Revista de Ciências Farmacêuticas Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

Rev Ciênc Farm Básica Apl., 2012;33(4):497-507
ISSN 1808-4532

Strategies used for to improve aqueous solubility of simvastatin: a systematic review

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ABSTRACT

A great variety of molecules with potential pharmacological activity have been discovered. However, the great majority of these molecules have poor bioavailability, mainly associated with their low solubility in water. Lately, a great deal of attention has been paid to existing drugs that are used chronically in the treatment of high levels of cholesterol and triglycerides. Among these drugs, simvastatin is the most frequently used, despite its poor solubility in water. This review discusses some of the strategies that have been used to enhance the aqueous solubility of simvastatin over the last 12 years (January 2000 – April 2012). Techniques employing solid dispersions, microencapsulation, supercritical fluid and the cyclodextrin inclusion system are described and systematically compared.
Keywords: Simvastatin. Solid dispersions. Solubility.

INTRODUCTION

The solubility of pharmaceutical drugs has in recent times been widely discussed by researchers in industry and academia. This is because day by day it is becoming harder to discover previously unknown molecules with pharmacological activity, so attention is now turning to molecules that are already established as drugs but suffer from some restriction, among which those with low aqueous solubility can be highlighted. This group includes Class II and IV drugs of the Biopharmaceutical Classification System (BCS), since Class II drugs have low aqueous solubility and high intestinal permeability, while Class IV drugs have low aqueous solubility and low intestinal permeability. In Class II drugs, the limiting factor for absorption is thus the aqueous solubility.

The Biopharmaceutical Classification System (BCS), as proposed by Amidon et al. (1995), is an important research tool, as it classifies drugs according to their bioavailability, on the basis of the parameters aqueous solubility and intestinal permeability. Therefore, drugs can be placed in one of the four groups shown in Table 1.

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Table 1. Groups of drugs in the Biopharmaceutical Classification System (BCS)

CLASS	AQUEOUS SOLUBILITY	INTESTINAL PERMEABILITY
I (Amphiphilic)	High	High
II (Lipophilic)	Low	High
III (Hydrophilic)	High	Low
IV (Hydrophobic)	Low	Low

It can be seen that Class I drugs are the only ones that have no problems related to bioavailability, whereas those in Class IV are the least easily absorbed by the oral route and therefore the most challenging (Amidon et al., 1995).

In this context, simvastatin, a well known statin with antilipemic activity, can be classified as a Class II drug (BCS) (Kasin et al., 2004).

The aim of this article is to report scientific articles published in the period January 2000 - April 2012, in which the enhancement of simvastatin solubility is described, comparing the various techniques and results. According to techniques used, the articles were grouped as follows: Solid Dispersion (SD), Microemulsion (ME), Nanoparticles (NP), Supercritical Fluid (SF), Cyclodextrin Inclusion Complex (CD) and Dendrimer Complex (DE); some of the articles were allocated to more than one group. Emphasis has been given to the physicochemical interactions that occur in SDs, as these have been widely studied with simvastatin and are easily prepared, promising for increasing the oral bioavailability of poorly soluble drugs and readily scaled up to the industrial scale (Silva, 2009).

Regarding the pharmacological approach, this has been highlighted for only a few articles, because of its importance to the results, as this is not the concern of this review.

The term solubility can be defined as the amount of a solute that can dissolve in a fixed volume of solvent at a given temperature. Although the definition of solubility sounds simple and straightforward, it has been the cause of confusion, as there are such a lot of variables involved. Solubility can be determined by kinetic and thermodynamic methods, the former being the commoner, though these are strictly dependent on time as well as the degree of saturation of the solution.

In addition, solubility is affected by factors such as particle size (the smaller the particles the greater the

solubility), temperature (generally, higher temperatures increase the solubility), pH of the medium (e.g. drugs with pKa in the acidic range are more soluble in alkaline media). The use of some excipients can sometimes enhance the solubility of drugs, as it can lead to the formation of polymorphs that are sometimes less soluble than the parent drug (Almeida, 2009).

Several strategies have been used to enhance the aqueous solubility of poorly soluble drugs. These include the reduction of the degree of crystallinity of the drug, decrease in the particle size and the formation of eutectic mixtures, co-crystals and salts (Alsenz & Kansy, 2007).

By increasing the aqueous solubility of poorly soluble drugs, it is possible to improve their bioavailability. This applies to simvastatin, about 95% of whose molecules bind to serum proteins and only 5% are absorbed. Thus, in order to overcome the poor bioavailability of this drug, a higher dose is used, which increases the chance of causing toxicity and side effects (Rang et al., 2004).

Simvastatin is in reality a prodrug with an inactive lactone, which is metabolized in the liver to its active form (the corresponding ß-hydroxyacid), as shown here in Figure 1 (Ungaro et al., 2011).

