

Solubility Enhancement of Simvastatin for Wound Dressing Preparation

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Abstract

Simvastatin (SMV) is a well-known antihyperlipidemic drug that has demonstrated wound healing effects. However, its clinical application is hindered by poor solubility. Therefore, the objective of this study was to enhance the solubility of simvastatin by utilizing various concentrations of solvents and co-solvents for formulation in selected topical dosage forms. Mixed-solvent systems, namely Buffer-methanol, Buffer-ethanol, and Buffer-dmsol, were employed. Additionally, the impact of different polymer concentrations, including carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), and chitosan (CHT), on drug solubility was investigated. The solubility profile of SMV in 2% w/v polymeric solutions (CMC, HPMC, and CHT) was found to be 73.5, 62.1, and 59.6 µg/mL, respectively. Notably, the use of a 2% w/v chitosan solution resulted in a remarkable 50-fold increase (73.5 µg/mL) in SMV dissolution compared to its aqueous solubility (1.45 µg/mL). This significant enhancement allows for the incorporation of large amounts of the drug in formulations. Our findings indicate that the Chitosan system with ethanol exhibited the highest solubilization effect and demonstrated the necessary characteristics for the preparation and handling of wound dressing films. This suggests a promising approach for the development of topical formulations with improved solubility and potential therapeutic benefits of simvastatin.

Keywords

simvastatin, solubility enhancement, polymers, wound dressings.

Introduction

simvastatin (SMV) is a well known antihyperlipidemic drug that exhibited wound healing effects. Various approaches have been assessed to expedite the healing of wounds and to prevent the progression of ulcers to advanced stages. These strategies aim to either prevent or treat wound infections [1-3]. It has been documented that statins exhibit various pleiotropic effects beyond their cholesterol-lowering actions. This aspect is regarded as a novel therapeutic approach for various pathological conditions, including psoriasis, sepsis, alopecia, wound healing, and other inflammatory diseases [4, 5]. The broad-spectrum pleiotropic effects of statins include anti-inflammatory [6], antioxidative [7], immunomodulatory, antibacterial activities [8] and Various animal models indicate beneficial effects on the wound-healing process [9].

Given the prognostic influence of statins on various levels of the wound healing process, the use of statins in wound healing is logical and appears to hold promise. Drugs with poor water solubility are associated with slow drug absorption [10]. The drug's solubility has a significant impact on its capacity to cross cellular membranes.

Simvastatin, like numerous other drugs, may face limited permeability through the skin's barrier. The outermost layer of the skin, known as the stratum corneum, serves as a robust barrier, preventing the entry of various substances, including drugs. Enhancing the permeability of simvastatin through the skin presents a significant challenge [11]. Solubility is the measure of a solute's capacity to dissolve in a set volume of solvent under specific temperature conditions. While the concept

of solubility may seem uncomplicated, it has led to confusion owing to a multitude of variables.

Solubility is influenced by elements such as particle size (smaller particles are more soluble), temperature (higher temperatures typically enhance solubility), and medium pH (drugs with pKa values in the acidic range are more soluble in alkaline media, for example). Additionally, certain excipients can occasionally improve the solubility of medications" [12].

Many solubilization techniques have been used with insoluble drugs such as: Changes to the crystal structure of a solute, reducing particle size or modifying the crystal form, and adjusting the solvent by incorporating solubilizing agents. The four frequently utilized approaches for modifying solvents are pH manipulation, co-solvency, micellization, and complexation [13, 14].

Different cosolvents were used for enhancing the solubility of simvastatin. *Organic co-solvents, including substances like DMSO, dimethylacetamide, ethanol, glycerol, poly(ethylene glycol), and propylene glycol, have found extensive application in solubility studies.* Due to their ability to effectively dissolve poorly soluble medications and their minimal level of toxicity [15].

The solubilization effect of cosolvents can be expressed by the logarithmic-linear equation, which is:

$$\log S = \log S_w + \sigma f$$

Here, S and S_w represent the solubilities in the cosolvent-water blend and pure water, respectively. f indicates the proportion of the cosolvent, and σ denotes the solubility potential.

