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Solubility Enhancement of Sunitinib by Solid Dispersion Technique

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Abstract

To improve dissolution of poorly water-soluble drugs and thus enhancing their bioavailability, the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state is used. This process is known as solid dispersion. It has engrossed significant interest as an efficient means of improving the dissolution rate. It happens due to dispersions of poorly water-soluble drugs with water-soluble carriers. The one of the most challenging aspects in formulation development is solubility behaviour of drugs. The number of poor water soluble compounds has radically increased. Compared to conventional formulations such as tablets or capsules, solid dispersions prepared by various methods can be used which have many benefits over the above conventional dosage form. it follows First order kinetic drug release models.

Key words: Sunitinib, Solubility enhancement, solid dispersion

Introduction

Solubility

"Solubility" is the principal circumstance in pharmaceutical formulation that plays very functional role in the formulation of diverse dosage forms. Solubility of a complex in a specific solvent is entitled as the concentration of a solute in a saturated solution at a certain temperature.[1]

Factors affecting solubilization: The solubility based on the nature and composition of solvent medium, the physical form of the solid along with temperature and pressure of system. Factors that affect the solubility are as follows-

A) Particle Size:

The particle size of the solid impacts the solubility since when the particle size is decreased the surface area will be increased. The larger surface area enables a greater interaction between the solvent and the solute. The effect of particle size on solubility can be catalogued.[2-5]

$$\log \frac{S}{S_0} = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

Where, S_0 is the solubility of unbelievably large particles, S is the solubility of fine particles, V is molar volume, r is the radius of the fine particle and D is the surface tension of the solid.

B) Pressure

Modification in pressure have practically no outcome on solubility of any solid or liquid solute but for gaseous solutes, when pressure is increased, there is increase in solubility and a decrease in pressure causes the decrease in solubility. [2-5]

C) Temperature:

When temperature is increased the solution process absorbs the energy and the solubility will be increased but if the process releases energy that is the process is exothermic so the solubility will decrease while increasing the temperature. A few solid solutes are less soluble in warm solutions.

D) Molecular size:

The molecules have higher molecular weight and higher molecular size is less soluble because larger molecules are more difficult to surround with solvent molecules in order to dissolve the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.[2-5]

Solid Dispersion

The term "solid dispersion" refers to the dispersion of one or more active ingredients—which are hydrophobic—in an inert carrier—which are hydrophilic—in a solid form after being prepared bymelting (fusion), solvent, and melting solvent technique. Both a hydrophilic matrix and a hydrophobic drug are present in the final product[6]

Classification of solid dispersion

Solid dispersions can be classified into the following categories depending on the molecular arrangement:

• **Eutectic mixtures:** The common method for creating solid eutectic mixes is to rapidly cool the co-melt of the two components to create a physical mixture of very thin crystals of the two components.

• **Solid solutions**: The two different categories of solid solutions, which depend on miscibility, are

a. Continuous solid solutions: The bonds between the components in continuous solid solutions are stronger than the bonds between the individual components because the components are miscible in all quantities.[7]

b. Discontinuous solid solutions: The solubility of each component in the other component in discontinuous solid solutions is constrained.

There are two different kinds of solid solutions, depending on how the solvates are distributed in the solvent:

• **Substitutional crystalline solution:** These are the types of solid solutions that are crystalline. In nature, where the solute molecules act as the solvent molecules' replacements in the crystal lattice.

• **Interstitial crystalline solid solution:** These solid solutions contain dissolved molecules that fit in the gaps between the solvent molecules in the crystal lattice.

• **Amorphous solid solutions:** In amorphous solid solutions, the solute molecules are molecularly scattered inside the amorphous solvent but not uniformly.

• **Glass solutions and glass suspension:** When the solute dissolves in the glassy solvent, the result is a homogeneous system known as a glass solution. Below the glass transition temperature, the glassy state is defined by transparency and brittleness. Glass is a phrase used to describe a pure chemical or a combination of pure compounds in their glassy form.[8,9]

Drug Profile

Sunitinib is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA on January 26, 2006. Sunitinib is a small molecule that inhibits multiple RTKs, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer.[11]

Structure

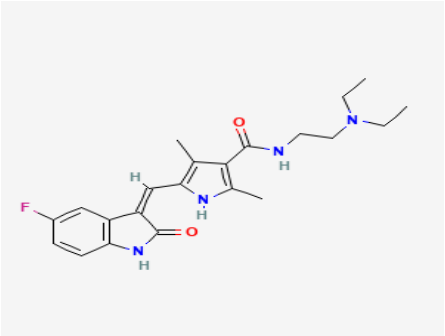

Fig. no. 1. Molecular Structure of Sunitinib

Half Life

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively.