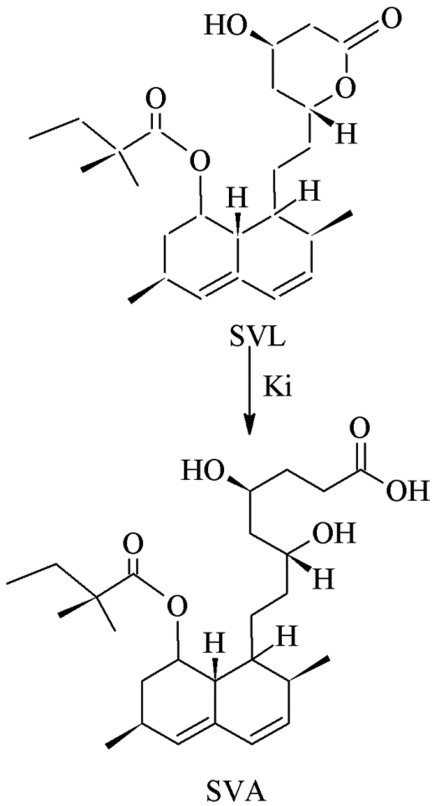

Fig. 1: Simvastatin lactone prodrug (SVL) conversion to form active ß-hydroxyacid (SVA). (Ungaro et al., 2011);

Dissolution versus Solubility

Drug dissolution rate can be defined as the amount of drug in the solid state or a solid dosage form that goes into solution in a certain amount of time. In the dissolution test, the drug solubility is the main parameter that affects the rate of dissolution (Banakar, 1992).

Therefore, the dissolution test is the main tool used to determine the aqueous solubility of drugs, as well as to study the *in vitro* drug release profile. The dissolution media are chosen with the purpose of simulating the *in vivo* conditions in which drug absorption is likely to occur. Buffers are generally used to match the pH values of the stomach or small intestine and specific enzymes can also be used. In addition, adequate stirring and heating are provided. In order to assess the amount of drug that has been dissolved in the medium, aliquots are withdrawn from the solution at fixed time intervals and analyzed to determine the drug concentration.

Standard dissolution tests are described in the pharmacopoeia and the methods vary with the dosage form. Table 2 lists the different types of dissolution apparatus defined in the United States Pharmacopeia (USP) and the main application of each, according to Storpirtis et al. (2009).

Table 2. USP dissolution apparatuses and their respective uses.

DISSOLUTION APPARATUS	USE
Basket (USP apparatus I)	Capsules
Paddle (USP apparatus 2)	Tablets
Reciprocating cylinder (USP 3)	Extended and controlled drug release dosage forms
Flow-through cell (USP 4)	All dosage forms except for chewing gums and transdermal patches.
Paddle over disk (USP 5)	A variation of apparatus 2. It is used to evaluate transdermal patches.
Rotating cylinder (USP 6)	This is simply a modification of apparatus 1. Mainly used for transdermal patches.
Reciprocating holder (USP 7)	Allows the attachment of different holders and therefore it can be used to test transdermal patches and osmotic pump pellets.

***In vitro* Permeation Study**

Besides the dissolution test, the *in vitro* permeation study is usually done while ensure the solubility and bioavailability of drugs. According to the BCS, the permeation study is essential, since an increase in aqueous solubility can decrease intestinal permeability (Amidon et al., 1995).

The *in vitro* permeation study is performed with the aid of experimental models based on tissues extracted from parts of the intestine, as well as cell cultures prepared from Caco-2, TC-7, 2/4/A1, MDCK and MDCK-MDR1 cells. Caco-2 cells are harvested from a human colon adenocarcinoma line and are differentiated into enterocytes, which can be attached to the dissolution apparatus. Although these techniques are important tools for determining the dissolution/permeation properties of drugs, they are not able to mimic properly some of the transport phenomena, such as active transport (Souza et al., 2007).

SOLUBILITY ENHANCING TECHNIQUES

According to Storpirtis et al. (2009), some methods can be used to enhance a drug's solubility without changing

its chemical structure. Table 3 lists and briefly describes each of these methods.

Table 3. Methods used to improve the aqueous solubility of drugs.

METHOD	DescrIPTION
Micronization	Reduction of drug particle size to below 10 µm.
First generation solid dispersion	Formation of eutectic mixtures between drugs and water-soluble carriers such as urea and mannitol.
Second generation solid dispersion	Decrease in the drug's crystallinity by mixing with amorphous polymers such as peg, pvp and cellulose derivatives. This technique allows the formation of solid solutions, solid suspensions or a simple physical mixture of drug and polymer.
Third generation solid dispersion	Mixture with surfactants (gelucire 44/14, polysorbates, etc.), Which can increase the drug's solubility by decreasing its interfacial tension.

On the other hand, Solid Dispersions (SD) can be produced by several further methods, as described in Table 4.

