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Review Article:

Scanning Sildenafil Citrate Solubility in Hydrotropic Solutions

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Abstract

Background: Sildenafil citrate (SC) is a selective phosphodiesterase-5 inhibitor with low aqueous solubility (4.1 mg/mL in water), resulting in only 40% bioavailability after oral administration. SC is classified as class II by the Biopharmaceutical Drug Classification System. Hydrotropic agents are ionisable organic salts that provide a simple, safe and effective technique for enhancing the solubility of poorly water-soluble drugs. **Method**: Solubility study of SC was conducted in water (as a reference) and in various hydrotropic solutions separately (including sodium benzoate, sodium acetate, Urea and mannitol). The concentrations of the hydrotropic solutions were at 10, 20 and 30 % solution concentration, as well as in the solution of 30 % concentration of mixed hydrotropic agents at a 1:1 ratio. **Results**: The results show marked enhancement of SC solubility in solution of urea at different concentrations while the solubility was enhanced only in 30% solution of sodium benzoate and slightly enhanced in 30% mannitol solution and mannitol-urea solution. The solubility enhancement in urea shows a positive relationship with solution concentration. In addition, the SC solubility was reduced in the solution of sodium acetate at all concentrations and in the solution of sodium benzoate at concentrations of both 10 and 20 % as well as in all mixed hydrotropic solution containing these two agents. **Conclusion**: urea shows promising data as a potential additive with SC to achieve higher solubility and bioavailability of the compound.

1. Introduction

Sildenafil citrate is a selective phosphodiesterase-5 inhibitor approved by the FDA (1)for erectile dysfunction. The ampholyte SC has pKa values of 4 (pyridinium ion) and 8.8. (benzimidazole)(2). Due to its low aqueous solubility, (4.1 mg/mL in water), sildenafil citrate has a weak bioavailability of 40% when taken orally (3). Sildenafil is categorized as biopharmaceutical drug class II by the Biopharmaceutical Drug Classification System due to its low solubility and high membrane permeability (4). Co-solvency complexation, particle size reduction, chemical modification, emulsions, and solid dispersion are among many other methods utilized for bypassing the low water solubility of pharmaceutical molecules (5). Hydrotropic agents are ionisable organic salts that had been suggested a long time ago to enhance the solubility of poorly water-soluble solutes at high concentrations (5). The hydrotropic solubilisation technique is preferable to alternative techniques such as micellar solubilisation, co-solvency, and salting because the nature of the solvent is pH-independent, has high selectivity, and does not require chemical modification of hydrophobic drugs, the use of organic solvents, or the preparation of an emulsion system. It supplies an efficient, simple, and green platform for various pharmaceutical industries through organic conversions. They are readily available and inexpensive. They are non-toxic and non-reactive (6).

The purpose of this study is to use hydrotropic solubilisation methods to investigate the effect of hydrotrope's type, concentration and combination synergistic effect on SC solubility

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2. Materials And Methods

2.1 Materials

All chemicals used in the experiments were of analytical grade

SC was obtained as a gift sample from Awa Medica Pharmaceutical Laboratory, Sodium benzoate, sodium acetate, urea, and mannitol were bought from private sources and the country of origin was China. Double-distilled water was obtained freshly from the College of Pharmacy/University of Mosul laboratories and used whenever needed.

2.2 Method

2.2.1 Determination of λ_{max} by UV Spectrophotometer

A stock solution (0.5 mg/ml) of SC in methanol was prepared and then diluted with distilled water to obtain a 0.05 mg/ml solution. A double-beam UV-visible spectrophotometer was used to scan the diluted solution at the wavelengths between 200 nm and 400 nm. (7) (8).

2.2.2 Preparation of calibration curve of SC in distilled water

A serial dilution of SC solutions (ranging from 5-30 microgram/ml) were prepared from a previously prepared stock solution. Absorbance was recorded for all the different concentration solutions at the predetermined λ_{max}.