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Wound dressings possess a combination of flexibility, moisture regulation, barrier function, adhesive properties, transparency, breathability, thinness, durability, customizability, easy application, and prolonged wearability. These characteristics collectively contribute to their effectiveness in promoting the healing of various types of wounds [16, 17].

In the present study, we examine the impact of certain solvents (ethanol, methanol, and DMSO) and polymers (CMC, HPMC, and CHT) on the solubility of simvastatin. Additionally, we investigate the physical and mechanical characteristics of the prepared dressings to identify the optimum formulations for handling and application.

Materials and Methods

1. Materials

Simvastatin is kindly provided by Eva pharm Company for pharmaceutical industries, Egypt. Chitosan is obtained from ARCOS organic, Belgium. Glycerol, methanol, and ethanol are supplied by EL-Naser Pharmaceutical Chem. Co., Cairo, Egypt. Glacial acetic acid, ethanol HPLC grade, hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) are obtained from (Aldrich Chem. Co, Inc. U.S.A). All other solvents and materials were of analytical grade.

2. Solubility Studies

Solubility measurement were performed according to Higuchi and Connors[18]. Excess amounts of drug were added to 10 mL mixture of phosphate buffer (pH6.8) and other solvents: methanol, ethanol and DMSO (0-30%v/v concentration range) in 10 mL screw capped tubes and shaken at 37C⁰ in the thermostatically controlled water bath for 24 hr . At equilibrium aliquots were withdrawn, filtered using a 0.45 µm syringe filter and immediately diluted with mobile phase before estimated by HPLC as previous studies[19, 20]. Also, The solubility of simvastatin in different aqueous polymeric systems; CMC, HPMC and CHT in concentration range (0-2%w/v) was investigated. The polymeric solutions were prepared by dissolving the required amount in solvent and SMV solubility was examined as previosly mentioned using HPLC analysis.

3.Preparation of SMV wound dressings

According to the data obtained from solubility study, Polymeric dressings were prepared using the solvent casting method[21]. The compositions of films containing different polymers, simvastatin concentrations and plasticizers (glycerol and PEG) are presented in Table (1). All polymers (HPMC, CMC and chitosan) were examined for its efficacy on the physical and mechanical properties of wound dressings.

The polymeric dressings were prepared by dissolving the polymers, and drug in mixture of buffer solution and ethanol containing plasticizer agent with a constant stirring at 500 rpm for 3 h at 40 C. The blank and drug-loaded gels were dried by pouring the gel (20 g) into a plastic die with a diameter 73mm and then drying in oven at 60 C for 12 h.

Then, prepared films were tested for its physical and mechanical characteristics (Folding endurance, Moisture uptake %, and Expansion %) to choose the optimum formulation for further studies.

Folding endurance

The resilience of wound dressings to folding was assessed by repetitively folding dressing strips at a fixed location until they experienced rupture. These films were sliced into squares measuring 5 cm² each. The folding endurance was gauged based on the number of times the dressings could be folded at a consistent position without undergoing rupture.

Percentage of expansion

The wound surface is mimicked using a gelatin model onto which dressings are positioned [22]. The disc-shaped dressings gradually expand in all directions. To prepare a transparent gelatin solution, 4 grams of gelatin powder are introduced into 100 mL of distilled water at 70 °C and continuously stirred at 700 rpm. Following this, 30 grams of the resulting 4% w/v gelatin solution are poured into a Petri dish and left in the refrigerator overnight to solidify into a gel. Each dressing is then cut into a specified circular shape (18 mm in diameter) and positioned on the gelatin gel in the Petri dish. The formulation of these dressings is designed for expansion upon application to an injury and absorption of wound exudate.