Table 4. Methods to obtain solid dispersions

fusion	The drug is melted inside the carrier and the system is cooled down and then micronized. The melting process has the purpose of dissolving or dispersing the drug into the carrier, and the cooling process is responsible for the solidification of the mixture, which facilitates the micronization. However, this technique is not suitable for thermolabile drugs.
Solvent evaporation	The drug is dissolved in a suitable solvent and dispersed in the carrier, where it is evaporated with in a rotary evaporator, dried in an oven or spray-dried.

In addition, spray-drying and supercritical fluid have been extensively used to improve the solubility of poorly water-soluble drugs:

Spray-drying – also known as drying by atomization, this method is based on the evaporation of the solvent by spraying the drug solution or suspension into a chamber with a current of hot air.

Supercritical fluid extraction – in this method, CO_2 is used above its critical temperature and pressure. First, the drug and carrier are dissolved in a certain solvent. Next, the solution is transferred to the equipment where the supercritical CO_2 extracts the solvent, forming the solid dispersion in small particles.

The term SD refers to the dispersion of one or more drugs in a matrix (usually a polymer) (Patel & Patel, 2008). In a drug-polymer mixture, physicochemical interactions occur with a loss of crystallinity of the drug and consequent increase in solubility. SDs are classified as physical modifications of drugs covered by a carrier (Leuner & Dressman , 2000).

There are many variants of techniques used to increase drug solubility, depending on the technique and on the nature of the matrix used. Often a particular technique is used, but the resulting mixtures undergo completely different interactions from those intended initially, because of the complexity of the mixtures. Therefore, a great number of characterization tests are needed, so that, when pooled, the data can provide an accurate assessment of the mixtures formed. The most commonly used analytical and characterization techniques are: Solubility Testing (ST), Dissolution Testing (DT), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), Fourier Transform Infrared (FTIR) Spectroscopy and Scanning Electron Microscopy (SEM).

Some explanations given for the increase in drug solubility when forming the SD are: decreased particle size, increased surface area, increased wettability due to the presence of hydrophilic carriers, the high porosity of the particles, the reduction or absence of clumping and aggregation and the possible presence of the drug in its amorphous form (Patel & Patel, 2008; Vasconcelos et al., 2007).

In the fusion-cooling technique, for example, a eutectic mixture is formed when two compounds are completely miscible in the liquid state (fusion) and to a limited extent in the solid state and, when cooled, they crystallize simultaneously at the eutectic composition. In this case, the matrix, which is soluble, envelops the drug and, in aqueous medium, dissolves rapidly, releasing the drug crystals as a fine powder; with such a large contact area exposed, the dissolution rate and, consequently, the bioavailability of the drug is enhanced (Sekiguchi & Obi, 1961; Goldberg et al., 1966).

In this last technique, there is an intention to change the crystalline drug to the amorphous form, but it is necessary to observe whether polymorphs are formed that act differently from the original drug or are inactive. In this context, Vargas et al. (2011) compared the physicochemical properties of simvastatin, after recrystallization from solvents dichloromethane, ethyl acetate, acetone and methanol, by XRD and IR analysis, with the original drug (control). The results showed no changes in the degree of crystallinity (amorphization), nor any physicochemical changes, demonstrating that simvastatin is quite stable in its crystalline form when dissolved in the solvents mentioned.

However, the fusion-cooling technique has a few limitations: for example, when there is no good miscibility between the drug and the carrier, dispersion may not occur; besides, the high temperature needed to melt the polymer (carrier) may degrade the drug. When organic polymers such as polyvinylpyrrolidone (PVP), polyethyleneglycol (PEG) or cellulose polymers are used, it is common for solid solutions to be formed, where the polymer is frequently present as an amorphous network, within which the drug is imprisoned. The molecules of the solute may also plasticize the polymer, resulting in a lowering of its glass transition temperature (Leuner & Dressman, 2000).

Regarding the SD with PVP, specifically, drug crystallization may be altered or inhibited, resulting in amorphous forms that are less thermodynamically stable and release the drug more rapidly. The inhibition may be due to hydrogen bonding between PVP and the drug or to the incorporation of drug molecules within the polymer matrix (Ford, 1986; Matsumoto & Zografi, 1999).

In the case of hydrophilic polymers such as cellulose derivatives (hydroxypropylmethylcellulose – HPMC, carboxymethylcellulose – CMC, etc.), semi-synthetic polymers (alginates, xanthan gum, chitosan, etc.) and acrylic polymers (carbomers) (Lopes et al., 2005), when in contact with water, the latter acts as a plasticizer, causing a change from the glass state (highly entangled polymer

configuration) to a malleable state, which is associated with a swelling/relaxation process (Colombo et al., 2000).

Regarding the use of PEG to produce SD, the researchers Leuner & Dressman (2000) state in their review article that the higher the proportion of carrier (PEG) relative to the drug, the greater is the chance of rendering the drug amorphous. Conversely, if a very large amount of drug is used relative to the carrier, there may be no dispersion, leaving large clusters of crystals, as can be confirmed by XRD.

