, researchers can explore intricate connections among drug concentration, exposure, and efficacy, thereby gaining valuable insights into how improvements in solubility and dissolution influence drug pharmacokinetic profiles.

It's important to acknowledge that while in-vivo pharmacokinetic assessments offer valuable insights into the effectiveness of formulations enhanced for solubility and dissolution, they frequently demand considerable resources and may entail risks linked to animal testing or clinical studies. Consequently, there has been increasing interest in the creation of more streamlined and less intrusive alternatives, such as computational modeling and sophisticated in vitro methodologies.

Importance of pharmacokinetic evaluation in drug development

Dose optimization: pk studies play a crucial role in optimizing dosing regimens for drugs by elucidating how the body metabolizes a compound. This knowledge enables the development of dosing schedules that balance therapeutic efficacy with minimal risk of toxicity.

Bioavailability assessment: pk assessment offers vital understanding regarding the degree and speed with which a drug enters the bloodstream. This data is critical in evaluating the bioavailability of a drug, which directly influences its effectiveness in therapy.

Safety and tolerability: Understanding how a drug is metabolized and eliminated through pharmacokinetic (pk) studies is crucial for identifying any potential safety issues and determining the appropriate safety margins. This knowledge is essential to ensure that the drug is tolerated

well and does not produce unwanted effects when administered at therapeutic levels.

Drug-drug interactions: Pharmacokinetic (pk) assessments are instrumental in recognizing possible interactions between the experimental drug and other pharmaceuticals. Grasping the impact of a novel compound on the pk characteristics of concurrently administered drugs is pivotal for safeguarding patient well-being and preventing unforeseen adverse responses.

Predicting variability: Pharmacokinetic (pk) investigations contribute to comprehending the diversity in drug reactions across various patient groups, such as differing age brackets or individuals with particular health conditions. Such insights are critical for customizing dosage plans to achieve the best possible results across a wide range of patient demographics.

Regulatory requirements: Regulatory agencies mandate thorough pharmacokinetic (pk) information to evaluate the safety and effectiveness of emerging pharmaceuticals. Pk assessments play a vital role in the submission process for investigational new drug (ind) applications and new drug approvals.

In conclusion, pharmacokinetic assessment plays a crucial role in the process of drug development. It guides the optimization of dosages, evaluates bioavailability, ensures safety, identifies interactions, predicts variability, and meets regulatory standards. Through illuminating the behavior of drugs within the body, pharmacokinetic studies substantially contribute to the successful advancement and eventual approval of novel pharmaceutical products.

Case studies and examples

Formulation Development for Specific BCS Class II Drugs

Instances and illustrations showcase diverse approaches utilized for increasing the solubility, dissolution velocity, and bioavailability of drugs categorized under the BCS as class ii, denoting their low water solubility. Noteworthy methods encompass.

Nanosuspensions: entail the creation of drug crystals at the nanoscale (known as nanocrystals), which are suspended within a liquid medium, commonly water, through processes like nano milling. Typically, stabilizing surfactants are incorporated to inhibit the aggregation of crystals[53,54].

Mucoadhesive floating systems: involve the creation of drug carriers that stick to mucosal surfaces while remaining buoyant in the gastrointestinal tract. This prolongs their presence and enhances absorption. As an illustration, sitagliptin phosphate, an antidiabetic medication, has been encapsulated in alginate beads coated with chitosan for this purpose.

Cyclodextrin: the use of cyclodextrins to envelop hydrophobic drug molecules, thereby boosting their solubility and dissolution rates.

Self-emulsifying systems: Involve the blending of oil, surfactant, and cosurfactant elements to generate a stable emulsion once exposed to water, thereby facilitating swift drug dissolution.

Regulatory guidelines suggest conducting food effect studies for all medications, including those categorized as BCS Class II, although exceptions are made for BCS class I drugs. The majority of food effect studies do not result in substantial alterations in the evaluation of food effects when the formulation remains constant[55].

CONCLUSION

Increasing solubility and dissolution rate is a crucial aspect of pharmaceutical development, particularly for drugs classified under the BCS as class II. These drugs, defined by limited solubility and extensive permeability, present challenges in formulation and delivery, impacting their bioavailability and therapeutic efficacy. Including solid dispersion, cyclodextrin complexation, nanoparticle formulation, and spray drying. These methods have shown promise in improving drug solubility, dissolution kinetics, and pharmacokinetic properties, ultimately enhancing patient outcomes. In vitro methodologies such as solubility determination and dissolution testing provide valuable insights into the effectiveness of these formulation strategies. However, it's essential to acknowledge their limitations in fully replicating in vivo responses. Therefore, in vivo investigations remain essential to validate findings derived from *in vitro* experiments. Pharmacokinetic evaluations play a pivotal role in assessing the effectiveness of drug formulations with enhanced solubility and dissolution characteristics. These studies provide crucial insights into how improvements in drug properties translate into heightened bioavailability and therapeutic effectiveness in living organisms. Overall, the continuous exploration and refinement of techniques for enhancing solubility and dissolution rate of BCS class II drugs hold immense promise for improving drug delivery, bioavailability, and ultimately, patient outcomes in the field of pharmaceuticals. By combining innovative formulation strategies with robust pharmacokinetic evaluations, we can pave the way for the successful development and approval of novel pharmaceutical products, ultimately advancing healthcare and improving the quality of life for patients worldwide.

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