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Advanced Formulation Strategies For Enhancing Solubility And Permeability Of Ritonavir: A Comprehensive Review

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Abstract

This review comprehensively examines advanced formulation strategies aimed at enhancing the solubility and permeability of ritonavir, an essential antiretroviral medication used in the treatment of HIV/AIDS. Ritonavir's therapeutic efficacy is hindered by its poor aqueous solubility and low oral bioavailability, necessitating innovative approaches to improve its dissolution properties and gastrointestinal absorption. Through an exploration of various techniques, including solid dispersions, nanosuspensions, complexation, lipid-based formulations, micronization, and salt formation, this review highlights the diverse methodologies employed to address these challenges. Each technique is scrutinized for its efficacy in enhancing ritonavir's solubility and permeability, along with considerations regarding feasibility, scalability, and regulatory approval. Furthermore, the review discusses the potential impact of these formulation strategies on the clinical efficacy and patient outcomes of ritonavir therapy, emphasizing the importance of continued research and development in this crucial area of pharmaceutical science.

Keywords: Ritonavir, Solubility, Permeability, bioavaibility, solid dispersion, lipid based formulation,

Introduction

Solubility[1, 2]
is a property of substance in a particular solvent. In quantitative terms it is concentration of dissolved solute in a saturated solution at a specific temperature. In qualitative terms it means continuous interaction of two or more compound to form one phase, clear homogeneous molecular dispersion. It is measured as maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution. A solubility chart gives a list of ions and how, when mixed with other ions, they can become precipitates or remain aqueous. Solubility equilibrium is a dynamic equilibrium that occurs when a chemical compound in the solid state exhibits chemical equilibrium with a solution of that compound. Solubility equilibria are important in pharmaceuticals. Drug with poor aqueous solubility (in other words Class II or even Class IV compounds of BCS) presents dissolution related absorption problems. In pharmaceutical sciences, when quantitative data are

available solubility may be expressed as parts, molarity, normality, formality, mole fraction percent solution, volume fraction and molality.

Techniques to overcome poor solubility [3-10]

I. Chemical Modifications:

1) Salt Formation
2) Co-crystallization
3) Co-solvency
4) Hydrotropy
5) Use of novel solubilizer
6) Nanotechnology

II. Physical Modifications:

1. Particle size reduction
a) Conventional method
b) Micronization
c) Nanosuspension
2. Modification of the crystal habit
a) Polymorphs
b) Pseudopolymorphs
3. Complexation
a) Physical mixture
b) Kneading method
c) Co-precipitate method
4. Inclusion Complex Formulation Based Techniques
a) Kneading method
b) Lyophilization/ Freeze- drying Technique
c) Microwave irradiation method
5. Solubilization by surfactants
a) Microemulsions
b) Self microemulsifying drug delivery system
6. Drug dispersion in carriers
a) Solid solutions
b) Solid dispersions-
i. Fusion Process
ii. Solvent Method
iii. Fusion solvent method
iv. Spray drying
v. Lyophilization (Spray Freeze Drying Method)
vi. Hot melt Extrusion
vii. Dropping Method

III. pH adjustment
IV. Supercritical fluid process
V. Liquisolid technique
VI. Polymeric alteration

Permeability[11]

The advancements in combinatorial chemistry and high throughput screening have revolutionized drug discovery by generating numerous drug candidates. However, this surge has also led to a significant proportion of drugs with poor solubility and absorption rates. This trend has prompted a shift towards drug development based on pharmacogenomics and molecular targeting, yet this approach doesn't always yield successful outcomes in terms of new drug development. Consequently, there's a growing need to enhance membrane permeability to improve drug absorption. Complex molecules like oligonucleotide vaccines, chimeric proteins, and small peptides exhibit absorption patterns distinct from traditional organic compounds, yet solubility and permeability remain crucial factors influencing drug absorption. To streamline drug delivery science and simplify regulatory processes for emerging compounds, drugs are now categorized according to the Biopharmaceutical Classification System (BCS), which classifies them into four categories based on solubility

