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Research Article

Enhancement of the Solubility of Simvastatin by Utilizing Two Distinct Types of Excipient Compositions, L-Isoleucine and Sodium Docusate

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ABSTRACT

The solubility of a drug plays an important role in determining its bioavailability and the subsequent effect it has on the body as a whole. Simvastatin is a BCS class II drug, classified as having high absorbability but low solubility. The study objective is to increase the solubility of simvastatin by using two excipients: sodium docusate and L-isoleucine. These excipients were incorporated in a solid dispersion at different ratios, left to dry, dissolved, and tested for increased solubility against a simvastatin calibration curve (which was prepared using a standard solution of simvastatin). The improvement in solubility for a 4:1:1 ratio was approximately 1.5-fold. A 2:1:1 ratio of simvastatin: docusate: isoleucine increased solubility more than 7-fold, and a 4:3:3 ratio increased the solubility nearly 5-fold. The synergistic effect of docusate and isoleucine showed improvement in the solubility of simvastatin at room temperature when incorporated in relatively low ratios.

Keywords: L-isoleucine, simvastatin, sodium docusate, solubility

INTRODUCTION

Drugs that are easily or completely soluble in the gastrointestinal (GI) media show complete oral absorption, resulting in high plasma levels or bioavailability. About 40% of drugs are practically insoluble in water and as such have slow absorption, which results in inadequate and unequal bioavailability, and GI toxicity.[1] Thus, the most critical phase and important aspect of drug development, especially for oral formulations, is the improvement of drug solubility and, consequently, its oral bioavailability. Bioavailability is defined as the amount of therapeutically active drug that enters the bloodstream, or systemic circulation, and is readily available at the drug's site of action. There are two reasons put forth for the low aqueous solubility of drugs:[2] (a) high lipophilicity and (b) strong intermolecular forces that cause the difficulty in solubilization of drugs.[3] Dissolution, which depends on solubility, is the rate-limiting step for both the rate and degree of drug absorption. Figure 1 shows an important insight into the relationship between solubility and permeability. As shown in Figure 1, the two factors of solubility and absorption form four classes of drugs. Many classic drugs, such as digoxin, piroxicam, chlorothiazide, and griseofulvin, as well as most new innovative pharmacological compounds, exhibit poor water solubility.[4] Here, excipients play a significant role in improving these compounds. In oral medications like simvastatin, the drug is required to be dissolved in gastric fluids to have better absorption and bioavailability.

Low aqueous solubility is one of the features of BCS class II and IV drugs and is a significant hurdle for drug development and delivery. Multiple technologies have been implemented to enhance the bioavailability of poorly water-soluble drug compounds, including solid dispersions, lipid-based formulations, co-precipitation, micronization, solvent evaporation, liquid–solid compacts, and solvent deposition inclusion complexation. Some commonly used excipients are hypromellose acetate succinate, cyclodextrin, povidone, hydroxypropyl cellulose, polyethylene glycol, sodium lauryl sulfate, and more.[6]

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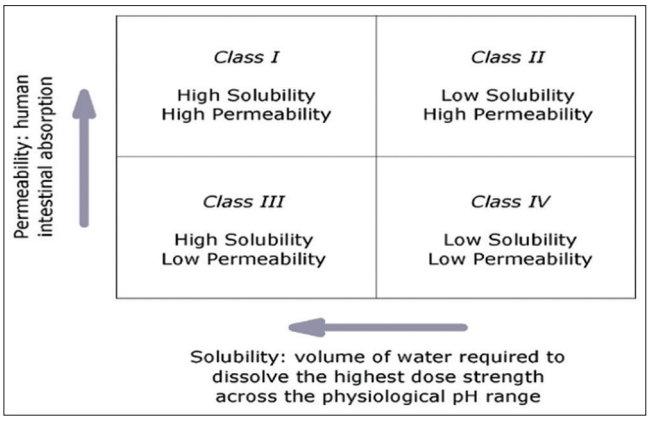

Figure 1: BCS categories[5]

Figure 2 shows the classification of drugs based on solubility in water.

