REVIEW ON : INVESTIGATION OF SIMVASTASTIN SOLUBILITY

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Abstract

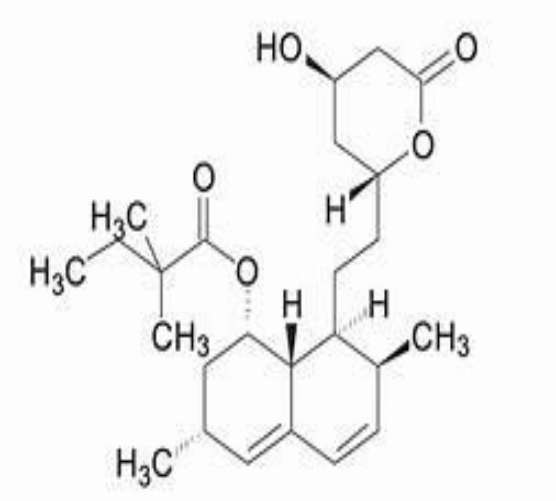
Solubility is main factor for drug effective. Simvastatin is poorly water-soluble drug and its bioavailability is very low. Solubility practical data from Simvastatin in a family of alcohols were obtained at different temperatures. . experimental solubility data an anomalous behavior was observed, since an increase the number of alcohol carbon atoms shows an increase in solubility only for the three alcohols, ethanol, 1-propanol and 1-butanol. A decrease in solubility was obtained for 1-pentanol, 1-hexanol and 1-octanol. VantHoff equation was used to obtain the theoretical solubility value and the ideal activity .Experimental mistake was very low and does not affect the plots and equations used. No polymorphic phenomenon was found from the Simvastatin characterization. Theoretical calculations were carried out in order to corroborate the experimental solubility data. Trends and results are similar in both cases. The solvent effect was treated using a continuum model as model in water, methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol and 1-octanol.

Keyword: *solubility, alcohol, enthalpy, density, functional theory, citric acid, co-crystal, nanosuspension, dissolution.*

Introduction:

Solubility (defined is maximum amount of substance that dissolve in solvent at given temperature). Simvastatin is one drug a low solubility to low blood cholesterol. It has low solubility water According to the Biopharmaceutical Classification System (BCS), oral medications are classified into four classes based on their solubility and permeability, class II and class IV the problem of low aqueous solubility. Simvastatin belongs to the statins family and it is an effective lipid drug compound.

The main purpose is increasing solubility and improved bioavailability is less soluble drug. simvastatin is a Cholesterol-lowering, hydrophobic techniques that have been discussed in detail, the fundamental properties of the molecular interaction involved are. Data such as conductometric and volumetric measurements at different temperatures are crucial to illustrate the thermodynamics involved and related solute–solvent interactions. which had been reported as a solubility enhance improving the solubility of SMV. solubility study, densities, and conductivities for several concentrations. solution m. The parameters related to this study such as the Gibbs free energy of transfer.



Structure; simvastatin (belong statin family)

Near about 35-40% of n problem of low aqueous solubility that affects drug absorption in the gastrointestinal tract (GIT) which leads to lower bioavailability, high inter and intrasubject variability, dose dumping chances, reduction in the effectiveness. formulations that will improve solubility and thus dissolution and bioavailability get improved. Various strategies involved are salt formation, solubilization, self-micro emulsifying drug delivery system, complexation, spray drying, solid solution/solid dispersion with hydrophilic carriers, nano-particular systems. According to Biopharmaceutical Classification System (BCS), oral medications are classified into four classes based their solubility and permeability. Out of the four classes, class II and class IV a low aqueous solubility, need to improve solubility by using different solubility enhancement techniques to improve in vitro dissolution and bioavailability of medications. . Solid dispersion is defined as a group of solid products consisting of at least two components, hydrophobic drug, and hydrophilic carrier. Simvastatin is a Cholesterol-lowering, hydrophobic drug having a log P value. It is a BCS Class II drug with low aqueous solubility (. It is a white crystalline powder. coenzyme A (HMG CoA) reductase which reduces HMG CoA to mevalonate thus blocking vital steps for cholesterol biosynthesis in the liver. a trials were taken to improve the solubility and thus dissolution rate of simvastatin by formulating its solid dispersions. Different concentrations of carriers were used for preparing solid dispersion.