Metabolism

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4.[12]

Indication

Sunitinib is indicated for the following conditions:

- Treatment of adult patients with gastrointestinal stromal tumor (GIST) following disease progression on (or intolerance to) imatinib mesylate
- Treatment of adult patients with advanced renal cell carcinoma (RCC)
- Adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy
- Treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in adult patients with unresectable locally advanced or metastatic disease[11,12]

Materials and methods

The raw material of Sunitinib malate (99.78%w/w) was obtained a gift sample, which was used as reference material throughout the experiment without any prior treatment.

Instruments used

• UV-Visible Spectrophotometer
• Digital balance.
• Sonicator.
• Class “A” grade glassware’s was used.

Solubility studies

The solubility studies of Sunitinib malate was carried out employing different solvent, and the results are as follows:

• Very freely soluble in water.
• Soluble in alcohol.
• Slightly Soluble in 0.1N HCl.
• Slightly Soluble in 0.1N NaOH.[13,14]

Selection of solvent

Sunitinib exists as a salt form of maleic acid and it is found that the drug is very freely soluble in water. Hence, water was chosen as thesolvent to solubilize Sunitinib malate and to carry out further analysis.

Preparation of standard stock solution of Sunitinib malate

The standard stock solution of Sunitinib malate was prepared by accurately weighing 25 mg of the drug and it was kept in a 25 ml standard flask. Half the volume of water was added. The solution was sonicated for 15 min and then the volume was made up to the mark with distilled water. The resultant solution was filtered and suitably diluting with distilled water to get the working standard solutions.[15]

Determination of λmax

The standard stock solution of Sunitinib malate was diluted suitably to get a concentration of 10µg/ml. The solution was scanned within the range of 200 nm-500 nm in D0 , D1 and D2 order derivative modes respectively.[10]

Assay

The sample stock solution of Sunitinib malate was diluted suitably to get a concentration of 10µg/ml. The above solution was scanned in the three modes and the UV spectra's were recorded and the percentage purity of Sunitinib malate in the pharmaceutical formulation was calculated.[16]

Formulation of solid dispersions

Solid dispersions was developed by the solvent evaporation technique, in this technique drug (Sunitinib) and carrier (Urea, PVPK-30) were diffused in organic solvent (methanol) after the diffusion, the solvent was evaporated by utilizing a water bath. The solid mass achieved were ground. Sieved through # 80 and dried.[17]

Table no. 1 formulae for solid dispersion

S. No.	Ingredients	F 1	F 2	F 3	F 4
1	Sunitinib(gm)	1	1	1	1
2	PVP K-30(gm)	1	-	2	-
3	Urea(gm)	-	1	-	2
4	Methanol(ml)	5	5	5	5

(C) Evaluation of solid dispersion

(i) Solubility studies

(ii) Dissolution Studies

(iii) Kinetic Models for Drug Release

(i) Solubility studies

Solubility studies of Sunitinib were moved out to know the possible solubilizing effect of the carrier by adding drug (20 mg) to 10 ml of aqueous solutions contained increasing concentration of carrier (1:0,1:1, 1:2)and glass containers were sealed maintained under stirring at

constant temperature (20°C)for (2 days). And the prepared solid dispersions were also subjected to solubility study; drug concentration was determined spectrophtometrically at 457nm [17]

(ii) Dissolution studies-

Dissolution studies were conducted using USP paddle dissolution technique by dispersed powder technique, for this reason in 900 ml of 0.1N HCl, at a stable temperature 37±0.5°C, with a speed of paddle rotation is 50 rpm. 50mg powdered samples of each formulation (solid dispersion of Sunitinib) were added to the dissolution medium. At a time interval of 15 minutes, 5 ml of the mixture was withdrawn, filtered and inspected for Sunitinib content by UV spectrophotometer at 457 nm. Percent dissolution efficiency (%DE) was evaluated to compare the respective presentation of dissimilar carriers in solid dispersion formulations. The greatness of %DE (%DE t min) for each formulation was computed as the percent ratio of area under the dissolution curve up to the time (t) to that of the area of the rectangle narrated by 100% dissolution at the same time.[18]

(iii) Kinetic modelling of drug release-

(a)Zero order kinetics models

Drug dissolution from dosage forms that do not disintegrates and deliver the drug slowly can be illustrated by the equation:

$$Q_0 - Q_t = K_0T$$

Reposition the above equation,

$$Q_t = Q_0 + K_0T$$

Where,

Q_t is the amount of drug dissolved in time t,

Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and

K_0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies, are plotted as cumulative amount of drug released versus time. [6-8]

(b)First order kinetics model

This model is used to describe absorption and elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis.