Simvastatin is a chemical derivative of lovastatin. It is a prodrug that lowers cholesterol levels by inhibiting liver cholesterol synthesis through inhibition of HMG-CoA reductase, and also by increasing low-density lipoprotein (LDL) receptors present on the liver's surface. Simvastatin, in patients with heterozygous familial hypercholesterolemia, reduces the total cholesterol and LDL cholesterol, and as a secondary action tends to reduce triglycerides and increase high-density lipoprotein cholesterol levels. This medication is also effective in patients with familial dysbetalipoproteinemia, polygenic hypercholesterolemia, and nephrotic syndrome where an excess of helpful proteins is lost.[8]

Chemically, simvastatin is a part of the class of hexahydronaphthalenes that includes lovastatin, in which the 2-methylbutyrate ester moiety has been replaced by a 2,2-dimethylbutyrate ester group as shown in Figure 3. Physiologically, simvastatin has a role as an HMG-CoA inhibitor, aLF endopeptidase inhibitor, a geroprotector, and a ferroptosis inducer.

There are multiple chemical classes that simvastatin belongs to: semi-synthetic statin, as well as a fatty acid ester and a delta-lactone.[9] It is a BCS class II drug, which, as mentioned previously, means it has low solubility in water but high absorption. The solubility is 0.012 g/L, or 0.012 mg/mL, which officially categorizes it as insoluble in water, according to the United States Pharmacopeia. The USP requires a drug to have a solubility of 33 mg/mL or more to be considered soluble, as shown in Figure 2. This is the problem that this experiment will try to remedy. Simvastatin is, however, freely soluble in ethanol, methanol, and chloroform.[10] It has a melting point of 135–138°C. The log K_{ow}, or octanol-water partition coefficient, is 4.68.[11]

Simvastatin is found as a white to off-white crystalline powder, and it has a molecular weight of 418.57g/mol. It is nonhygroscopic.[12]

Sodium docusate is the common pharmaceutical and chemical name of the anion bis (2-ethylhexyl) sulfosuccinate, also called dioctyl sulfosuccinate. Dioctyl sodium sulfosuccinate is used as a surfactant in many different applications. It is unique in that it can form microemulsions without the presence of

Solubility definition in the United States Pharmacopeia

Description forms (solubility definition)	Parts of solvent required for one part of solute	Solubility Range (mg/mL)
Very soluble	<1	>1000
Freely Soluble	1 to 10	100-1000
Soluble	10 to 30	33-100
Sparingly Soluble	30 to 100	10-33
Slightly Soluble	100 to 1000	1-10
Very slightly Soluble	1000 to 10,000	0.1-1
Practically insoluble	>10,000	<0.1

Figure 2: Solubility definition[7]

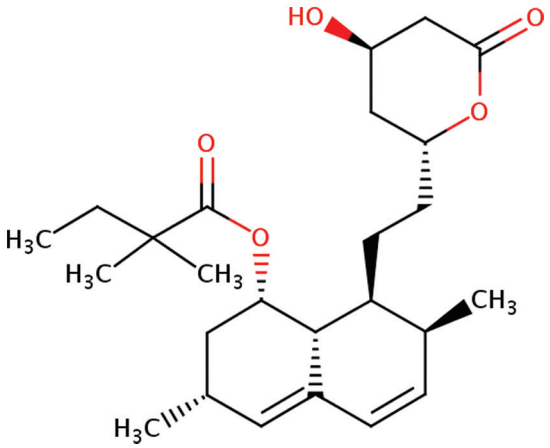

Figure 3: Simvastatin structure[13]

co-surfactants, and it has varied aqueous-phase actions, which include several liquid crystalline phases.[14] The compound is a white, wax-like, plastic solid and has an odor reminiscent of octanol. It starts to degrade at 220°C. The solubility of dioctyl sodium sulfosuccinate in water is 14 g/L at 25°C.[15]

Solubility of docusate is better in solvents with a lower polarity, with ratios of 1:30 in ethanol, 1:1 in diethyl ether and chloroform, and practically unlimited in petroleum ether, all at room temperature (25°C). In general, its uses include a wetting agent, anionic surfactant, solubilizer, and fecal softener.[16] The chemical structure of sodium docusate is shown in Figure 4.