Drug solubility is one of the most important physical and chemical properties, useful in great number of several part in the pharmaceutical chemical, biotechnological and food drug industries. Simvastatin solubility in a family of alcohols was experimentally determined, also it is characterized with several method and the melting temperature, enthalpy of fusion and differential m melting point. These data were used for calculating the solubility of SVS in order to estimate its infinite dilution activity coefficient in the corresponding alcohols. However, accurate differential heat capacity data should be used for obtaining real consistent activity coefficients. oral drug delivery is the simplest and easiest way easy given drugs. oral drug delivery is the simplest and easiest way of administering drugs due to its convenience, good patient compliance, greater stability. Several methods have been developed to increase the solubility of SV such as the technique of forming a complex, solid dispersion [addition of a surfaceactive

agent particle size reduction by microemulsion and supercritical anti solve.

Diabetes is complex disorder and type 2 diabetes risk factor for cardiovascular disease. the simvastatin reduce glucose level and vascular disease, diabetics patient. Various method increase method solubility these comprise solubility comprise size, solid dispersation, nanosuspension formation. In research, trials were taken to improve the solubility and thus dissolution rate of simvastatin by formulating its solid dispersions. Main purpose of increase solubility and bioavailability of less aqueous soluble drug like simvastatin.

It is low cholesterol, which a white, non-hygroscopic, crystalline powder have a low solubility and bioavailability. Simvastatin is a reality a crude drug is a inactive lactone, which metabolise in liver (from beta hydroxy acid).

Factor affecting solubility

1. Particle size: (a small particle size has greater solubility)
2. Temperature
3. PH medium
4. Other excipients

Why solubility is increase?

1. Improved efficacy
2. Reduced variability
3. Increased bioavailability
4. Easy formulation
5. Reduced side effect
6. Improved stability
7. Expanded drug development

Solubility enhancement using a was based on our previous work . which is expanded in this study using polysorbate. Arginine studied it is the best amino acid that improves solubility of a hydrophobic drug like while polysorbate 80 as the non-ionic surfactant is typically used as an emulsion of a hydrophobic drug both surfactants are safe chemicals to be employed to human. The hydrogel is a drug carrier many part which crosslinked with a water-soluble polymer. Different concentration carrier used prepare solid dispersion and preparing flowing free dispersion valuated for soluble. Surfactants are known to be safe chemicals to human.

Chemical detaial

Simvastatin belongs to statins family and it is effective lipid decreasing drug compound.

It is inhibitor of the (3,5)-hydroxy-3-methylglutaryl coenzyme (HMGr-CoA) reductase, this enzyme the conversion HMA–CoA to an intermediate in an early rate-limiting step in the cholesterol biosynthesis in human body. Depletion of intracellular cholesterol results in compensatory increase in cholesterol up-take by means of low density lipoprotein

(LDL) receptors and the consequent decrease in plasma cholesterol. It is used for control of hyper-cholesterol due to their well proven efficacy and safety Simvastatin is obtained from a process where lovastatin is used as raw material. Lovastatin is a natural product, a secondary metabolite, derived from fermentation of Aspergillus lovastatin isolation, the compound is purified by a set of crystallization steps prior to milling the final product and drug formulation. There are very few reports of statins solubility in organic solvents, in one of them it is reported a method using laser monitoring observation technique to determine lovastatin solubility in acetone, ethyl acetate, butyl acetate, ethanol and methanol at different temperatures. In our work, temperature dependence of simvastatin (SVS) solubility is obtained by the thermodynamic relationship. gas constant and temperature respectively. In low solubility drugs such as statins; the equilibrium mole fraction or solubility of statins in alcohols is very low (10^2 for SVS at room temperature)

The influence of the solvent on the solute solubility is represented by the activity coefficient ln c^1_2 , which is originated by the solvent–solute molecules interactions while ln X^{ideal}_2 is temperature dependent and is determined from pure solute properties .