and permeability. This classification aids regulatory authorities in assessing and approving diverse compounds efficiently.
The Biopharmaceutics Classification System (BCS) categorizes drugs based on their solubility and permeability, with classes 3 and 4 drugs often exhibiting poor intestinal permeability, limiting their effectiveness via oral delivery. Due to the inherent challenges in modifying their unfavorable physicochemical properties, many drugs struggle with poor permeability, necessitating the addition of external excipients to transiently enhance permeation. While alternative delivery routes like injection, transdermal, or pulmonary routes are utilized for drugs with poor oral absorption, oral delivery remains preferred due to its therapeutic effectiveness and patient compliance. Tablets and capsules offer convenience and cost-effectiveness, making oral bioavailability a critical factor in drug discovery lead optimization. The FDA's adoption of Amidon's BCS underscores the significance of solubility and permeability in granting biowaivers for in vivo bioavailability and bioequivalence studies. Various experimental systems, including in vitro models, aid in understanding permeability enhancement mechanisms, particularly for drugs classified in BCS classes 3 and 4, facilitating the development of strategies to improve their permeability for enhanced drug delivery efficacy.

Potential absorption barriers:

Review has been done comprehensively to determine the barriers for the intestinal permeability of drugs. The location of these barriers may be in the unstirred water layer, the mucous layer,the apical and basal cell membrane and cell contents, the tight junctions and the wall of lymph and capillaries. Metabolic barriers of the mucosal peptidases are the other barriers which extensively condense the bioavailability of peptides and proteins.

Mucous:

The mucous layer covering the epithelial cells of the intestine comprises water, glycoproteins (mucins), electrolytes, proteins, and nucleic acids. This layer, crucial for intestinal function, is anchored to the apical surface by the glycocalyx, a glycoprotein structure covalently linked to lipids and proteins of the brush border membrane. The unstirred water layer, partially composed of the mucous layer, plays a vital role in nutrient absorption. The mucous layer serves as a buffer, maintaining the pH of the epithelial surface at 6, thus creating an acidic microclimate conducive to proper intestinal function. This complex interplay of mucous layer constituents ensures optimal conditions for nutrient absorption and overall intestinal health.

The apical cell membrane:

resembling a 1µm thick brush border, consists of a double layer of polar lipid molecules, approximately 10nm thick, containing both hydrophobic and lipophilic components. Key lipid constituents include phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, phosphatidylserine, phosphatidylinositol, phosphatidic acid, cholesterol, and other lipids. Divalent metal ions like Ca2+ play a role in maintaining membrane structure integrity by binding with negatively charged phospholipids, thus regulating membrane permeability. Proteins are embedded in the lipid bilayer via hydrophobic segments, and fluidity of the membrane is crucial for optimal enzyme activity. Cholesterol modulates membrane fluidity, with sphingomyelin potentially enhancing its effects. Membrane order is influenced by natural fatty acids, impacting lipid organization and fluidity. Fluid state membrane fluidity may increase with specific lipid ratios or increasing double bond index, affecting permeability. In rat colonocytes, membrane fluidity decreases from proximal to distal segments, correlating with enzyme activity levels. The transport of molecules across the phospholipid bilayer is often linked with the lipid-water coefficient, limiting the absorption of strongly hydrophilic substances such as certain antibiotics and peptides. Transcellular transport of water, ions, and polar solutes relies on mechanisms like diffusion through pores and carrier-mediated transport due to lipid bilayer restrictions

The basal cell membrane:

Comprises a phospholipid bilayer approximately 9 nm thick, interspersed with proteins. In contrast to the apical membrane, the lipid fluidity of the basolateral membrane is higher, likely due to a lower content of glycosphingolipids. Consequently, the barrier function of the basal membrane may be less prominent compared

to the apical membrane. This difference in lipid composition and fluidity between the apical and basolateral membranes highlights the diverse functional roles of these membrane regions within epithelial cells.

Tight junctions:

Tight junctions also known as zonula occludentes, serve as regions of close communication between the apical ends of epithelial cells. These junctions consist of a network of strands, and their permeability increases with decreasing strand number, ultimately determining the epithelium's "leakiness." In the small intestine, which contains leaky epithelium, intestinal permeability decreases in the distal direction parallel to the permeability of the apical cell membrane. The proximal colon exhibits moderate leakiness, while the distal colon is moderately tight. Tight junctions play a crucial role in allowing the passage of medium-sized solutes, ions, and water, facilitating passive ion permeation. They are cation-selective and have been suggested to be impermeable to cations with a molecular weight exceeding 350 nm or a diameter surpassing 0.8 nm. However, it's possible that there is a distribution of pore sizes, with numerous small pores and a few larger ones. The structure of tight junctions can be destabilized by exposure to hypertonic solutions and depletion of Ca2+. In the small intestine of hamsters, sodium-coupled solute transports have been proposed to increase junctional permeability to small peptides, sugars, and amino acids, highlighting the dynamic nature of tight junction regulation in epithelial tissues.

