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REVIEW ARTICLE

SOLUBILITY ENHANCEMENT OF MICONAZOLE NITRATE FOR FORMULATION AND EVALUATION OF MUCOADHESIVE GEL

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ABSTRACT

The goal of the present investigation is formulation and evaluation of a mucoadhesive gel for buccal delivery after solubility enhancement of very slightly water-soluble drug Miconazole Nitrate. Miconazole Nitrate is imidazole derivative useful in treatment of oropharyngeal Candidiasis, the most common infection in AIDS patients. The method namely solvent deposition with inclusion complex, solid dispersion with inclusion complex and solvent deposition with solid dispersion are used for solubility enhancement. Various polymers such as Lactose, β-CD and PEG-6000 are those polymers which were used for individual methods like SolD, IC and SD respectively all the batches are evaluated for their water solubility and *In-vitro* release. Enhancement of dissolution rates with increasing quantity of β-CD, Lactose and PEG in the complexes is observed. Water solubility of Miconazole Nitrate is enhanced up to 321.9 times by using combination of methods (solvent deposition with inclusion complex) and mucoadhesive antifungal gel of Miconazole Nitrate is prepared with improved drug release in to the buccal cavity which ensures effective treatment of local fungal infection-Oropharyngeal Candidiasis.

Keywords: Mucoadhesive, dissolution rate, solubility enhancement.

INTRODUCTION

Solubilisation of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. If any drug has very less solubility, then therapeutic effectiveness of that drug will be lesser because of very less systemic availability of it. Bioavailability is defined as the rate and extent to which the active drug is absorbed from a dosage form and becomes available at the site of drug action. Bioavailability depends on drug solubility in an aqueous environment and drug permeability through lipophilic membranes[1].This is a well-known fact that only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action (vascular system for instance). A drug can be defined bioavailable if it belongs to the class I (high solubility and high permeability) of Biopharmaceutical Classification System (BCS). Poorly soluble compounds belong to class II of the (BCS). It is difficult to develop a new molecule with good pharmacological activity having desired solubility and permeability. It has been reported that about 40% of the compounds being developed by the pharmaceutical industries are poorly water soluble out of which up to 40% of pharmacologically active new molecules failed to reach the market only due to little or no water solubility. Today pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, those with aqueous solubility of less than 0.1 mg/ml present some unique challenges. These drugs are particularly good candidates for advanced solubilisation technologies developed by companies specializing in drug delivery2.From Noyes Whitney equation, possibilities for improving drug dissolution are to increase the surface area of drug available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface[3]. Therefore, various formulation strategies have been investigated to improve solubility and dissolution rate of poorly water soluble drugs such as inclusion complexation with cyclodextrins, solid dispersion, salt formation, particle size reduction, use of surfactants, co-solvency, hydrotropy etc[4].

TECHNIQUES OF SOLUBILITY ENHANCEMENT[5, 6]

1. **Chemical Modifications**
2. **Physical Modifications**

- Particle size reduction:
  - I. Micronization
  - II. Nanosuspension
- Modification of the crystal habit:
  - I. Polymorphs
  - II. Pseudo polymorphs
- Drug dispersion in carriers:
  - I. Eutectic mixtures
  - II. Solid dispersions
  - III. Solid solutions
- Complexation
  - I. Complexing agents
- Solubilisation by surfactants
  - II. Micro emulsions

III. Self-micro emulsifying system

CHEMICAL MODIFICATIONS [7,8]

Salt Formation:

It is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Example of acidic or basic drug which is converted into salts has more solubility than that of respective drug like aspirin**,** theophylline, barbiturates etc.

Co-crystallisation:

Anew approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. Co-crystals may be defined as crystalline material that consist of two or more molecular (electrical neutral) species held together by non-covalent forces. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds.

Co-solvency:

It is well-known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. The solvent used to increase solubility is known as co-solvent. It is commonly referred to as solvent blending.

Hydrotropy:

It designates to increase in solubility in water due to presence of large amount of additives. It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, and urea) and solute e.g.sublimation of theophylline with sodium acetate and sodium alginate.

Solubilising Agents:

The solubility of poorly soluble drug can also be improved by various solubilising materials. PEG 400 improves the solubility of hydrochlorothiazide.

Nanotechnology Approaches

Nanotechnology can be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometre (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation.

PHYSICAL MODIFICATIONS [7, 9]

Particle Size Reduction:

The techniques of size reduction using various milling processes are well established and these practices are a standard part of formulation development. This can be done mainly by micronisation &Nano suspension. As particle size decreases, surface area of particle increases resulting in increase in solubility. Sonocrystallisation technique is also used for particle size reduction.