2.3 Solubility study

The solubility of SC in distilled water was evaluated using the shaker flask technique. An excess of SC was added to 10 ml of D.W., which was mechanically shaken at room temperature for 24 hours at 100 rpm. The mixture was then centrifuged at 2000 rpm for 10 minutes and filtered using Whatman® 0.45uM filter paper. Distilled water was used to dilute the supernatants. and absorbance was recorded (9).

2.3.1 Solubility of SC in different hydrotropic agents(7) (8)(10)

Each hydrotropic agent: urea (U), sodium benzoate (SB), sodium acetate (SA), and mannitol (M) was produced as a solution in water at concentrations of 10%, 20%, and 30% w/v. An excess amount of medication SC was added to a specified solution of a hydrotropic agent in a 10-ml vial, and the mixture was mechanically agitated until a saturated solution was achieved. Each vial was shaken for 24 hours on the mechanical shaker, and the solution was given another 24 hours to equilibrate. The mixture was then further filtered using Whatman® 0.45uM filter paper and centrifuged at 2000 rpm for 10 minutes in an ultracentrifuge. A sufficient dilution of the sample with distilled water was used before it was examined with a UV spectrophotometer at specified λ_{max}.

The following formula was used to calculate enhancement ratios in solubility(11):

$$\text{Enhancement ratio} = \frac{Solubility\ of\ S.C\ in\ hydrotropic\ solution}{Solubility\ of\ S.C\ in\ water}$$

2.3.2 Solubility of SC in mixed hydrotropic agents solution(7) (8)(10)

A series of six solutions of two hydrotropic agents (Sodium benzoate + Sodium acetate, Sodium benzoate + Urea, Sodium benzoate + Mannitol, Sodium acetate + Urea, Urea + Mannitol, Sodium acetate + Mannitol) at a 1:1 ration with total concentration equal 30% each were prepeared and an excess amount of medication SC was added to a specified solution of a mixed hydrotropic agent in a 10-ml vial, and the mixture was mechanically agitated until a saturated solution was achieved. Each vial was shaken for 24 hours on the mechanical shaker, and the solution was given another 24 hours to equilibrate. The mixture was then further filtered using Whatman® 0.45uM filter paper and centrifuged at 2000 rpm for 10 minutes in an ultracentrifuge. A sufficient dilution of the sample with distilled water was used before it was examined with a UV spectrophotometer at specified λ_{max}. The following formula was used to calculate enhancement ratios in solubility(11):

$$\text{Enhancement ratio} = \frac{Solubility\ of\ SC\ in\ mixed\ hydrotropic\ solution}{Solubility\ of\ S.C\ in\ water}$$

3. Results and discussion

3.1 Determination of λ_{max} by UV Spectrophotometer:

Scanning SC solution absorbance yielded a **λmax of** 291.5 nm as shown in **Figure 1**.

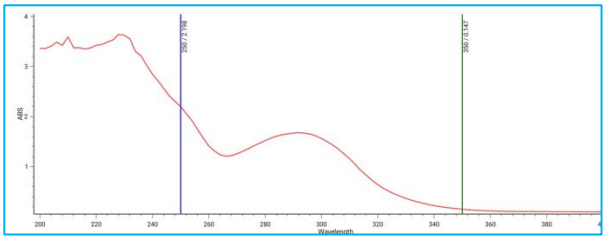

Figure 1. Determination of **the λmax** for the SC in distilled water at room temperature

Preparation of calibration curve of SC in distilled water.:

The calibration curve was produced for SC in D.W. and the obtained curve were shown in **Figure 2**. With R square equal to 0.994

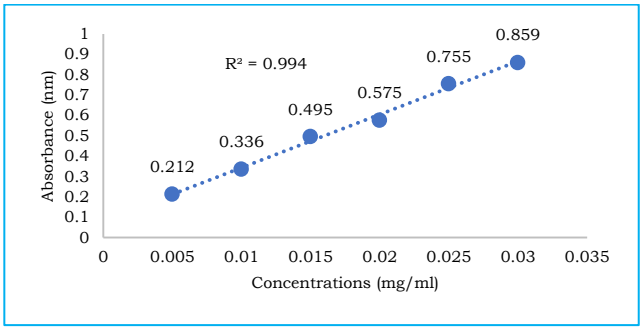

Figure 2. Calibration curve for SC in distilled water at pH 7 and room temperature

Solubility studies:

The solubility of SC in distilled water was found to be equal to 4.33 mg/ml (S.D. ± 0.47) and this result was agreed by the result reported in the researched articles (9)

The results of sildenafil citrate solubility in various single hydrotropic agents are shown in **Table 1**.