Sodium docusate has anionic surfactant properties that are useful in solid dispersion and that enhance the wettability of the molecules they attach to, and the more solvation that occurs, the more soluble the compound becomes.[17] Surfactants in general form micelles; these micelles form at a certain concentration, called the critical micelle concentration (CMC), and work to solubilize insoluble products, with an increase in the amount of surfactant correlating to an increase in solvation and solubilization.[18]

The CMC depends on the molecular and chemical properties of the surfactant, such as polarity and charge. Micelles are normally made up of amphiphilic polymers which mean they have both hydrophilic and hydrophobic parts. The best size for micelles is 10–100 nm, and in aqueous solutions, they spontaneously assemble to form sphere- or sphere-like shapes, with a hydrophobic core and hydrophilic external shell. Due to these properties, simvastatin, or other drugs with low water solubility, can dissolve in micelles.[19]

Isoleucine is one of the essential amino acids. Isoleucine is required for hemoglobin formation, stabilization, and

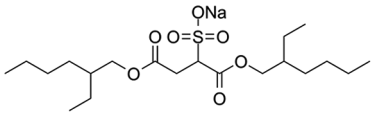

Figure 4: Sodium docusate structure[20]

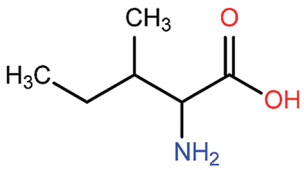

Figure 5: L-isoleucine structure[26]

regulation of blood sugar and energy levels. It is one of the three branched-chain amino acids, and these amino acids increase endurance, improve energy, and help in muscle tissue repair. Isoleucine also has an important role in immunity.[21] Isoleucine is found as a white to off-white powder with a sweet odor.[22] The solubility of isoleucine is 34.4 g/L, with a molecular weight of 131 g/mol. Its boiling point is 168–170°C, with two pK_a values: 2.32 and 9.76.[23] The structure of L-isoleucine is shown in Figure 5.

Amino acids have already proven effective in enhancing the solubility of simvastatin.[24] Isoleucine has, in previous experiments, been used to improve the solubility of atorvastatin with positive results, and here those properties were shown to be even more potent.[25] Isoleucine is also easily available, which makes it useful in solubility enhancement. Because both isoleucine and docusate are inert and have minimal side effects, they are acceptable excipients to use for improving solubility.

A solid dispersion is defined as a group of solid products consisting of a hydrophobic drug that is dispersed in at least one hydrophilic carrier, with a subsequent increase in surface area and thus enhanced drug solubility and dissolution rate. There are several advantages in using solid dispersion, such as increased wettability, easier formulation as a solid dosage form, and greater effectiveness in dissolution when compared to salt preparations, which require an ionized drug compound.[27] In addition, one of the most important advantages to using solid dispersion occurs with the interaction of hydrophilic carriers with the drug. This interaction can decrease agglomeration and release when there is supersaturation, which means a more rapid absorption, in addition to solubility, and consequently improved bioavailability.[28] Solid dispersion also produces amorphous forms of simvastatin, which have a higher solubility than crystalline simvastatin.[29]

The key idea in solvent evaporation is that the drug in question and a carrier are dissolved in a volatile solvent to achieve a homogeneous mixture. The solid dispersion is fully formed after the evaporation of the solvent.[27] It was used in this experiment for its relative ease and simplicity. The disadvantages of solvent evaporation include difficulty in fully removing the solvent and choosing a common solvent for the solutes.[30] Simple ethanol was satisfactory, however, in dissolving simvastatin and its excipients.