Table 1. Composition and formulation of the prepared topical films

formulation code	C1	C2	C3	C4	C5	C6	C7	C8	C9
Composition / weight									
SMV (% w/v)	0.2	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1
chitosan (% w/v)	1	1	1	-	-	-	-	-	-
HPC (% w/v)	-	-	-	2	2	2	-	-	-
CMC (% w/v)	-	-	-	-	-	-	2	2	2
GLY (mL)	1	1	-	1	1	-	1	1	-
PEG 400(mL)	-	-	1	-	-	1	-	-	1

The alteration in film diameter is assessed 24 hours later. The process is replicated for each formulation, and the average value is utilized to compute the expansion behavior using the subsequent equation:

$$E = \frac{D_t - D_o}{D_o} \times 100$$

Here, E denotes the expansion ratio, D_t signifies the film diameter after expansion, and D_o indicates the film diameter before expansion.

Results and Discussion

Solubility Studies

The solubility of simvastatin in water and buffer was determined and found to be 1.4 and 24.7 $\mu\text{g}/\text{mL}$ respectively at 37°C. The phase solubility of simvastatin in different solvents and polymers used is given in figures (1). simvastatin exhibits poor water solubility (1.45 $\mu\text{g}/\text{mL}$) due to its lipophilic characters. The effect of different concentrations ranging from 0.5 to 2% (w/v) of chitosan, HPMC and CMC on the aqueous solubility of simvastatin was studied (Table 2 and figure 1). It is clearly obvious that all polymers displayed an increase in simvastatin solubility, and there was a direct relationship between the solubility and the concentration of the polymers used. The highest solubilization power for SMV was recorded for 2% chitosan solution (73.5 $\mu\text{g}/\text{mL}$), followed by 2% HPMC (62.1 $\mu\text{g}/\text{mL}$) and eventually 2% CMC (59.6 $\mu\text{g}/\text{mL}$). The solubilization of simvastatin was enhanced in aqueous buffer solution of either HPMC or CMC.

Table 2. Solubility of SMV in different concentrations of polymers.

Concentration of polymer	Solubility ($\mu\text{g}/\text{mL}$) in Presence of		
	Chitosan	HPMC	CMC
0%	1.45 ± 0.08	24.8 ± 1.5	24.8 ± 1.5
0.50%	27.5 ± 1.9	26 ± 1.8	25.7 ± 1.6
1%	36.2 ± 2.1	33.9 ± 2.2	32.3 ± 1.9
1.50%	51 ± 2.6	46.2 ± 2.3	44.5 ± 2.4
2%	73.5 ± 3.1	62.1 ± 2.9	59.6 ± 2.7

Also, the solubility of SMV in different solvents was shown in Table 3. In Figure (1) the effect of some different alcohols (ethanol, methanol, and DMSO) on Simvastatin solubility was illustrated. The results showed that Simvastatin solubility in aqueous buffer DMSO solution was higher than that in aqueous ethanol or methanol buffer solutions. Also, increasing the concentration of co-solvents results in a significant improve in drug solubility. In prepared wound dressings, ethanol is used is used in our study as a co-solvent with buffer solution because it is more safe compared to DMSO that has a rapidly penetration power into skin which resulted in negative skin reactions [23].

Table 3. Solubility of SMV in different concentrations of solvents.

Concentration of alcohol	Solubility (mg/mL) in Presence of		
	Methanol	Ethanol	DMSO
10%	$1 \pm 0.080.9$	0.6 ± 0.05	1.4 ± 0.09
%20	$2 \pm 0.121.4$	1 ± 0.07	1.9 ± 0.14
%30	$4 \pm 0.151.8$	1.3 ± 0.11	2.6 ± 0.18
%40	$5 \pm 0.172.1$	1.7 ± 0.13	3.1 ± 0.23

