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SOLUBILTY ENHANCEMENT OF DOMPERIDONE BY DESPERSION METHOD

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ABSTRACT
Domperidone, a dopamine antagonist, enhances gastrointestinal motility and breast milk production through its peripheral dopamine receptor blocking properties. However, its poor aqueous solubility limits bioavailability and therapeutic efficacy. This review explores solubility enhancement techniques, including solid dispersions, micronization, co-solvency, and lipid excipients, to improve domperidone's solubility and bioavailability. By facilitating gastric emptying and decreasing small bowel transit time, domperidone's gastroprokinetic properties make it an effective treatment for gastrointestinal disorders and lactation support.

Keywords:
Increase solubily, bioavailablity, dessolution rate, fast on set of action

INTRODUCTION

Domperidone anti-emetic drug, suffers from low aqueous solubility, impacting its bioavailability and absorption. This poor solubility leads to variable drug release and limited therapeutic effect
. To overcome this limitation, researchers have explored dispersion methods to enhance Domperidone's solubility, including the use of PVP , PEG etc
The solubility of low water-soluble drugs has always been a challenge to the discovery and design of new drugs.[1] More than 40% of the recent developed drugs are practically insoluble in water, their poor solubility in water (<0.1 mg/ml) results in their slow and incomplete absorption, low and variable bioavailability, as well as gastrointestinal toxicity.
Solubility enhancement techniques are divided into physical and chemical modification and other methods. Physical methods include particle size reduction (micronization and nanosuspension), changing in the crystal habit, solid solutions, solid dispersions, andsize reduction. Chemical modifications consist of pH adjustment, complexation.
Domperidone works to boost breastmilk supply by increasing the level of a hormone called prolactin, which stimulates the production of breastmilk.
Domperidone is available on prescription and in some places as an over-the-counter (OTC) medicine. It is available in many places around the world, including the UK, Europe, Canada and New Zealand. Approved uses of the drug vary from country to country.
It is also used for off-label or unapproved conditions, including boosting breastmilk supply. Domperidone is not approved for use in the US, but some patients with severe gastrointestinal motility disorders can still access it through an expanded access investigation new drug (IND) application. Domperidone first became available in the late

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OBJECTIVES

Improve bioavailability
Enhance therapeutic efficacy
Increase absorption
Ensure consistent and reliable drug delivery
Achieve better patient outcomes
Formulation Goals:-
Develop stable and effective formulations
Optimize drug delivery
Enhance solubility using techniques like solid dispersions, hydrotropy, nanotechnology.

METHODOLOGY

Solid Dispersions:
Solid dispersions involve dispersing a drug in a carrier material, typically a polymer, to improve its dissolution rate and solubility. Techniques like cogrinding or kneading can be used to prepare solid dispersions. Studies have shown that solid dispersions, particularly using polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP), can significantly enhance the solubility and dissolution of domperidone.
Properties of PEG and PVP
PEG (Polyethylene Glycol)
Obtained from ethylene glycol and ethylene oxide reaction
Molecular weight range: 1500-20,000 for solid dispersions
Viscosity increases with molecular weight
Good solubility in water and organic solvents

PVP (Polyvinylpyrrolidone)
Molecular weight range: 2500-3,000,000
Soluble in water, ethanol, chloroform, and isopropyl alcohol
Decomposes at high temperatures, limiting melt method use
Suitable for solvent method due to excellent solubility in organic solvents

Both PEG and PVP are used in solid dispersion preparation, with PEG suitable for melt method and PVP for solvent method.
Polyethylene glycol (PEG)
These are compounds are obtained from a reaction of ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 150020,000 are usually employed. As the MW rises, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800 -1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20,000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but reduces with MW. A meticulous advantage of PEGs for the solid dispersions is that they have good sol…