Many attempts at improving the solubility of simvastatin have been made, using various methods, most commonly with solid dispersions. In one such attempt, arginine was used as a cosolvent with simvastatin in different molar concentrations, and the results showed a massive improvement in the aqueous solubility of the drug. The final maximum solubility showed an incredible almost 13,000-fold improvement, in which the intrinsic solubility jumped from 0.003164 mmol/mL to 70.4 mmol/mL.[24] The authors' proposed explanation for this increase is the formation of a more favorable environment for the solubility of simvastatin. This is achieved through both solute-solvent and solute-cosolute interaction in which the arginine forms a complex with the simvastatin, making it more polar and readily soluble.

Another experiment improved simvastatin's solubility more than 5-fold using polymeric blends of polyvinylpyrrolidone and similar substances, with solid dispersion. This time, however, no solvent was used. Instead, the hot melt and twin-screw melt granulation methods were used. The release profile of these mixtures was the same as that of normally formulated simvastatin. In one of their product results, the values showed a large increase in miscibility, but not a proportional increase in solubility, which shows they are not always directly correlated.[31]

Yet another experiment utilized citric acid and co-crystallization as a method in the improvement of simvastatin's solubility.[32] This showed an increase in solubility, and also in the release profile and stability of the drug. Simvastatin has even been used topically to improve wound healing, and an experiment was done to enhance topical simvastatin's solubility to make it more practical to use externally.[33] The experiment used various solvents such as buffered ethanol, methanol, and dimethyl sulfoxide, along with polymers such as chitosan, and cellulose derivatives such as carboxymethyl cellulose and hydroxypropyl methyl cellulose. The findings showed a remarkable 50-fold increase in simvastatin's solubility with ethanol and chitosan.

The objective of this experiment is to improve the solubility of simvastatin by forming a solid dispersion, using the solvent evaporation method with ethanol as in previous experiments, with sodium docusate and L-isoleucine combined in various ratios in order to ascertain which combination has the greatest improvement. All the ingredients are easily available, making it easy to fine-tune all the measurements in repeated experiments.

INSTRUMENTS AND METHODOLOGY

Materials and Instruments

- Simvastatin 100 g (powder form) as shown in Figure 6
- L-isoleucine 100 g Simson brand (powder form)
- Sodium docusate 50 g (semisolid form)
- Ethanol 100%
- Distilled water
- Volumetric flasks (10 mL)
- Pipette
- Graduated cylinder (25 mL)
- Mortars and pestles (ceramic and glass)
- Filter paper, Whitman brand (42 ashless)
- Various beakers (10, 20, and 50 mL)

- Highly accurate balance
- Spectrophotometer
- Magnetic stirrer and heater
- Oven (set at 32°C).

Methodology

Two solvents were prepared in separate beakers, both consisting of 80 mL of pure ethanol and 20 mL of distilled water. Ten milligrams (mg) of simvastatin were added to one beaker, which resulted in a concentration of 10 mg/100 mL (100 μg/mL) and was used as the stock solution. The solvent without simvastatin was used as a diluting agent for the linear dilution process.

For this process, 1 mL of stock solution was poured into a 10-mL volumetric flask using a pipette and then diluted to 10 mL using the dilution agent. This gave a concentration of 10 μg/mL (Flask 1). Flask 2 had 1.5 mL of the stock solution and was also diluted to 10 mL with the diluting agent, to produce a flask of 15 μg/mL. This process was repeated until concentrations of 10, 15, 20, 25, 30, and 35 μg/mL were made. A saturated solution of simvastatin was also made by adding 10 mL of distilled water to a small beaker, where a magnetic stirrer was added at 900 rotations. Then, simvastatin powder was slowly added until saturation, which was evident by a turbid solution and a persistent powder being present on the bottom of the container. The filter paper was used to strain the solution, and it was measured in a quartz cuvette in the spectrophotometer.