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Advantages;

1. Effective cholesterol reduction only(30% to 40%)
2. Cardiovascular risk reduction. ; heart attack, stroke, death .
3. Anti- inflammatory effect.
4. Triglyceride reduction.
5. long acting.
6. High Potency.
7. Well tolerate.
8. Rapid onset.
9. Cost effective.

Disadvantage;

1. Muscle pain or weakness.
2. Liver enzyme elevation.
3. Headache.
4. Nausea, abdominal pain.
5. Muscle damage.
6. Memory loss
7. Increase risk of diabetes.
8. Severe allergic reaction.
9. Skin and mucous membrane disorder.

Potential Benefits

1. Reduced inflammation: Simvastatin's anti-inflammatory properties may mitigate COVID-19-induced cytokine storm.

2. Improved endothelial function: Simvastatin may help maintain vascular integrity, reducing cardiovascular complications.

3. Enhanced immune response: Simvastatin's immunomodulatory effects may support the body's natural defences.
4. Antiviral effects: Simvastatin may inhibit SARS-CoV-2 replication.

Mechanisms:

1. Reduction of IL-6 and TNF-α cytokines.

2. Increased production of anti-inflammatory cytokines.

3. Modulation of immune cell activity.

Clinical Implications:

1. Reduced severity of COVID-19 symptoms.

2. Lower risk of cardiovascular complications.

3. Improved outcomes in high-risk patients.

4. Potential prophylactic benefits.

Limitations and Uncertainties:

1. Small sample sizes in existing studies.

2. Variability in simvastatin dosing and duration.

3. Limited understanding of simvastatin's effects on SARS-CoV-2 variants.

4. Potential interactions with other COVID-19 treatment.

Here's general information about Simvastatin:

Chemical Information:

- Chemical Name: Simvastatin

- Molecular Formula: C25H38O5

- Molecular Weight: 418.57 g/mol

Pharmacological Classification:

- Statin (HMG-CoA reductase inhibitor)

Therapeutic Uses:

- Hypercholesterolemia (high cholesterol)

- Hypertriglyceridemia (high triglycerides)

- Prevention of cardiovascular disease.

- Reduction of risk of myocardial infarction (heart attack)

- Stroke prevention.

Mechanism of Action:

- Inhibits HMG-CoA reductase enzyme.

- Reduces cholesterol synthesis in liver.

- Increases LDL receptor expression.

- Enhances clearance of LDL cholesterol.

Pharmacokinetics:

- Absorption: 85% bioavailability.

- Distribution: Highly bound to plasma proteins.

- Metabolism: Liver (CYP3A4 enzyme).

- Excretion: Feace(85%), Urine (10%).

Dosage and Administration:

- Typical dose: 20-80 mg/day

- Maximum dose: 80 mg/day

- Taken orally, once daily, in the evening

Side Effects:

- Muscle pain or weakness (myopathy)

- Liver enzyme elevation (transaminases)

- Increased risk of diabetes.

- Cognitive impairment.

- Headache, dizziness, nausea.

Contraindications:

- Pregnancy or breastfeeding.

- Active liver disease.

- Unexplained elevations in liver enzymes.

- Hypersensitivity to simvastatin.

Interactions:

- Gemfibrozil (increases risk of myopathy)

- Cyclosporine (increases risk of toxicity)

- Warfarin (increases risk of bleeding)

- Grapefruit juice (increases simvastatin levels)

Storage and Stability:

- Store at room temperature (20-25°C/68-77°F)

- Protect from light and moisture

Regulatory Status:

- Approved by FDA (December 1991)

- Approved by EMA (1992)

- Available in over 100 countries

Brand Names:

- Zocor

- simcard

- Sinvacor

Manufacturer:

- Merck.

- Pfizer.

- Ranbaxy.

Solubility simvastatin;

-Simvastatin is a lipophilic compound with low aqueous solubility.