The solubility results show a clear increase in the SC solubility enhancement ratio in response to increase in the concentration of urea and sodium benzoate. The highest enhancement ratios were 2.9 and 10 for benzyl benzoate and urea solutions, respectively. Reported improvement in the solubility of SC in different hydrotropic agents follow the order (urea> sodium benzoate> mannitol). Urea Aliphatic and linear compound classes exert their solubilizing effect by structure-breaker and structure-maker. Solutes such as urea that are capable of both donation and hydrogen uptake to help increase solubility. Urea exerts their solubilizing effect by changing the nature of the solvent Specifically, the solvent's ability to participate in structure development or engage in structure creation via intermolecular hydrogen bonding. (13).

Sodium benzoate from class Aromatic avionics, the concentration of hydrotrope plays an essential role in the solubilisation process of medicinal compounds. Hydrotropes at high concentrations form aggregates and reduce the cloud point of amphiphilic drugs, whereas hydrotropes at low concentrations raise the cloud point of amphiphilic drugs depended on their type and structure of hydrotrpe (12).

Solubility is affected by factors such as molecular size, nature of the solute and solvent, temperature, pressure, particle size, complex formation, and polarity (15). SC solubility was slightly enhanced in mannitol solutions and harshly reduced at different concentrations of sodium acetate in comparison to the solubility of the same compound in water. The order of enhancement of the solubility of SC display a positive relationship between the solubility of SC and the concentration of the hydrotropic solution in both urea and sodium benzoate to obtain the highest solubility at solution concentration of 30% w/v in both solutions.

The results of SC solubility in combined hydrotropic solutions composed of two hydrotropic agents (at 1:1 ratio) are shown in **Table 2**. The data show a reduction in SC solubility at almost all hydrotropic combinations except the combination of urea and mannitol where the solubility was increased by 2.23 folds

Table 1: solubility of sildenafil citrate in different hydrotropic solutions.

Hydrotropic agent	Solution concentration	SC solubility mg/ml	Slandered deviation (S.D.) ±	Solubility enhancement ratio
Sodium benzoate	10%	0.6	0	0.139
	20%	2.633	0.0471	0.612
	30%	12.633	0.471	2.937
Urea	10%	13	0.816	3.023
	20%	21	0.471	4.883
	30%	43.33	4.714	10.076
Mannitol	10%	4	0	0.930
	20%	4.6	0.471	1.069
	30%	5.333	0.471	1.240
Sodium acetate	10%	0.057	0.009	0.013
	20%	0.005	0	0.001
	30%	0.004	0	0.0009

Table 2: Results of equilibrium solubility of sildenafil citrate in 1:1 mixed hydrotropic blend.

Mixed Hydrotropic agent	Hydrotropic agents' ratio	Total solution concentrations (w/v)	SC solubility mg/ml	Standered deviation (S.D.) ±	Solubility enhancement ratio
Sodium benzoate+Sodium acetate	1:1	30%	0.29	0.008	0.066
Sodium benzoate + Urea	1:1	30%	0.766	0.047	0.177
Sodium benzoate + Mannitol	1:1	30%	0.467	0.047	0.12
Urea + Sodium acetate	1:1	30%	0.14	0	0.032
Urea + Mannitol	1:1	30%	9.67	0.942	2.23
Sodium acetate + Mannitol	1:1	30%	0.08	0	2.23

Mixed hydrotropic solubilisation is a technique used to improve the solubility of medications that are poorly water-soluble.