Modification of Crystal Habit:

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug, are-

Amorphous >Metastable polymorph >Stable polymorph.

Complexation:

Complexation is the association between two or more molecules to form a non bonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers and inclusion complexes cyclodextrins.

Solubilisation by Surfactants:

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or non-ionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilisation is very important in industrial and biological processes. The presence of surfactants may lower the surface tension but increases solubility of drug. Although salt formation, particle size reduction, etc. have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion. Solid dispersion of an amorphous drug in a polymer matrix has been demonstrated to be an effective tool for solubility and subsequently,bioavailability enhancement.

Temperature

Generally, an increase in the temperature of the solution increases the solubility of a solid solute. For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the

solubility. For solids and liquid solutes, change in pressure has practically no effect on solubility.

Nature of the Solute and Solvent

Only 1 gram of lead (II) chloride can be dissolved in 100 gram of water at room temperature while 200 gram of zinc chloride can be dissolved within same volume of water. The difference in the solubility of these two substances is the result of differences in their nature.

Molecular Size

Larger the molecule or higher molecular weight ensures less solubility of the substance. In case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Polarity

Polarity of the solute and solvent molecules affect the solubility. Generally non-polar solute molecules dissolve in non-polar solvents and polar solute molecules dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecules are polar then positive end of solvent molecules attract negative end of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. Molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.

Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs show different solubility. Generally the range of solubility between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

Rate of Solubilization

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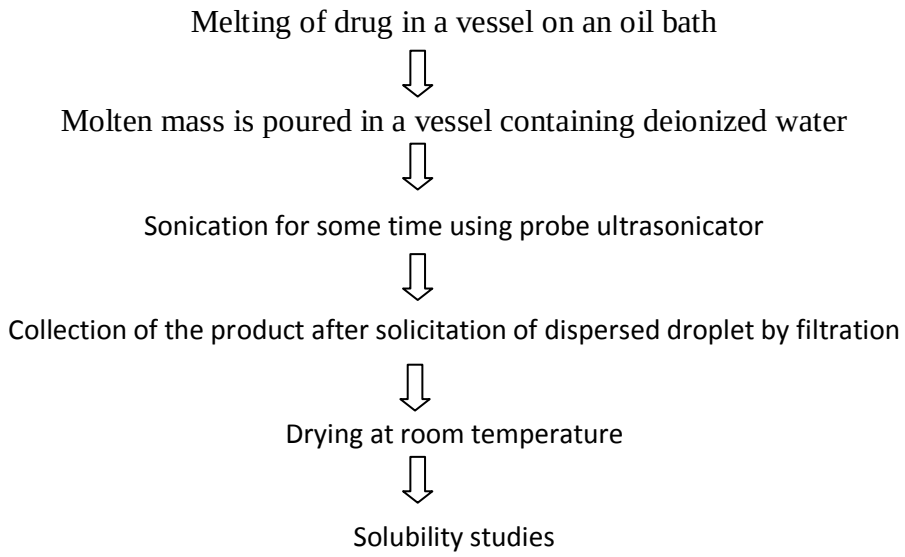
Methods of Choice

Particle Size Reduction: Melt-sonocrystallisation Particle engineering techniques are being developed to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. Numbers of particle design techniques is reported, such as spherical crystallization, extrusion spheronization, melt solidification, spray drying, pastillation, solution atomization and crystallization by sonication (SAXS), where simultaneous crystallization and agglomeration occur. It is used to enhance dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. It forms drug agglomerates with number of shallow circular pits on the surface and leads to increase in solubility. The effect of application of US energy on the properties of melt sonocrystallized (MSC) valdecoxib was characterized by scanning electron microscopy (SEM), differential scanning calorimetery (DSC), X-ray powder diffraction (XRPD), infrared spectroscopy and saturated solubility studies.

PROCEDURE:



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Solid Dispersions:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug; the matrix can be either crystalline or amorphous.

Carriers for Solid Dispersions:

The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib, halofantrine can be improved by solid dispersion using suitable hydrophilic carriers.

Table 1: Example of Carriers[7]

Sr. No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Sodium alginate
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans

ADVANTAGES OF SOLID DISPERSIONS [8,9]

Particle Size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

Wettability

A strong contribution to the enhancement of drug solubility is related to the drugwettability improvement verified in solid dispersions. It was observed thateven carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity such as cholic acid and bile salts when used can significantly increase the wettability property of drug. Moreover, carriers' caninfluence the drug dissolution profile by direct dissolution or co-solvent effects.

Porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Amorphous State

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process In solid dispersions, drugs are presented as supersaturated solutions after dissolution and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by selecting carriers, which exhibit specific interactions with them.