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303. [6-8]

(c)Higuchi model

Higuchi proposed this model in 1961 to describe the drug release from matrix system. Higuchi model is based on the hypotheses that:

(i) initial drug concentration in the matrix is much higher than drug solubility

(ii) drug diffusion takes place only in one dimension (edge effect must be negligible)

(iii) drug particles are much smaller than system thickness

(iv) matrix swelling and dissolution are negligible

(v) drug diffusivity is constant and

(vi) perfect sink conditions are always attained in the release environment.

The data obtained were plotted as cumulative percentage drug release versus square root of time.[6-8]

(d)Korsmeyer–Peppas Model (The power law) A simple relationship which described drug release from a polymeric system equation was derived by Korsmeyer et al. in 1983.

The following assumptions were made in this model:
i. The generic equation is applicable for small values of t or short times and the portion of release curve where $Mt/M\infty < 0.6$ should only be used to determine the exponent n.
ii. Drug release occurs in a one dimensional way.
iii. The system's length to thickness ratio should be at least 10.
To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.[6-8]

Results and discussion

(A)Drug Study

1. Selection of detection wavelength

The λmax was observed at 431, 457 and 489 nm in D0 , D1 and D2 order derivative modes respectively and the UV spectra's was shown in the fig. 2, 3 & 4 respectively

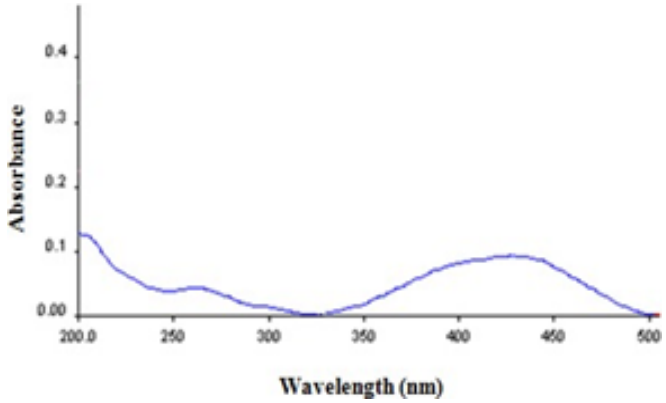

Fig no. 2. UV spectra showing maximum absorbance at D0 mode

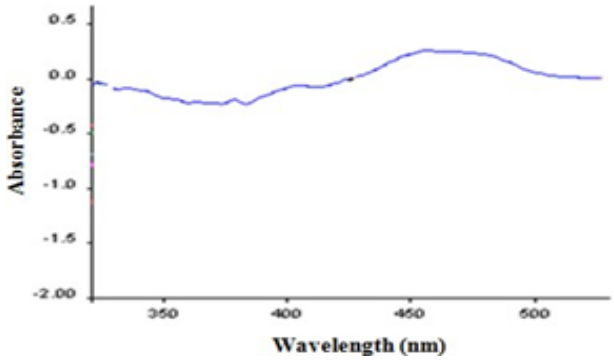

Fig. no. 3. UV spectra showing maximum absorbance at D1 mode

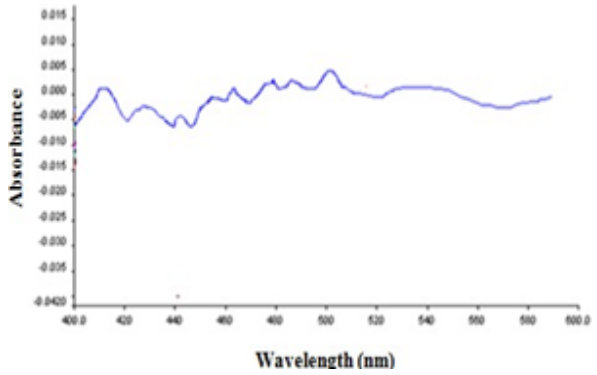

Fig. no. 4. UV spectra showing maximum absorbance at D2 mode

2. Callibration curve of Sunitinib Maleate

Table no. 2 Callibration curve of Sunitinib Maleate

Mode	**D0**			**D1**			**D2**		
Conc. (µg/ml)	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**
Absorbance	0.1659	0.2573	0.3714	0.5831	0.9342	1.3384	0.01	0.0155	0.0219
	0.1639	0.2548	0.3753	0.582	0.9332	1.3392	0.0096	0.0156	0.0226
	0.1626	0.2541	0.3672	0.5813	0.935	1.3389	0.0098	0.0158	0.0215
	0.1632	0.2557	0.3702	0.5792	0.9338	1.3402	0.0099	0.0159	0.0223
	0.1645	0.2568	0.3692	0.584	0.9351	1.3368	0.0099	0.0152	0.0225
	0.1632	0.2555	0.372	0.5754	0.9202	1.3372	0.0096	0.0158	0.022
Mean (±SD)*	0.1638±0.0	0.2557±0.	0.3708±0.	0.5808±0.	0.9319±0.00	1.3384±0.00	0.0098±0.00	0.0156±0.00	0.0221±0.00
	11	11	27	31	57	12	1	2	4
%R.S.D	0.72	0.47	0.74	0.54	0.62	0.095	1.7	1.65	1.87