The capillary wall:

The capillary wall lies approximately 500 nm beneath the basal membrane, and it consists of endothelial cell membranes containing small perforations ranging from 0.4 to 1 nm in radius. Blood capillary walls are fenestrated, with fenestrate radii measuring between 20 and 30 nm. In contrast, lymphatic capillaries feature larger intracellular junctions, allowing passage of particles with radii up to 300 nm. Particles smaller than 6 nm in radius are not retained by the basement membrane surrounding fenestrated capillaries. While the presence of large pores suggests that intestinal blood and lymph capillaries are not significant barriers for drug absorption, strongly hydrophilic drugs may be transported slowly across the capillary wall compared to hydrophilic compounds, as their absorption site is limited to the pore area. This understanding sheds light on the mechanisms governing drug absorption across capillary walls and informs drug development strategies targeting absorption optimization.

Permeability enhancement techniques:

Permeability enhancement techniques are methods used to improve the absorption of drugs across biological barrier. Here are some common techniques:

1. Chemical Modification: Altering the chemical structure of the drug molecule to enhance its permeability. This could involve adding functional groups that increase lipophilicity or altering the molecule's size to better fit transport mechanisms.

2. Prodrug Approach: Converting the active drug molecule into a prodrug, which is then metabolized into the active form after administration. Prodrugs are often designed to improve membrane permeability or to target specific transport mechanisms.

3. Use of Absorption Enhancers: Certain compounds, known as absorption enhancers or permeation enhancers, can temporarily disrupt the integrity of biological membranes, allowing for increased drug absorption. Examples include surfactants, bile salts, and chelating agents.

4. Nanotechnology: Utilizing nanoparticles or nanocarriers to encapsulate drug molecules can improve their solubility, stability, and permeability. Nanoparticles can also be engineered to target specific cells or tissues, enhancing drug delivery efficiency.

5. Lipid-Based Formulations: Formulating drugs with lipid-based carriers such as liposomes, micelles, or lipid nanoparticles can improve their solubility and permeability. Lipid-based formulations mimic natural lipid bilayers, facilitating drug transport across biological membranes.

6. Physical Methods: Techniques such as iontophoresis, electroporation, sonophoresis, and microneedle-mediated delivery involve the application of physical energy to disrupt cellular barriers temporarily, thereby enhancing drug permeation.

7. Protein-Based Delivery Systems: Utilizing carrier proteins or peptides that can bind to specific receptors on cell membranes can facilitate drug uptake and transport across biological barriers. Examples include cell-penetrating peptides and antibody-drug conjugates.

8. Permeation Enhancing Excipients: Incorporating excipients such as penetration enhancers, solubilizers, or complexing agents into drug formulations can improve drug permeability by altering membrane properties or increasing drug solubility.
9. pH Modification: Modifying the pH of drug formulations or the local environment can influence drug solubility and membrane permeability, thereby enhancing absorption. pH modifiers can be added directly to formulations or induced through co-administration of acidic or basic compounds.
These permeability enhancement techniques can be applied individually or in combination to optimize drug delivery across biological barriers, improving the bioavailability and therapeutic efficacy of drugs.

Formulations used on ritonavir for enhancing the solubility & Permeability

1.Using Phase solubility/ Solid Dispersion methods[12]
The primary objective of this study is to enhance the bioavailability of ritonavir utilizing Polyvinyl Pyrrolidone (PVP) K-30 through the solid dispersion technique. Various formulations were developed with differing concentrations of the polymer. Solid dispersion is a widely recognized method for improving the solubility and dissolution rate of poorly water-soluble drugs like ritonavir. By dispersing ritonavir within a hydrophilic polymer matrix such as PVP K-30, the aim is to increase its solubility, thereby enhancing its bioavailability. The study likely evaluates the influence of different polymer concentrations on the dissolution behavior and bioavailability of ritonavir, aiming to identify the optimal formulation that maximizes drug solubility and ultimately improves its therapeutic efficacy.