The spectrophotometer was calibrated by setting the device to scan mode from 200nm to 400 nm and putting the diluting agent as the test sample to form the reference and cancel all external factors. The spectrophotometer was also used to create a wavelength intensity chart from the saturated simvastatin solution; then the highest peak, at 252 nm, was chosen as the maximum wavelength (λ_{max}). Once this was found, each of the test samples of concentrations 10–35 μg/mL was measured three times and plotted. A calibration curve was fitted to the plotted absorbance values. After this plotting, the absorbance of the saturated simvastatin was measured in the same way, and the concentration was calculated using the reverse of the calibration curve equation.

The solubility-modifying agents were L-isoleucine and sodium docusate. In combining them, the first sample was made of 1 g simvastatin and 0.25 g each of sodium docusate and isoleucine; the second sample was 1 g simvastatin and 0.5 g each of docusate and isoleucine, and the third sample was 1 g simvastatin and 0.75 g each of docusate and isoleucine. The combination ratios are shown in Table 1. These components were weighed separately on an accurate scale and then combined in a mortar and pestle. A sufficient amount of ethanol was added to submerge all the ingredients in the mortar, where they were manually levigated until a single-phase solution was formed for complete homogenization. The samples were left in a hot air oven for several days to dry, and the dry products were taken out and ground into a powder with a pestle. These products were made to be incorporated into modified-simvastatin solutions.

Table 1: Excipient ratios

Sample	Simva.(g)	Docus.(g)	Isoleuc.(g)	Ratio
S1	1	0.25	0.25	4:1:1
S2	1	0.50	0.50	2:1:1
S3	1	0.75	0.75	4:3:3

The modified solutions were prepared by adding 10 mL of distilled water in a small 20-mL beaker and placing it on the magnetic stirrer plate, while small amounts of the powdered product were added to it until saturation. It was kept at 900 rpm for 10-min intervals until there was evident precipitation.

Finally, filter paper was used on the solution, and it was put in a cuvette to measure with a spectrophotometer, where the reading was repeated 3 times. This was done for all products before the final absorbance measurements.

RESULTS AND DISCUSSION

Results

The results of the calibration curve are shown in Table 2.

The recorded absorbance values shown in Table 2 were plotted to get the best-fitting curve presented in Figure 7. The fitting curve represents the actual values with an equation of y = 0.00303x-0.00051 which relates absorbance with concentration, where *y* is the absorbance and *x* is the concentration.

When mathematically reversed, the equation of best fit can form a new equation, which is written as $x = \frac{y + 0.00051}{0.00303}$, and it can be used to find the concentration of the saturated simvastatin solution from absorbance, as shown in Table 3.

Table 4 contains the results of the absorbances and solubilities of the simvastatin: docusate: isoleucine solid dispersion mixtures.

The solubility of Sample 1, Sample 2, and Sample 3 was increased 1.5-fold, 7.18-fold, and 4.8-fold, respectively, from the solubility of pure simvastatin.

Discussion

The smallest concentration of 1 g simvastatin to 0.25 g of excipients yielded the smallest improvement of only 1.5-fold.