Solubility in various solvents:

1. Water: 0.012 mg/mL (pH 7.4, 25°C)

2. Ethanol: 10.4 mg/mL (25°C)

3. Methanol: 20.6 mg/mL (25°C)

4. Acetonitrile: 1.8 mg/mL (25°C)

5. Chloroform: 50 mg/mL (25°C)

6. DMSO: 20 mg/mL (25°C)

pH-dependent solubility:

-Simvastatin solubility increases at acidic pH:

1. pH 1.2: 0.25 mg/mL

2. pH 4.5: 0.12 mg/mL

3. pH 7.4: 0.012 mg/mL

Temperature-dependent solubility:

1. 37°C: 0.021 mg/mL

2. 50°C: 0.035 mg/mL

Solubilization method improve solubility:

1. Cosolvents (e.g., ethanol, propylene glycol)

2. Surfactants (e.g., Tween 80)

3. Complexation (e.g., cyclodextrins)

4 .Nanoparticle formulation.

Formulation strategies:

1. Solid dispersions.

2. Lipid-based formulations.

3. Self-emulsifying drug delivery systems (SEDDS).

4. Nanosuspensions.

Experimental section;

Material;

simvastatin was from Sigma Aldrich, Singapore, (pharmaceutical grade) as an active substance of hydrophobic drug. The surfactants employed were arginine (ARG) and polysorbate 80 (POL 80),

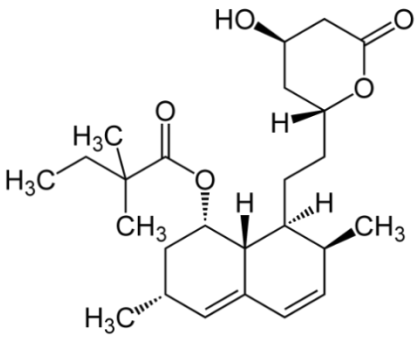

Fig 1. Molecular structure of simvastatin

available in a pharmaceutical grade provided by Sigma Aldrich, Singapore. Type B Gelatin was obtained from Nitta Gelatin(Osaka, Japan) as the polymer for preparing a hydrogel.

SMV was kindly donated by HovidBerhad (Ipoh, Malaysia). ARG was purchased from Sigma-Aldrich Co. (St Louis, MO, USA), while ethanol and methanol were procured from HmbG Chemical (Hamburg, Germany). The water used was obtained from Select Bio O Purite (Oxfordshire, UK) water system. All other chemicals used were of analytical grade unless otherwise stated.

Simvastatin ($C_{25}H_{38}O_5$) was provided by Bio Fine Pharmaceuticals (Pvt.) Ltd (Pakistan). Citric acid ($C_6H_8O_7$) was purchased from Sigma Aldrich (Germany). Sodium hydroxide (NaOH) was pSigma Aldrich .

Simvastatin ($C_{25}H_{38}O_5$) was provided by Bio Fine Pharmaceuticals (Pvt.) Ltd (Pakistan). Citric acid ($C_6H_8O_7$) was purchased from Sigma Aldrich (Germany). Sodium hydroxide (NaOH) was purchased from Sigma Aldrich

(Netherlands). Methanol (MeOH), potassium hydroxide (KOH), hydrochloric acid (HCl) and potassium dihydrogen phosphate (KH_2PO_4) were bought from Merck (Germany

METHOD:

1.Physicochemical characterization of drug

The Drug was identified by various physicochemical properties such as CoLOR, Odour, Melting point, DSC and IR spectroscopy.

2. Determination of saturation solubility of SIMVASTATIN

Solubility of simvastatin was determined by the shake flask method in different solvents like water, ethanol, methanol, chloroform, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. Saturated solutions of simvastatin were prepared in different solvents and were stirred for 24 h using a rotary shaker. The concentration of simvastatin was determined using a UV spectrophotometer .

3).Preparation of solid dispersions (SDs) ;SOLID dispersions of simvastatin were prepared using solvent evaporation methods employing PEG 6000 and PVP K30 as carriers. Prepared solid dispersionswere compared with pure drug and physical mixtures of drug and polymer. Physical mixture Simvastatin

and were mixed in mortar and pestle to obtain physical mixtures.

5).PHYSICAL MIXTURE;

SIMVASTATIN AND CARRIER WERE MIXED IN MORTOR AND PESTLE OBTAIN PHYSICAL NATURE.