2.Influence of carrier (polymer) type and drug-carrier ratio in the development of amorphous dispersions[13]
The study aimed to investigate the impact of the ratio of Eudragit® L100-55 or Kolliphor® P188 on the solubility, dissolution, and permeability of ritonavir in order to prepare solid dispersions (SDs) of the drug. SDs were formulated using either solvent evaporation or lyophilization techniques and were evaluated for their physical-chemical properties. Dissolution and permeability assessments were conducted to evaluate the functionality of the SDs, while preliminary functional stability was assessed over six months of accelerated storage conditions.
Results indicated that Ritonavir: Eudragit® L100-55 (RE, 1:3) SD showed a 36-fold increase in solubility compared to pure ritonavir, while Ritonavir: Kolliphor® P188 (RP, 1:2) SD exhibited a 49-fold increase in solubility. Ritonavir dissolution from RE formulations increased with higher ratios of Eudragit® L100-55, peaking at a ritonavir:carrier ratio of 1:3. Similarly, ritonavir dissolution from RP formulations was highest at a ritonavir:Kolliphor® P188 ratio of 1:2. Dissolution efficiencies of these formulations were consistent with and supported the dissolution results.
Furthermore, permeability studies revealed that ritonavir permeability across the biological membrane from the optimized formulations RE (1:3) and RP (1:2) was significantly higher (~76% and ~97%, respectively) compared to pure ritonavir (~20%). Additionally, a preliminary stability study demonstrated the functional stability of the prepared solid dispersions over the six-month period.
Overall, the study underscores the importance of selecting an appropriate carrier polymer and optimizing its amount in SD formulations to achieve significant improvements in solubility, dissolution, and permeability of ritonavir. These findings hold promise for enhancing the bioavailability and efficacy of ritonavir through tailored solid dispersion formulations.

3.Hot Melt Extrusion[14]
Hot-melt extrusion (HME) is a process used to embed drugs in a polymeric carrier, resulting in complex dosage forms consisting of the active pharmaceutical ingredient (API), functional excipients, and processing aids. This mixture is blended using standard industry equipment and processed at elevated temperature and pressure, leading to the dispersion of the drug within the polymer matrix at a molecular level, forming a solid solution. HME, a form of solid dispersion technology, is particularly useful for enhancing the dissolution rate of poorly soluble drugs. Soluplus, an amphiphilic polymer, has been employed as a carrier to increase the dissolution of poorly water-soluble ritonavir. With a glass transition temperature of 70°C, Soluplus is suitable for the hot-melt extrusion process. Leutrol F 68, Leutrol 127, and TPGS are utilized as solubilizers and plasticizers. The primary aim of this study is to improve the dissolution rate of poorly water-soluble ritonavir by preparing a solid solution using hot-melt extrusion.

4. Self-Microemulsifying Drug Delivery System (SMEDDS)[15]

The optimized Self-Microemulsifying Drug Delivery System (SMEDDS) demonstrated a notable enhancement in the dissolution rate of ritonavir (RTV) compared to pure RTV powder. The droplet size of the resulting microemulsion from the SMEDDS formulation ranged between 16 and 22 nm and remained consistent regardless of pH variations (i.e., in 0.1 N HCl and water). X-ray diffraction analysis revealed the conversion of the crystalline form of RTV to an amorphous state upon formulation into SMEDDS. In vitro dissolution studies and stability assessments of the optimized formulation confirmed its stability and significantly improved dissolution of RTV. Furthermore, in male Wistar rats, the relative bioavailability of RTV was evaluated, and pharmacokinetic parameters were calculated by comparing the optimized SMEDDS with an aqueous suspension of RTV. The results indicated that the SMEDDS formulation markedly improved the plasma profile, exhibiting nearly twofold higher maximum plasma concentration (Cmax) and area under the curve (AUC0-24h) compared to the aqueous suspension of RTV. Overall, these findings highlight the effectiveness of the optimized SMEDDS formulation in enhancing the dissolution and bioavailability of RTV, which could potentially lead to improved therapeutic outcomes.

5.Liquisolid techniques [16]

The classic theory of liquisolid systems describes them as powdered forms of liquid medications that exhibit acceptable flowability and compressibility. These systems typically involve incorporating a drug solution or dispersion in a non-volatile solvent, such as liquid polyethylene glycols or polysorbates, into solid excipients referred to as carriers (e.g., microcrystalline cellulose) and coating materials (e.g., amorphous silicon dioxide). The final dosage form is prepared by converting the liquisolid formulation into capsules or tablets, known as liquisolid compacts, often with the addition of additional excipients like disintegrants and lubricants as needed. This approach allows for the transformation of liquid medications into solid forms, facilitating ease of handling, storage, and administration while maintaining drug stability and bioavailability.