Table 2: Simvastatin absorbances

Conc. (μg)	Abs. 1	Abs. 2	Abs. 3	Avg. Abs.
10	0.0280	0.0305	0.0258	0.0281
15	0.0448	0.0448	0.0446	0.0447
20	0.0595	0.0645	0.0623	0.0621
25	0.0788	0.0802	0.0757	0.0782
30	0.0881	0.0858	0.0874	0.0871
35	0.1060	0.1035	0.1068	0.1054

Table 3: Saturated simvastatin

Abs. 1	Abs. 2	Abs. 3	Avg. abs.	Conc (μg/mL)
0.1969	0.1979	0.1954	0.1967	65.085

Table 4: Simvastatin, docusate, isoleucine concentration

Sample	Abs. 1	Abs. 2	Abs. 3	Avg. abs.	Conc.(μg/mL)
1	0.293	0.296	0.294	0.294	97.495
2	1.447	1.408	1.392	1.416	467.53
3	0.943	0.948	0.949	0.947	312.78

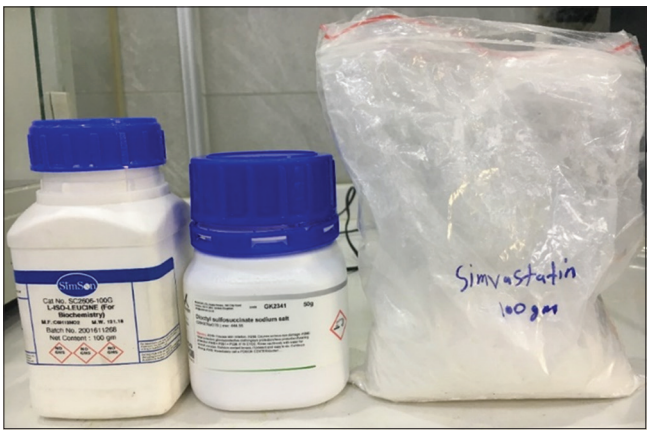

Figure 6: Starting materials

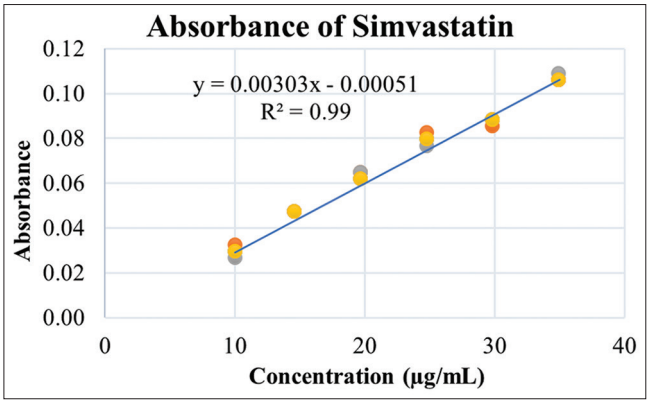

Figure 7: Simvastatin calibration curve

A possible theory could be that 0.25 g is below the CMC of sodium docusate, which would mean it is too low to allow micelles to form. At this concentration, there may be only weak solubilization due to isoleucine alone or weak anionic interaction with docusate, without its strong surfactant properties. Based on the results given, there seems to be a range at which the excipients have optimal solubilizing effects, and this is at around a 2:1 ratio with simvastatin: excipients.

The 2:1:1 sample ratio showed a sevenfold improvement while the 4:3:3 ratio was improved fivefold. This indicates that an excess of docusate and isoleucine may hinder the solubility process. This could be due to interactions with the chemical bonds of simvastatin or due to the saturation of the solution preventing further solubility. Theoretically, the formation of sodium docusate micelles may be hindered at specific concentrations of isoleucine, which would require more refinements to determine for certain.

A possible mechanism may involve the interaction between the anionic, i.e., the negative part of sodium docusate, and the potentially positive amine group in isoleucine, or amino acids in general. If this is the case, substituting an amino acid with an exposed positive group, such as lysine, arginine, or histidine, may yield even more positive results. This is supported by the fact that adding arginine into the solution resulted in a huge improvement in the solubility of simvastatin.[24] Isoleucine may also have formed a complex with the simvastatin, making it more polar and soluble, as in the experiment with arginine. Arginine has multiple NH groups, while isoleucine only has one, and that may contribute to its greater effectiveness. On the other hand, a more negatively charged amino acid may decrease the effectiveness of the excipients' actions alone or together.