Solubilisation breaks intermolecular or inter-ionic bonds in the solute, separating the solvent's molecules to find space for the solute, and interacting between the solute's molecules or ions with the solvent. In this study the result show that mixed hydrotrope has no effect on SC solubility that is poorly soluble in water because there is no synergistic effect of different hydrotropic agents together. The enhancement of water solubility by hydrotrope is based

on a mechanism it is yet not clear. The mechanism of hydrotropic solubilisation is determined by the fluctuation theory of solutions.

Two key factors of hydrotrope-induced solubilisation had been identified hydrotrope-solute interaction and decreased water activity. Nature and concentration of each hydrotropic agent are the attracting forces for hydrotrope's solubilizing potential. Urea from aliphatic and linear compounds solubilizes medicinal agents via modifying the nature of the solvent, specifically the solvent's ability to participate in structure formation or engage in structure building via intermolecular hydrogen bonding (13). Sodium benzoate from class Aromatic anionics raise the cloud point at low concentrations but lower it at higher concentrations. The amount to which different hydrotropes vary in cloud point depends on their type and structure. The concentration of hydrotropes is critical to the mechanism of drug molecule solubilisation(13).

4. Conclusion

Enhancement of SC solubility could be a key factor for achieving better oral bioavailability for the compound, Today, a wide range of methods and strategies are available to get the required goal, however many of them failed due to one reason or another. Solubility enhancement by hydrotropic agents found a great reputation because of their simplicity, availability and safety. Scanning SC solubility in different hydrotropic agents at various concentrations and mixed hydrotropic solutions provide a firm base to choose the best agent that provide the mentioned advantages of the technique, the result of this study shows that urea at several ratio and concentrations could have a potential value in the field of achieving better SC bioavailability.

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مسح ذوبانيه سترات السيلدينافيل في محاليل الهيدروليكيه

الخلاصة

المقدمة: سترات السلدنافيل هي SC مثبط انتقائي لفوسفوديستيراز -5 مع قابلية منخفضة للذوبان في الماء (4.1 مجم / مل في الماء) ، مما يؤدي إلى توافر حيوي بنسبة 40 ٪ فقط بعد تناوله عن طريق الفم. تم تصنيف SC على أنها الفئة الثانية من قبل نظام تصنيف الأدوية الصيدلانية الحيوية. العوامل المائية هي أملاح عضوية قابلة للتأين توفر تقنية بسيطة وآمنة وفعالة لتعزيز قابلية ذوبان الأدوية ضعيفة الذوبان في الماء. **طرق العمل**: أجريت دراسة قابلية الذوبان للـ SC في الماء (كمرجع) وفي مختلف المحاليل المائية بشكل منفصل (بما في ذلك بنزوات الصوديوم وخلات الصوديوم واليوريا والمانيتول). كانت تركيزات المحاليل المائية بتركيز 10 و 20 و 30٪ محلول ، وكذلك في محلول بتركيز 30٪ من العوامل المائية المختلطة بنسبة 1: 1. **النتائج**: أظهرت النتائج تحسنًا ملحوظًا في قابلية الذوبان في محلول اليوريا بتركيزات مختلفة بينما تم تعزيز الذوبان فقط في محلول 30٪ من بنزوات الصوديوم وتعزز بشكل طفيف في محلول مانيتول ومانيتول-يوريا بنسبة 30٪. يُظهر تعزيز الذوبان في اليوريا علاقة إيجابية مع تركيز المحلول .بالإضافة إلى ذلك ، تم تقليل SC في محلول أسيتات الصوديوم في جميع التركيزات وفي محلول بنزوات الصوديوم بتركيزات كل من 10 و 20 ٪ وكذلك في جميع المحاليل المائية المختلطة المحتوية على هذين العاملين. **الاستنتاج**: تُظهر اليوريا بيانات واعدة كمادة مضافة محتملة مع SC لتحقيق قابلية ذوبان عالية وتوافر حيوي للمركب.

الكلمات المفتاحية: سترات السلدنافيل، العوامل المائية، الذوبانية، العوامل المائية المختلطة