In sum, SDs are of great interest, and they can easily be scaled up to the industrial scale, especially in solid pharmaceutical forms; they have great stability, lower manufacturing cost and allow dose-combination.

Cyclodextrin inclusion complexes

Cyclodextrins (CD) are soluble compounds that have a hydrophobic cavity where lipophilic drugs are incorporated. CD can be made by the degradation of starch, with 6, 7 or 8 glucose units, which are called α. ß and γ cyclodextrins, respectively. There are several ways of producing CD inclusion complexes, which are listed in Table 5.

Table 5. Methods of preparing CD inclusion complexes.

Kneading	Drug and CD are mixed with a small amount of water or hydroalcoholic mixture and the resulting material is dried in air or oven.
Coevaporation	The drug is dissolved in an appropriate solvent and an aqueous solution of CD is added. The mixture is stirred and dried under vacuum in a rotary evaporator.
Lyophilization	A drug-CD aqueous solution is prepared and then lyophilized, giving the resultant complex an amorphous character.
Spray-drying	The drug is first dissolved in ethanol and the CD in water and the two solutions are then mixed and subjected to spray-drying.
Extraction in supercritical fluid	After water is added to a mixture of drug and CD, the complex is transferred to a pressure chamber, where supercritical CO2 extracts the water, which is eliminated after depressurization.

The use of hydroxypropylmethylcellulose (HPMC) to increase the solubility of drugs was proposed by Mourão et al. (2011), who suggested the polymer be used together with ß-CD (at room temperature), as HPMC has limited aqueous solubility. A threefold increase in the solubility of praziquantel was achieved. The researchers also tried adding the HPMC and ß-CD to praziquantel and heating the mixture by autoclaving (120 °C for 20 minutes) and the result was a ninefold increase in the solubility of praziquantel (Mourão, 2012). In this case, inclusion complexes were formed instead of solid dispersions.

According to Cunha-Filho & Sá-Barreto (2007), inclusion complexes with CD have a wide range of application and can be produced on an industrial scale very efficiently by lyophilization and spray-drying, so that there are already about 30 medicines with this excipient on the world market.

Cyclodextrin inclusion complexes in liposomal dispersion

An interesting experiment was performed on ß-CD inclusion complexes with simvastatin and lovastatin dissolved in a liposomal dispersion of L-α-dipalmitoyl phosphatidylcholine (DPPC). First, liposomes were produced by dissolving DPPC in ethanol; a fraction of this solution was then added dropwise to an aqueous solution of ß-CD-statin. The mixture was sonicated and an opalescent solution was thus obtained. The complex obtained was compared with that formed with ß-CD-statin alone.

Phase-solubility studies and photon correlation spectroscopy (PCS) were used to assess the physical stability of the liposome (Csempesz et al., 2010). The results are summarized in Table 13.

Microemulsions (ME)

Microemulsions are defined as thermodynamically stable, isotropic, translucent mixtures of two immiscible liquids (usually water and oil), stabilized by an interfacial membrane of surfactant located at the oil/water interface, with particle size ranging from 10 to 300 nm. In order to form the microemulsion, it is necessary to have an intimate mixture of the two immiscible liquids. Initially, one of these liquids is dispersed into the other by mechanical stirring. The surfactant is then added, resulting in the formation of a homogeneous and stable mixture with an internal or dispersed phase (Damasceno et al., 2011).

Method of nanoencapsulation

Nanoparticles (ranging from 100 to 200 nm in size) prepared from aliphatic polymers are often used to entrap lipophilic drugs whose water solubility is extremely low. Regarding the methods of preparing nanoparticles, the use of preformed polymers is easier to control and the yield is higher than when they are prepared by the polymerization of monomers. Nanoparticles can be prepared by the emulsification-solvent evaporation method (preparation of an O/A emulsion which gives rise to the nanospheres), by displacement of the solvent, which causes precipitation of the preformed polymer at the O/W emulsion interface, by the salting-out method, which is based on the separation of the water-miscible solvent from an aqueous solution by the salting-out procedure, leading to the formation of the nanoparticles) and finally by the emulsification-solvent diffusion method, which involves the preparation of an O/W emulsion, whose internal phase is formed by an organic solvent partially soluble in water. This method can be considered as a modification of the salting-out method, but the use of salts is avoided, which facilitates the process of purification of the nanoparticles formed (Souto et al., 2012).

Drug-dendrimer conjugates

This innovative method, in which dendrimers were used to enhance simvastatin solubility, was introduced by Kulhari et al. (2011).

Dendrimers are highly branched synthetic macromolecules with a nanoscale 3D structure. The main advantage of using dendrimers is their ability to enhance the biopharmaceutical and pharmacokinetic properties of some drugs (Svenson & Tomalia, 2005).