In the dissolution process for each ratio, the time required until complete saturation varied. The lowest excipient concentration of 4:1 simvastatin: excipients required only about 15 min on the magnetic stirrer due to the relatively low solubility of the product. The middle sample, with a 2:1 ratio, took much longer, at about 45 min. The final ratio of 4:3 took 1.5 h to solubilize and become saturated, even though ultimately, it had a lower simvastatin concentration in the solution. This may be due to the drying out of the excipients to form a physical coating, similar to a hard shell, that did not allow water to penetrate past it. Another possibility is that micelle formation was not completely successful and resulted in incomplete solubilization for some of the particles, as a result of excess saturation, interaction with isoleucine or simvastatin, or another unknown mechanism.[34]

Although some positive results were found, there were many combinations and ratios that did not yield satisfactory solid dispersions, and these occurred when too much isoleucine or docusate was added. When large amounts of docusate were incorporated into the mixture, the product did not dry correctly and stayed as a jelly-like semisolid. This made it impossible to grind into a powder and to dissolve into water easily. A viscous liquid that did not pass through the filter paper was the result of attempting to solubilize it.

With excess isoleucine added to the mixture, the product did not dry into a powder, and there was a distinct separation between the two layers of the solution, with a turbid supernatant on top and a thick yellowish layer on the bottom. In solutions that had a 1:3 ratio of isoleucine in a 1g: 3g mix, there was adequate drying of the solution into a solid, but there was an inhomogeneous product obtained, which meant the isoleucine was unevenly distributed. This could be due to precipitation,[35] or uneven solvation and solid dispersion formation due to high solution saturation. The percentage of isoleucine in the solution should not be dramatically more than simvastatin to have a stable solid dispersion.

The final concentration of the modified simvastatin in water is not enough to change its classification from being insoluble to soluble, though it is certainly a step in the right direction. As previously mentioned, in order to be classified as soluble, a drug must have a solubility of 33 mg/mL or more, according to the USP. The smallest improvement resulted in a solubility of 97.5 μg/mL, which is still within the "insoluble" category. The next higher solubility was 312.8 μg/mL, which is 0.3 mg/mL. This is enough to take simvastatin out of the "insoluble" category and raise it to "very slightly soluble" category. The greatest change was 467.5 μg/mL, which is approximately 0.5 mg/mL. This also removes simvastatin out of "insoluble" and to "very slightly soluble." Though these findings are modest when looked at in the absolute, they represent an open pathway that may lead to greater improvements if certain variables and parameters are changed.

For example, a change in the amino acid used may yield different results. A combination of amino acids with another form of surfactant, such as certain polymers, may allow for greater solubility depending on the strength of the surfactant. Another form of solvent may be used in place of ethanol, such as chloroform or acetone and water, which may affect the extent of homogeneity or dissolution, and thus affect the resulting solid dispersion.

A study to determine the exact drug content of the solid dispersion after it is dissolved in water may be helpful to understand how much of the solid dispersion is truly effective material. It will also give a clue about what excipient played a bigger role in the simvastatin's solubility or lack thereof.

CONCLUSION

In this experiment, simvastatin was incorporated into a solid dispersion of docusate and isoleucine to improve its solubility. The best improvement had a 7-fold increase from normal simvastatin, with 1.5-fold being the lowest improvement. The best improvement corresponds with a 2:1:1 ratio of simvastatin and excipients.

These results indicate that the surfactant properties of docusate in conjugation with isoleucine improve the solubility of simvastatin to a large degree. This combination is optimized when the ratio of excipients is relatively low compared to the mass of simvastatin. In future, a study can be done that replaces the solvent with something similar, or the sodium docusate with a polymer surfactant. Another measure could be to calculate how much simvastatin is found per milligram of solid dispersion, which may provide insight into the content of each solution, and how much of the mixture is actually an active ingredient.

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