For obtaining the formulations, microcrystalline cellulose was used as a carrier; polyethylene glycol 400 (hydrophilic polymer), Tween 80 and Kolliphor EL (surfactant agents) were tested as non-volatile solvents; and crospovidone was used as a new coating material recently introduced by our group

6. Microwave irridation technique:A green chemistry approach [17]

This research aimed to enhance the aqueous solubility of Ritonavir (RIT), an important antiretroviral (ART) drug, by preparing solid dispersions (SD) using both solvent methodology and the microwave irradiation (MWI) technique as a green chemistry approach. In the MWI method, various SD batches were formulated using a 32 factorial approach, with time of exposure (X1) and power of radiation (X2) as variable quantities and dissolution rate as the response (Y1). β-CD was utilized as the hydrophilic carrier, with a drug-carrier ratio of 1:1 determined by phase solubility analysis. The SD formulations underwent assessment for drug content, percentage dissolution rate studies, and analysis through FTIR, XRD, DSC, and SEM techniques. Results from these analyses indicated no interaction between RIT and the excipient. Additionally, the SD formulations demonstrated the conversion of RIT from a crystalline to an amorphous state, enhancing dissolution. Among the batches, F2 showed the most promising results. The F2 batch, coded as RIT: β-CD in a 1:1 ratio with a time of exposure of 4 minutes and power of radiation of 450 Watts, exhibited a six-fold increase in dissolution rate (58%) compared to plain RIT (9%) and SD (47%) within 60 minutes. These findings underscore the potential of MWI-based SD preparation as an effective strategy for improving the dissolution rate of RIT, offering significant implications for the pharmaceutical industry and HIV/AIDS treatment.

7. fusion method and solvent evaporation technique [18]

The study focused on preparing solid dispersions of ritonavir using PLASIDONE-S-630 and HPMC AS carriers via the fusion method and solvent evaporation technique. XRD and DSC analyses confirmed the transformation of crystalline ritonavir into amorphous ritonavir within the solid dispersions, indicating the efficacy of solid dispersion technology in this transformation. Additionally, saturation solubility and in vitro dissolution studies revealed significant enhancements in both solubility and dissolution rates compared to ritonavir solid dispersions prepared using these carriers individually. The dissolution behavior of ritonavir from these solid dispersions followed the Higuchi kinetics model. The study concluded that the improved solubility and dissolution of these newly prepared ritonavir solid dispersions utilizing PLASIDONE-S-630 and HPMC AS carriers could be attributed to enhanced wettability and reduced drug crystallinity, which can be optimized through appropriate levels of hydrophilic carriers. These findings underscore the potential of solid dispersion technology in improving the dissolution characteristics of ritonavir, offering implications for enhanced drug delivery and therapeutic efficacy.

8. Lipid based drug delivery system[19]

The focus of recent formulations for improving the oral bioavailability of ritonavir, such as pro-liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), has primarily been to enhance absorption or target lymphatic pathways to bypass first-pass metabolism. However, ritonavir's known toxicity, even at lower doses, suggests that reducing pill burden may not fully address the drug's main issue. While the exact mechanism of ritonavir-induced hepatotoxicity remains unclear, increased reactive oxygen species (ROS) levels could be a contributing factor. To address this concern, there's a need for novel formulations that not only enhance ritonavir's bioavailability but also reduce its toxicity.

Cells naturally produce reactive nitrogen species (RNS) and ROS during regular functioning, and maintaining a balance with antioxidant enzymes and molecules is crucial to prevent oxidative stress. Previous studies have shown the protective effects of antioxidants like alpha-tocopherol (vitamin E) against hepatotoxicity induced by other drugs. Vitamin E plays a vital role in immune system maintenance, which is particularly important for HIV-infected individuals. HIV infection can lead to decreased vitamin E levels, and supplementation may be necessary during treatment.

In this study, antioxidant-loaded NLCs of ritonavir were prepared using alpha-tocopherol, not only as a source of antioxidant but also as a liquid lipid to encapsulate ritonavir. The hypothesis is that alpha-tocopherol could help improve antioxidant levels in the body and mitigate ritonavir's adverse effects by reducing ROS levels. This approach represents a potential solution to the dual challenge of enhancing ritonavir's bioavailability while simultaneously addressing its toxicity concerns.

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