Poly(amidoamine) (PAMAM) was used to incorporate simvastatin, with the purpose of increasing its aqueous solubility, as well as to produce a controlled-release system. The effects of the concentration of the dendrimer, pH and the type of functional group linked to the dendrimer were assessed. In addition, diffusion through dialysis membrane, dissolution and stability of the conjugated drug were investigated. The results are summarized in Table 14.

GROUPS OF ARTICLES USING DIFFERENT METHODS TO ENHANCE THE AQUEOUS SOLUBILITY OF SIMVASTATIN

Formation of Solid Dispersions by Solvent Evaporation

Table 6. Increase in solubility of simvastatin by solvent evaporation to form SD

Excipients	Drug-Carrier Proportions	Increase in solubility of of simvastatin (times)	Authors
Sodium Glycolate Starch (SGS), Sodium Croscarmellose (SC)	1:1, 1:2, 1:3	SC (1:3) – approximately 5 times	Rao et al. (2010)
PVP K30	1:1, 1:2.5, 1:5, 1:10	PVP (1:10) – approximately 2 times	Patel & Patel (2008)
HPMC K3LV (Rotary Evaporator)	1:1	HPMC (1:1) – approximately 1.3 times	Pandya et al. (2008).
HPMC K3LV (Spray Dryer)	1:1	HPMC (1:1) – approximately 1.75 times	Pandya et al. (2008).
PVP, Aerosil 200 (Spray Dryer)	1:1:0, 1:1:1, 1:2:2 (Drug: Aerosil:Carrier)	1:2:2 - 4.6 times	Ambike et al. (2005)
PVP	1:1, 1:2, 1:3, 1:4, 1:5	1:3 – approximately 3 times	Silva (2009).

Formation of Solid Dispersions by Fusion-Cooling

Table 7. Increase in solubility of simvastatin through SD by fusion-cooling

Excipients	Drug-Carrier Proportions	Increase in solubility of of simvastatin (times)*	Authors
PEG 4000	1:1, 1:2.5, 1:5, 1:10	1:10 – approximately 2 times	Patel & Patel (2008).
PEG 4000, PVP and PEG 6000	1:1, 1:2, 1:3, 1:4 and 1:5	1:5 – approximately 2.7 times (PVP).	Silva (2009)

Formation of Solid Dispersions by Fusion-Evaporation

Table 8. Increase in solubility of simvastatin through SD by fusion-evaporation

Excipients	Drug-Carrier Proportions	Increase in solubility of of simvastatin (times)	Authors
PEG 4000 and PEG 6000	1:5 (PEG 6000)	Approximately 1.5 times (water)	Silva (2009)

Articles with microemulsified systems techniques

Table 9. Increase in solubility of simvastatin through microemulsified system techniques

Excipients	Drug-Carrier Proportions	Increase in solubility of simvastatin (times)	Authors
Capryol 90 Transcutol P® , Gelucire 44/14, Akoline® MCM, Capmul MCM C10, Cremophor EL colloidal silicon dioxide (Aerosil 200). Tween 20®(T20), Glycofurol(GF).	Simvastatin (20mg) and varying proportions of excipients*.	F5 – 1.3 times (15 minutes) (medium simulating the intestinal fluid without enzymes, pH 6.8 containing 0.025% of sodium lauryl sulfate–SLS).	Dixit & Nagarsenker (2010)
Polyglycerol, KOH, ethylene oxide, nitrogen gas, acetic acid	Simvastatin incorporated in micelles of polyglycerol diisostearate ethoxylates	Unable to determine the increase in solubility of simvastatin from the information about the solubility test presented in the article.	Ding et al. (2007)
Soy Lecithin, Tween 80, n-Butyl Acetate , ethanol.	Produced microemulsions, incorporated simvastatin and lyophilized (100nm nanoparticles,10.8% simvastatin), tablets then made with 24% of freeze-dried material.	approximately 50 times greater than conventional tablet (dissolution medium simulating the gastric medium – pH 1.2).	Margulis-Goshen & Magdassi (2009)

*In these articles many proportions of the excipients are not supplied.