Characteristics of Polyethylene Glycol (PEG)
Synthesis: PEGs are obtained through the reaction of ethylene glycol with ethylene oxide.
Molecular Weight Classification: PEGs with molecular weights above 300,000 are referred to as polyethylene oxides.
Molecular Weight Range for Solid Dispersions: PEGs with molecular weights of 150020,000 are typically used for solid dispersion and solution preparation.
Viscosity and Consistency: The viscosity of PEG increases with molecular weight, resulting in varying consistencies: - Fluid (MW up to 600)
Vaseline-like (MW 800-1500)
Waxy (MW 2000-6000)

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Hard, brittle crystals (MW 20,000 and above)
Solubility: PEGs generally have good solubility in water, which decreases with increasing molecular weight. Advantage: PEGs have good solubility in numerous organic solvents, making them suitable for solid dispersion preparation.
Melting Point:
PEG with average molecular weight 4600 (range 4400-4800): 57-61°C - PEG with average molecular weight 6000 (range 5000-7000): 60-63°C

Characteristics of Polyvinylpyrrolidone (PVP)
Molecular Weight Range: PVP molecular weights range from 2500 to 3,000,000.
Solubility: PVP is soluble in solvents like water, ethanol, chloroform, and isopropyl alcohol.
Thermal Stability: PVP decomposes at high temperatures, making it unsuitable for melt method preparation.
Classification: PVP can be classified according to the K value, calculated using Fikentscher's equation. Glass Transition Temperature (Tg): PVP has a high Tg, dependent on molecular weight and moisture content (e.g., PVP K25 has a Tg of 155°C).
Application: Due to excellent solubility in organic solvents, PVP is mostly suitable for solvent method preparation of solid dispersions.
Micronization:
Reducing the particle size of domperidone through micronization increases its surface area, leading to faster dissolution and potentially improved solubility.
This is achieved by using a nonsolvent precipitation technique, where domperidone is dissolved in a solvent, and a nonsolvent is added to precipitate the drug into micron-sized particles.
Co-solvency:
Using a mixture of solvents, where one solvent is a good solvent for the drug and the other is more compatible with water, can enhance solubility.
This approach can be particularly useful for drugs that are poorly soluble in water but more soluble in certain organic solvents.

Procedure
Trituration: 0.01 mg Domperidone + 0.1 mg PEG + 0.1 mg PVP triturated with 1 mL water for 30 minutes.
Ethanol addition: 10 ml ethanol added, triturated for 30 minutes.
Drying: Mixture dried in hot air oven.
Solution preparation: 0.01 mg of dried powder dissolved in:
10 ml water (Solution A)
10 ml ethanol (Solution B)
UV Analysis: Both solutions shaken and analyzed under UV to compare solubility rates of Domperidone.
The procedure involves the preparation of Domperidone solutions using a Dispersion method, where 0.01 mg of Domperidone is mixed with 0.1 mg of polyethylene glycol (PEG) and 0.1 mg of polyvinylpyrrolidone (PVP) in 1 ml of water for 30 minutes, followed by the addition of 10 ml of ethanol and further trituration for 30 minutes, after which the mixture is dried in a hot air oven, and the resulting powder is then dissolved in either 10 ml of water or 10 ml of ethanol to prepare two separate solutions, Solution A and Solution B, respectively, which are subsequently analyzed under UV spectroscopy to compare the solubility rates of Domperidone.
Importance of solubility enhancement
Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, costeffectiveness, least sterility constraints, and flexibility in the design of dosage form.
As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products [10].
However, the major challenge with the design of oral dosage forms lies with their poor bioavailability.

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RESULTS AND DISCUSSION

Domperidone's low solubility in water can be significantly improved through various techniques, including solid dispersions, cyclodextrins, and liquisolid formulations.

In conclusion, this study demonstrates that domperidone's poor aqueous solubility significantly impacts its bioavailability and therapeutic efficacy. However, employing solubility enhancement techniques such as solid dispersions using PEG and PVP, micronization, co-solvency, and lipid excipients can substantially improve its solubility and bioavailability. These approaches have the potential to enhance the therapeutic effects of domperidone, making it a more effective treatment for gastrointestinal disorders and lactation support. Further research is warranted to optimize these techniques and explore their clinical applications.

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CONCLUSION

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