6). Co-crystallization of simvastatin with citric acid; Co-crystals of SIM-CA were synthesized using various methods 4 -grinding, liquid-assisted grinding, solvent evaporation and slurry technique. The drug and co-former were taken in equimolar ratios for development of formulations. In co grinding method, SIM and CA were milled or mixed together at the stated stoichiometric ratios for 45 min, using pestle and mortar without adding any solvent. method, SIM and CA were milled at the indicated stoichiometric ratios for 30 min using pestle. AND MORTAR PESTLE.

7).Solubility studies of SIM-CA co-crystals; Solubility studies were performed for pure drug and SIM:CA co-crystals in aqueous, acidic and by adding excess amount of drug or co-crystal to 10 mL of each medium. The mixture of drug and medium was stirred at 400 rpm at room temperature for 48 h. Then, samples were withdrawn in triplicate, filtered using Whatman filter paper no. 42, and diluted prior to spectrophotometric analysis. The samples were collected in triplicate.

8). **Traditional Methods:**

1. Shake Flask Method: Mix Simvastatin with solvent, shake, and measure concentration.

2. Solvent Titration Method: Add solvent to Simvastatin until dissolution.

3. Saturation Method: Excess Simvastatin in solvent, measure concentration.

9) **Instrumental Methods**:

1. High-Performance Liquid Chromatography (HPLC).

2. Ultraviolet (UV) Spectroscopy.

3. Nuclear Magnetic Resonance (NMR) Spectroscopy.

10)Modern Methods:

1. Dynamic Light Scattering (DLS)

2. Zeta Potential Measurement.

3. Micro dissolution Testing.

-Methods Solubility Enhancement:

1. Co-solvency.

2. Surfactant Addition.

3. Complexation (e.g., cyclodextrins).

4. Nanoparticle Formation.

5.SOLID DISPERSION.

6. MICRONIZATION.

7. AMORHIZATION.

RECENTLY RESECHES;

1. Simvastatin reduces cardiovascular events in patients with chronic kidney disease (CKD) (Journal of the American Society of Nephrology, 2022)

2. Simvastatin improves cognitive function in patients with Alzheimer's disease (Neurology, 2022)

3. Simvastatin decreases mortality risk in patients with heart failure (Journal of Cardiac Failure, 2022)

4. Simvastatin reduces inflammation in patients with rheumatoid arthritis (Arthritis & Rheumatology, 2022)

5. Simvastatin enhances anti-cancer effects of chemotherapy in breast cancer cells (Cancer Research, 2022)

Ongoing reserch

1. Evaluating Si mvastatin's efficacy in reducing cardiovascular events in patients with type 2 diabetes (link unavailable), NCT04567823).

2. Investigating Simvastatin's effects on cognitive decline in older adults ((link unavailable), NCT04363359).

3. Assessing Simvastatin's safety and efficacy in patients with liver disease ((link unavailable), NCT04111676). Research A

Emerging ongoing research:

1. Simvastatin's potential anti-viral effects against COVID-19

2. Simvastatin's role in modulating the gut microbiome

3. Simvastatin's effects on bone health and osteoporosis

4. Simvastatin's potential benefits in neurodegenerative diseases (e.g., Parkinson's, multiple sclerosis)..

SIMVASTATIN SOLUBILTY DATA:

1 Water: 0.012 mg\ml.

2.Ethanol:10.4 mg\ml.

3.methanol:20.6 mg\ml.

Method are found for enhancement solubility of simvastatin**;**

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Technique	Methods	Polymer	Reference
Inclusion complex formation techniques	Anti-solvent induced-crystallization method	Polymer not involved	Varshosaz et al. (18)
	Simple physical mixing, kneading and spray drying methods	Hydroxypropyl β-cyclodextrin	Shiralashetti et al. (19)
	Simple physical mixing, kneading and fusion methods	Polyethylene glycol PEG 6000 (PEG) 4000, or hydroxypropyl β-cyclodextrin	Mandal et al. (25)
	Supercritical anti-solvent (SAS) method	Hydroxypropyl β-cyclodextrin	Jun et al. (26)
Solid dispersion techniques	Combination of adsorption equilibrium and solvent evaporation method	Polymer not involved	Zhang et al. (30)
	Solvent evaporation by spray drying and rota-evaporation methods	Hydroxypropyl methylcellulose-K3LV	Pandya et al. (34)
	Physical mixtures and melting method	Polyethylene glycol-4000	Silva et al. (35)
	Ball milling method	Polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA64)	Zhang et al. (36)
	Spray drying method	PVP	Ambike et al. (37)
Solubilization by surfactants techniques	Solvent evaporation from spontaneously formed oil-in-water micro-emulsions method	Polymer not involved	Margulis-Goshen and Magdassi (38)
	Self-microemulsifying method	Polymer not involved	Meng and Zheng (39)
	Microemulsion method	Polymer not involved	Lee et al. (40)
	Emulsification method	Polymer not involved	Ding et al. (41)
	Antisolvent recrystallization method	Polymer not involved	Oh and Lee (42)
Particle size reduction techniques	Milling method	Polymer not involved	Zimper et al. (43)
	Nano-precipitation method		Patil et al. (45)