Articles with methods of nanoencapsulation

Table 10. Increase of simvastatin solubility by nanoencapsulation

Excipients	Drug-Carrier Proportions	Increase in solubility of of simvastatin (times)	Authors
PVPK-30, PVA, Tween-80, SLS, Poloxamer-407 Poloxamer-188	Various proportions of excipients: formulations P1-P6.*	P2 - rate of solubilization increased 25.7 times (water) (t50 % = 14 min, compared to 6 h for micronized simvastatin).	Pandya et al. (2010)
Capryol 30 (37%), Cremophor EL (28%), Carbitol (28%) SMEDDS (Self-emulsified Drug Release System)	Various proportions of excipients, formulations SMEDDS-A/SMEDDS-E).*	Best results (dissolution in simulated gastric medium) with SMEDDS-A and D, increasing solubility by 1.8 and 1.5 times, respectively. In SMEDDS-A the release was faster.	Kang et al. (2004)
Glyceryl Monooleate (GMO), Poloxamer 407	Various proportions of excipients, formulations for the preparation of Cubic Nanoparticles.*	90% of crystalline simvastatin released in 1 h. Less than 3% was released from cubic nanoparticles of simvastatin in 10 h, so dissolution profile showed sustained release and the increase in solubility should be better studied.	Lai et al. (2009)
Eudragit L100 , Poloxamer 407.	Various proportions of excipients/ simvastatin.*	Of the eight formulations produced, F8 showed the best results, increasing the solubility of simvastatin about 5 times.	Patil et al. (2011)
Tetraethyl orthosilicate (TEOS), cetyl trimethyl ammonium bromide (CTAB), 1,3,5-trimethylbenzene (TMB), ,	Various proportions of excipients, formulations for the preparation of nanoparticles.*	Nanoparticles called MCF and SBA-15 increased simvastatin solubility 3.8 (MCF) and 3.5 (SBA-15) times in solubility test. In the dissolution test, there were increases of 7 (MCF) and 4 (SBA-15) times.	Zhang et al. (2011)
Glyceryl monostearate, poloxamer 407and oleic acid .	Various proportions of of excipients.*	11 formulations were tested. F4 showed the best result in the dissolution test (88.3% in 55 hr). It was not possible to assess the increased solubility in time due to lack of data.	Tiwari & Pathak (2011)

*In these articles many proportions of the excipients are not given.

Articles with supercritical fluid techniques

Table 11. Increase in solubility of simvastatin by supercritical fluid techniques

Excipients	Drug-Carrier Proportions	Increase in solubility of of simvastatin (times)	Authors
HP-ß-CD, supercritical CO2, microcrystalline cellulose PH 101, lactose and magnesium stearate	Simvastatin: HP-ß-CD (1:1 molar) (Supercritical Anti-Solvent Technique – SAS)	Simvastatin / HP-ß-CD (SAS) - 8 times.	Jun et al. (2007)

OBS.: The above article uses cyclodextrins, but also a Supercritical Fluid technique, which is rarer, so it was placed in item 2.4.

Articles using cyclodextrins to form inclusion complexes

Table 12 Enhancement of aqueous solubility of simvastatin by CD inclusion complex formation

Excipients	Drug-Carrier Ratio	Increase in solubility of of simvastatin (times)	Authors
Chitosan,tripolyphosphate, HP-ß-CD	1:1 (mol/mol – Simvastatin: HP-ß-CD), tripolyphosphate/ chitosan 0.3%.	11.5 times (10 mM / L of HP-ß-CD). There was a further slight increase (to 13.1 times) on addition of chitosan (0.3% w / v).	Vyas et al. (2010)
1-ethyl-2-pyrrolidone, PVP K30, β-CD	Various proportions of β-CD.*	Simvastatin solubility increased with increasing β-CD concentration, to a maximum of 8times at 50 mg/mL of β-CD.	Süle & Csempesz, (2008)
HP-ß-CD (hydroxypropyl beta cyclodextrin).	HP-β-CD: simvastatin(1:1).	Inclusion complex simvastatin / HP-ß-CD produced by kneading: 2 times; complex produced by spray-drying: 6 times.	Ungaro et al. (2011)
α ,ß,γ and HP-ß-CD PEG 1500, PEG 4000, Povidone, Copovidone, Crospovidone, Maltodextrin and HPMC.	Various proportions of excipients in binary and ternary complexes.*	Complex with ß-CD and crospovidone: 3.5 times (best result).	Takahashi (2009)
α and ß-CD	Simvastatin: α and ß-CD (1:1).	Complex with α-ß-CD: 4 times; complex with ß-CD: 6 times.	Wen et al. (2005)

*In these articles many proportions of the excipients are not given.

Table 13. Enhancement of aqueous solubility of simvastatin by CD inclusion complex in liposomal dispersion.

Excipients	Phase solubility assay	Increase in solubility of of simvastatin (times)	Authors
ß-cyclodextrin (ßCD) L-α-Dipalmitoyl phosphatidyl choline (DPPC)	This method follows the procedure described by de Higuchi & Connors, (1965), for 24 h at 25ºC with stirring.	No increase when only ß-CD is used. When complexed with ß-CD in liposomal dispersion, drug solubility was proportional to the quantity of ß-CD in liposomal dispersion: around 9 times	Csempesz et al. (2010)

Article with drug-dendrimer complex to enhance solubility

Table 14. Enhancement of simvastatin solubility by drug-dendrimer complex formation.