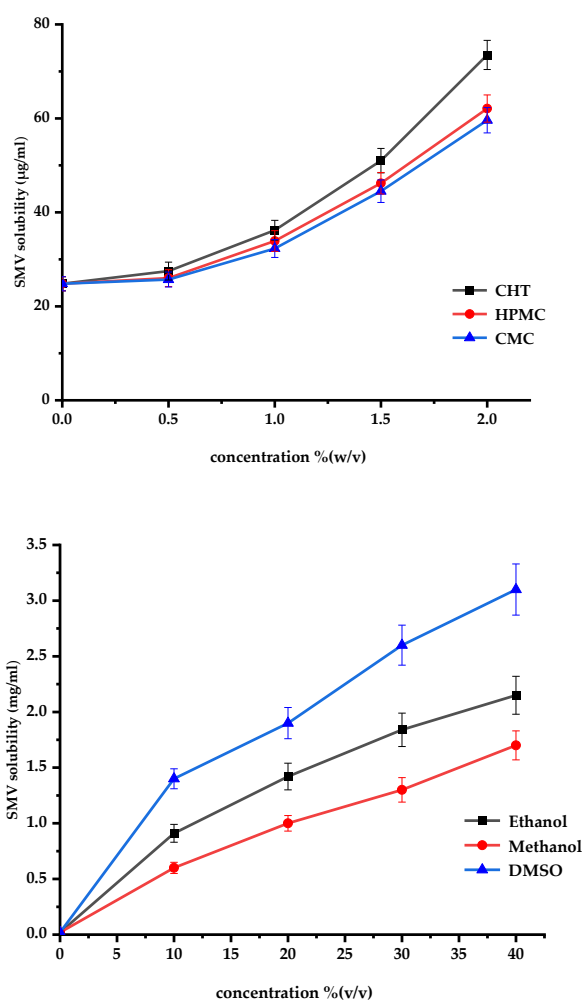


Figure 1. Solubility of simvastatin in different polymers and solvents.

Preparation of SMV wound dressings

Polymers play the major role in determining the physical and mechanical properties of films. Also, they affect the rate of drug release and the process of wound healing. The data from solubility study indicates that the incorporation of ethanol will significantly enhance the preparation of wound dressings. After Chitosan, HPMC, and CMC increasingly changed the solubility of SMV, they were tested for its physical and mechanical characteristics to determine the optimum polymer for dressings' preparation. It is crucial that the dressings be removed gently to prevent further harm to the wound surface. Wound dressings should provide optimal conditions for wound healing while safeguarding against microbial infection and preventing additional harm[24]. The amount of the drug strongly affects the morphology of the prepared films. Excess amount of SMV (0.2% w/v) in the preparation resulted in precipitations and turbidity in the polymeric films which further affect the film handling and

drug release so the formulations C1, C4 and C7 were rejected as shown in figure (2). Other formulations were tested for physical and mechanical characteristics (Folding endurance, Moisture uptake %, and Expansion %) as shown in figure (3). as a polymer of choice in preparation of films for further studies. Also, Chitosan demonstrates significant efficacy according to previous studies in wound care due to its ability to control bleeding, promote healing, exhibit antimicrobial properties, and its characteristics of being non-toxic, biocompatible, and biodegradable[25]. During extraction and handling, the dressing prepared from chitosan (1% w/v) and glycerol (C2) showed a required performance, so it was used for further studies. Chitosan formulations were more elastic and had high folding of endurance than other polymers which make it more suitable for application on skin.

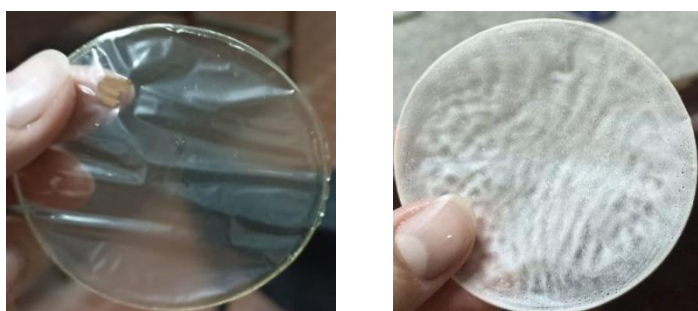


Figure 2. The difference in appearance between the Clear film contains 0.1% of drug and turbid film contains 0.2% of drug.