DISADVANTAGES OF SOLID DISPERSION METHOD[9, 11]

The limitations solid dispersions include:

1. Laborious and expensive method of preparation
2. Reproducibility of physicochemical characteristics
3. Difficulty in incorporating into formulation
4. Scale-up of manufacturing process
5. Stability of the drug and vehicle

Carrier and Solvent Selection

Carrier and solvent selection is influenced by the chemistry of the drug. It should optimize solubility of the drug in the carrier.

Carrier Selection:

- ***1st Generation*:**Crystalline carriers like urea, sugar and organic acid
- ***2nd Generation***:Amorphous carriers like PEG, PVA, povidone and cellulose derivatives
- ***3rd Generation:***Surface active self-emulsifying carriers like poloxamer 407, tween 80, gelucire 44/14, compritol 888 ATO +/- polymer

Preparation of Solid Dispersions

Various preparation methods for solid dispersions have been reported:

1. Fusion method
2. Solvent Evaporation Method
3. Melt agglomeration
4. Surface-active Carriers

5.

CHARACTERIZATION OF SOLID DISPERSION[9, 10]

Table 2: Characterization of Solid Dispersions

S. No.	Characterization	Methods	Significance
1	Drug-carrier Miscibility	Hot stage microscopy DSC (conventional modulated) pXRD (conventional and variable temp), NMR 1H spin lattice relaxation time	To find out the complex formation between drug and carrier.
2	Drug-carrier interactions	FT-IR spectroscopy, Raman spectroscopy and Solid state NMR studies	To find out the integration between drug and carrier and formation of inclusion complex.
3	Physical structure	SEM Surface area analysis	To find out the particle size and shape.
4	Surface properties	Dynamic vapour sorption, Inverse gas chromatography, Atomic force microscopy and Raman microscopy	To study the morphology and degree to study the morphology and degree of crystallinity.
5	Amorphous content	Polarized light optical microscopy Hot stage microscopy, Humidity stage microscopy, DSC (MTDSC), ITC, Pxrd	To find out the amorphous form of drug.
6	Stability	Humidity studies Isothermal Calorimetry DSC (Tg, temperature recrystallisation) Dynamic vapour sorption Saturated solubility studies	To find out the degree of crystallinity
7	Dissolution enhancement	Dissolution, Intrinsic dissolution, Dynamic solubility and Dissolution in bio-relevant media	To find out the rate and extent of dissolution

Application of Solid Dispersion in Pharmaceutical Industries: [9, 10, 11, 12]

The application of solid dispersions for increasing drug bioavailability is by no means a new field of pharmaceutical research. Different applications are enlisted below-

- Increases oral bioavailability of poorly water-soluble drugs.
- Suitable for oral delivery.
- No change in chemical properties of the drug.
- Relatively simple processing techniques.
- Uses conventional equipment's.
- Increases dissolution due to metastable solid state apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compound.

Complexation:

Complexation is the association between two or more molecules to form a no bonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

LIST OF COMPLEXING AGENTS[13, 14]

Table 3: Examples of Complexing Agents

S. N.	Types	Examples
1	Inorganic	Iodide (I^-)
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA, EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular Complexes	Polymers

Solvent Deposition Method:

The principle of solvent deposition technique is deposition of the drug in "minuscular form" from an organic solvent on to the surface of an inert excipient. Due to micronization the surface area of drug increases which in turn improves dissolution rate. Drug solvent deposition system (SDS) was prepared by adsorbing drug over lactose particles[14, 15]

Procedure

1. Proportions of drug: lactose.
2. Required amount of drug powder is dissolved in organic solvent to form a clear solution.
3. A known amount of lactose is dispersed in the drug solution.
4. The solvent is evaporated at room temperature with constant stirring.
5. Products thus obtained are kept in vacuum oven at 37 °C for 24 hrs to allow complete evaporation of organic solvent.
6. The SDS thus formed is passed through 60-mesh sieve to get dry free flowing powder.
7. Fraction of drug powder is used for saturated solubility study[16, 17, and 18].

CURRENT & FUTURE DEVELOPMENTS

Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problems of many drugs their bioavailability gets affected and hence solubility enhancement becomes necessary. It is possible to increase the solubility of poorly water soluble drugs with the help of various techniques as mentioned above. All the above methods are applicable not only to molecules of a specific physical and chemical nature, but to a wide range of crystalline materials, although a comprehensive knowledge of drugs at the molecular level is required to determine the appropriate approach to improve solubility and dissolution rate. A probable candidate for solubility enhancement could be Miconazole Nitrate since it belongs to BCS class II. It is a popular drug of choice for treatment of local fungal infections.

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