Excipients	Phase-solubility assay	Increase in solubility of of simvastatin (times)	Authors
poly (amidoamine) (PAMAM): G4-PAMAM–NH2, G4-PAMAM–OH and G4-PAMAM–PEG	Method described by Higuchi-Connors(1965). The effects of the concentration of the dendrimer, pH and type of functional group linked to the dendrimer were assessed	Functional group: best result with G4-PAMAM–PEG (33 times) pH: best at pH 10.2 (10.6 vezes)	Kulhari et al. (2011)

DATA COMPARISON

Comparison of the Techniques Used to Change the Solubility of Simvastatin

Analyzing the related articles, it can be inferred that the technique used most commonly to improve drug solubility is the formation of a Solid Dispersion (9 articles; 33% of the total), followed by technique separately from the others as it can be used to obtain both solid dispersions and inclusion complexes with cyclodextrins. Nanoencapsulation and Inclusion Complex with CD (each with 6 papers; 22% of the total). This is probably due to the fact that solid dispersion formation is the cheapest and fastest method. As for nanoencapsulation, it can be explained by the fact that a lot of research has been done in the area of nanobiotechnology, with the goal of achieving greater drug bioavailability. A graphic representation can be seen in Figure 2. Note that the figure displays the supercritical fluid

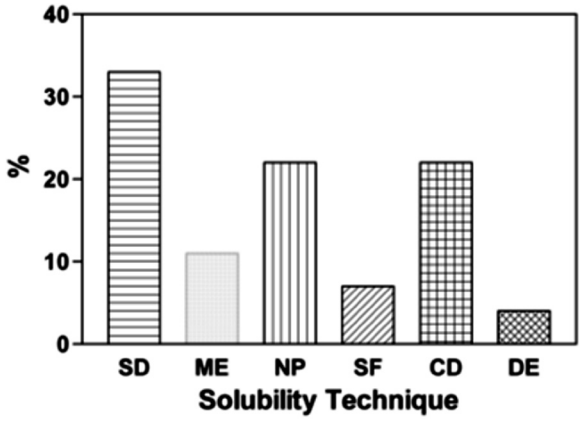

Fig. 2: Bar chart of percent distribution of the various techniques used to improve the solubility of simvastatin.

Efficacy of various techniques used to increase simvastatin solubility

The increase in solubility achieved by each technique is shown in Figure 3. The values presented were the results of solubility and/or dissolution testing and the numerical values in various units (%, mg/mL, etc.) 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 (Margulis-Goshen & Magdassi, 2009). The second best result was from the drug-dendrimer technique (G4-PAMAM–PEG: 33-fold increase in the solubility of simvastatin) (Kulhari et al., 2011). The NP technique gave the third best result, with an increase of 25.7 times (Pandya et al., 2010).

It is important to note that the mechanism responsible for the increase in the aqueous solubility of simvastatin varied among the different methods.

According to Margulis-Goshen & Magdassi (2009), in the paper that reports the highest increase in simvastatin aqueous solubility (50 times), the production of nanoparticles by lyophilization rendered a decrease in the crystallinity of simvastatin. This was the cause of the increase in its aqueous solubility.

On the other hand, Kulhari et al. (2011) (second best results regarding increase in water solubility of simvastatin: 33 times) reported the use of simvastatin-dendrimer complexes, the dendrimer produced from G4-PAMAM–PEG being the best at increasing the aqueous solubility of the drug. The FT-IR spectra of the simvastatin-dendrimer showed the disappearance of two characteristic peaks attributed to N-H and C-N. Moreover, the interaction of dendrimer and drug was confirmed by the appearance of a new peak due to amide formation. However, the authors did not hypothesize a mechanism for the increase in the aqueous solubility.

Pandya et al. (2010) (third best result, with an increase in aqueous solubility of 25.7 times) produced a nanosuspension, with PVP-K30 as stabilizer, to prepare particles with diameters between 100 and 1000 nm.

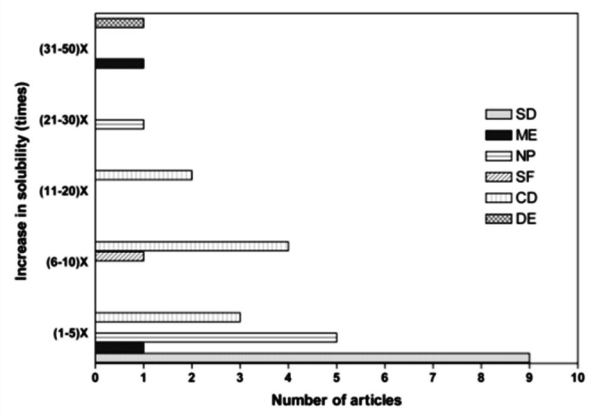

Fig. 3: Increase (times) in simvastatin solubility by each technique used.