Simvastatin is a lipophilic statin with poor aqueous solubility (approximately 0.003 mg/mL), limiting its bioavailability.

Solubility Enhancement Techniques:

1. Nanoparticles

2. Solid dispersions

3. Inclusion complexes (e.g., cyclodextrins)

4. Micronization.

5. Self-emulsifying drug delivery systems (SEDDS)

6. Liposomes

7. Hydrorophylic polymers (e.g., HPMC, PVP).

Solubility Enhancers:

1. Hydroxypropyl methylcellulose (HPMC)

2. Polyvinylpyrrolidone (PVP)

3. Sodium lauryl sulfate (SLS)

4. Poloxamer 188

5. Vitamin E TPGS

Patent:

1. US Patent 7,101,840: Nanoparticle formulation of simvastatin

2. US Patent 8,119,630: Solid dispersion of simvastatin with HPMC

3. US Patent 9,044,470: Self-emulsifying formulation of simvastatin

Physical Properties:

1. Molecular weight: 418.57 g/mol

2. LogP (octanol/water partition coefficient): 4.68

3. Solubility in water: 0.003 mg/mL (pH 7.4, 25°C)

4. Melting point: 135-140°C

6. Chloroform: 20 mg/mL

7. Ether: 5 mg/mL.

Solubility in Various Solvents:

1. Water: 0.003 mg/mL

2. Ethanol: 10 mg/mL

3. Methanol: 20 mg/mL

4. Acetonitrile: 5 mg/mL

5. DMSO: 50 mg/mL

Solubility Enhancers:

1. Hydroxypropyl methylcellulose (HPMC)

2. Polyvinylpyrrolidone (PVP)

3. Sodium lauryl sulfate (SLS)

Efficacy of various techniques used to increase simvastatin solubility

The increase in solubility achieved by each technique i. The values presented were the results of solubility and/or dissolution testing and the numerical values in various units were standardized as the solubility increase, in times (solubility of the simvastatin product / solubility of simvastatin alone), so that they could be compared.

It can be observed that the greatest number of published experiments occurred in SD, while the highest increases were found in ME and NP, the highest reported result being found in ME: an increase of 50 times

. The second best result was from the drug-dendrimer technique (G4-PAMAM–PEG: 33-fold increase in the solubility of simvastatin). It is important to note that the mechanism responsible for the increase in the aqueous solubility of simvastatin varied among the different methods.

CONCLUSION:

The solubility of simvastatin is a critical factor influencing its bioavailability and therapeutic effectiveness. Various studies indicate that its solubility can be affected by several factors, including pH, temperature, and the presence of different solvents or excipients. Enhancing the solubility of simvastatin through formulation strategies such as salt formation, solid dispersions, or the use of surfactants can significantly improve its absorption and overall clinical efficacy. Continued research into novel solubilization techniques will be essential

for optimizing simvastatin delivery and maximizing its benefits for patients managing hyperlipidemia

Objective:

Simvastatin is a medication used to lower cholesterol, but it doesn't dissolve well in water. Instead, it is more soluble in organic solvents like ethanol. Because of its poor water solubility, it can be challenging for the body to absorb effectively.

To improve how well it works, scientists often use special techniques in its formulation, such as creating tiny particles or mixing it with other compounds to help it dissolve better. This helps ensure that patients get the full benefits of the medication. If you have more specific questions about simvastatin or its solubility.

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