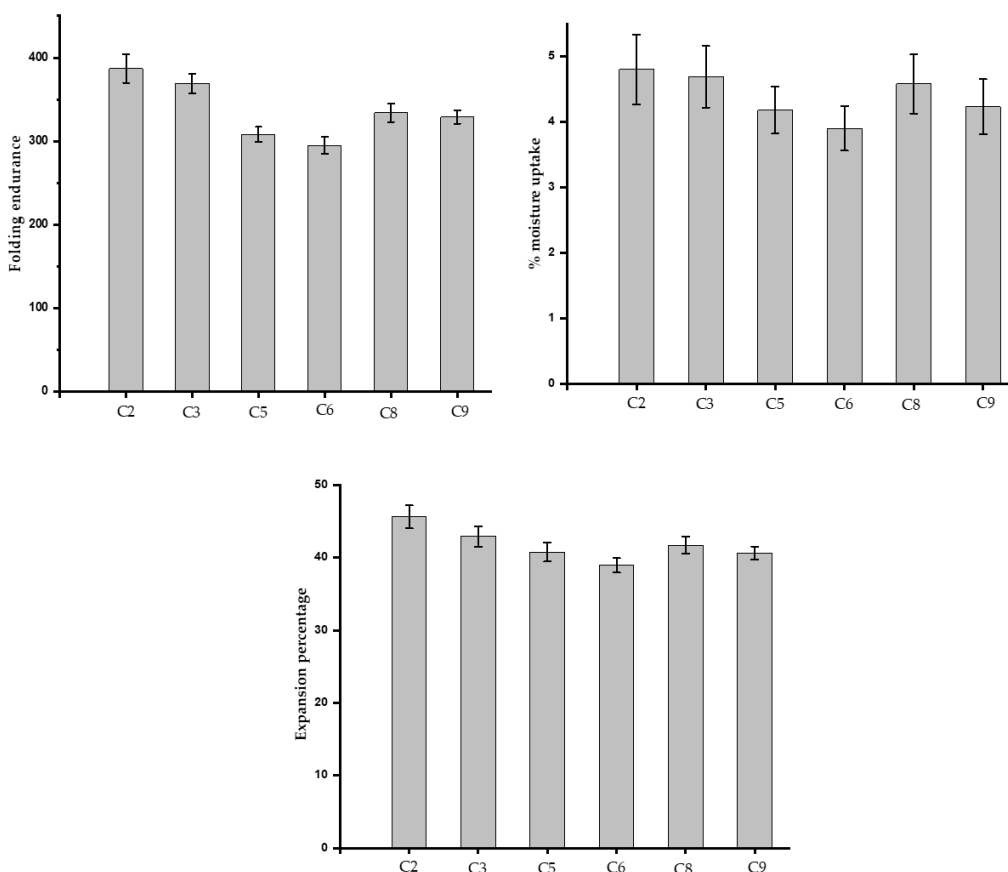


Figure 3. Folding endurance, % moisture uptake and Expansion percentage of the selected formulations.

Polymeric films made of chitosan show desired physical and mechanical characteristics as shown in figure 3, so it was chosen as a polymer of choice in preparation of films for further studies. Also, Chitosan demonstrates significant efficacy according to previous studies in wound care due to its ability to control bleeding, promote healing, exhibit antimicrobial properties, and its characteristics of being non-toxic, biocompatible, and biodegradable [25]. During extraction and handling, the dressing prepared from chitosan (1% w/v) and glycerol (C2) showed a required performance, so it was used for further studies. Chitosan formulations were more elastic and had high folding of endurance than other polymers which make it more suitable for application on skin.

Conclusion

The present study successively examined and compared the aqueous solubility enhancement of simvastatin using various pharmaceutically accepted solvents like ethanol, methanol, and DMSO, and different polymers (CMC, HPMC, and CHT) which will be useful in development and formulation design of various dosage forms containing simvastatin. Ethanol was recommended to be used for further preparation of SMV wound dressings as it enhanced the solubility of SMV and show less side effects comparing to other solvents. Additionally, Chitosan has been an optimum polymer in terms of most efficient solubilizing cosolvent, side-effect profile and high impact on healing wounds. Chitosan shows the highest folding endurance, expansion percentage and % of moisture uptake so it was recommended in further preparation of wound dressings.

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