The formation of inclusion complexes with CD also led to good increases in solubility; thus, in the study of Vyas *et al* (2011) there was an increase of 13.1 times in simvastatin solubility when HP-ß-CD was used with 0.3% chitosan, producing particles of a nanometric size. Ungaro et al. (2011) used HP-ß-CD and simvastatin alone, employing spray-drying to make a SD, and achieved an increase of 15 times in the simvastatin solubility. However, the authors do not refer to particle size, so we have no criterion to decide if the solubility increase could also be related to the decrease in particle size.

***In vivo* experiments performed in articles with change of simvastatin solubility**

In some articles which used the NP formation technique, *in vivo* testing was performed and these should be highlighted, because they allow an *in vitro-in vivo* correlation to be made, which is generally not possible, certainly for the innumerable variables involved. However, this is not the objective of this paper and this subject is not treated in depth here.

An example is the study of Lai et al. (2009): in the dissolution testing (*in vitro*), about 90% of pure simvastatin was dissolved in the medium in 1 hour, while less than 3% of the simvastatin in NE dissolved in 10 hours. However, in the Bioequivalence Testing, the final blood concentration was 53 ng/mL of SIN in the animals to which NE was administered, compared to those administered pure simvastatin, in which the final blood concentration was 42 ng/mL; in other words, *in vivo* there was an increase of 1.26 times, with a prolonged release profile, which was the objective of the article and seems to be the purpose of the NE formation; besides, CTEM, TEM, ADN2, RAD, AFM, PTI were used exclusively to obtain NP, whereas MS and MOD were used exclusively in CD characterization.

Characterization of the product as a criterion for stability monitoring

Emphasis should be given to the Margulis-Goshen & Magdassi (2009) article, in which the authors used XRD results to assay the ME crystallinity of simvastatin employing the program TOPAS V3.0 to estimate the size and shape of the crystals. The stability was followed for 11 days and it was observed that at room temperature 14% of the simvastatin molecules returned to the crystalline form and that this process stopped if the product was kept at -12ºC, at which it was conserved in the amorphous form for up to 4 months. This article is the only one in the review that focused on the question of stability, though this is the great problem with products of raised solubility, especially if there is an interest in scaling up to an industrial scale.

FINAL CONSIDERATIONS

After comparing all the results on improving the solubility of simvastatin, taken from papers published from January 2000 to April 2012, it was observed that the best results were obtained with methods involving the formation of microemulsions and nanoparticles. However,

since there are several factors that can influence the success of a given method, such as the excipient combination and the experimental parameters, we cannot assume that these two methods are definitely the most appropriate ones. Moreover, it is always necessary to relate the *in vitro* to *in vivo* experiments.

Another aspect that the researcher should keep in mind when working with simvastatin is its high stability in the crystalline form. Therefore, the formation of amorphous derivatives of this drug may make the product unstable.

Researchers show great interest in increasing the solubility of poorly water soluble drugs, but comparing the numbers of articles shown in this review, it is observed that there is not the same interest in assessing the same results *in vivo*. In addition, with the intention of converting a Class II drug (low aqueous solubility and high intestinal permeability) into a Class I drug (high solubility, high intestinal permeability), there is a risk of converting it into a Class III drug (high aqueous solubility, poor intestinal permeability).

Another parameter that was not investigated in the articles reviewed here is the stability of the final products, with the exception of the article Magdassi & Margulis-Goshen (2010). However, this is a route to finding solutions to bioavailability problems, bearing in mind that every physical and/or chemical change in the simvastatin molecule may result in modifications in its stability and pharmacokinetics, with the purpose of finding biological models most likely to detect these possible changes.

RESUMO

Estratégias utilizadas para melhoria da solubilidade da sinvastatina – revisão sistemática

Uma grande variedade de moléculas com potencial atividade farmacológica tem sido descoberta, mas em sua grande maioria com problemas de baixa biodisponibilidade, algumas vezes por apresentarem baixa solubilidade em água. Desse modo os olhares têm se voltado às moléculas já existentes e, nesse contexto, inclui-se a sinvastatina, com baixa biodisponibilidade e solubilidade aquosa, de uso crônico em pacientes com taxas aumentadas de colesterol e triglicerídeos. Esse trabalho tem por objetivo relacionar a literatura científica em que foi feita alguma modificação de solubilidade da sinvastatina num período de 12 anos (janeiro de 2000 - abril 2012), utilizando para isso técnicas como formação de dispersões sólidas, microemulsões, nanopartículas, fluido supercrítico e complexos de inclusão com ciclodextrinas. Além de relacionar, este artigo compara e avalia os resultados como gráficos, destacando ainda aspectos como técnicas de caracterização e estudos de estabilidade. Portanto, este trabalho tem características de uma revisão sistemática com coleta e análise de dados, de modo simples, ajudando na busca das informações.

Palavras-chave: **S**invastatina. Dispersões sólidas. Solubilidade.

ACKNOWLEDGEMENTS

The authors would like to thank CAPES for financial support.

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Received on May 4th, 2012

Accepted for publication on August 14th, 2012