mean±SD* = average of six determinations

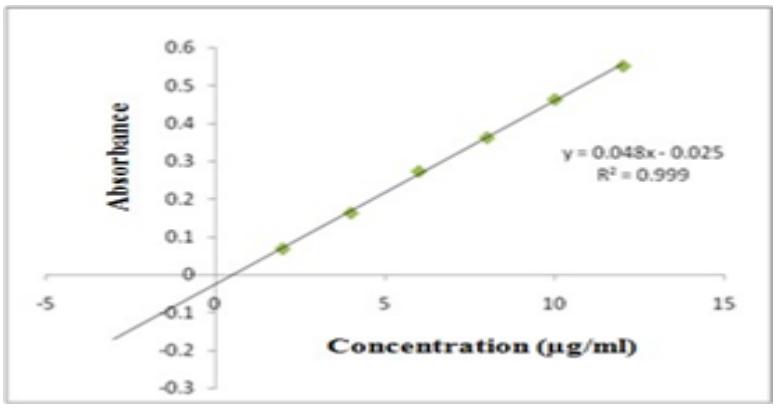

Fig. no. 5. Calibration graph of D0 mode

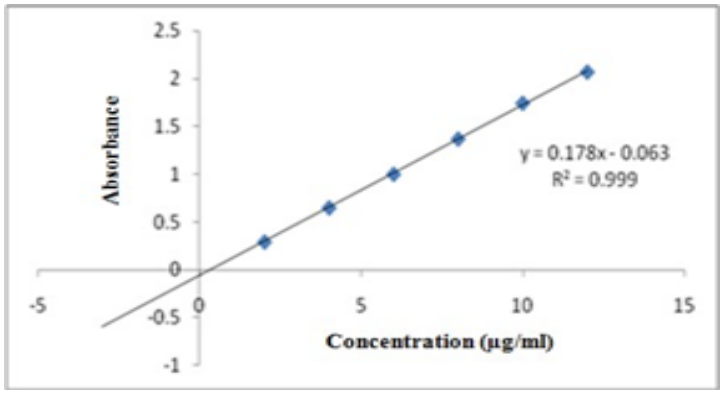

Fig.no. 6. Calibration graph of D1 mode

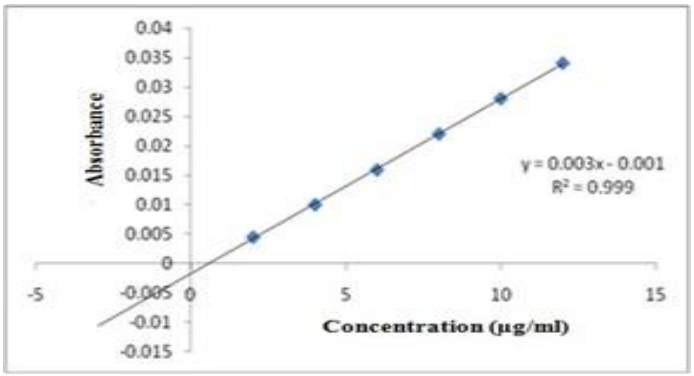

Fig. no. 7. Calibration graph of D2 mode

(B) Evaluation of solid dispersion

(i) Solubility studies

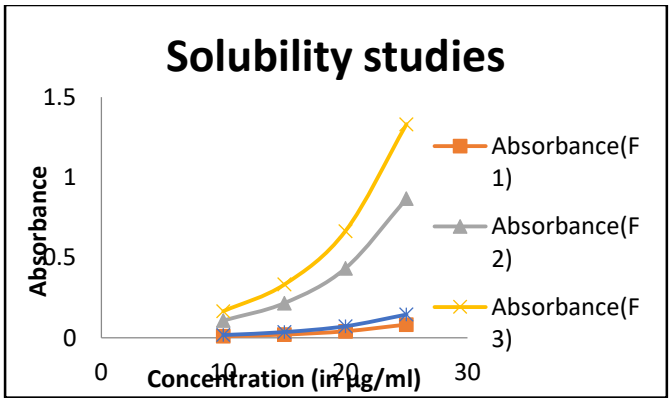

Fig. no. 8. Phase solubility study

(ii) Dissolution Studies and Kinetic Models for Drug Release

Table no. 3 Evaluation of solid dispersion

S.No.	formulation	Dissolution studies drug release (in90 min.)	First order	Zero order	Higuchi model	Korsmeyer-Peppas model
1	F1	129.69(µg/ml)	0.936	0.856	0.770	0.318
2	F2	86.3(µg/ml)	0.929	0.947	0.837	0.749
3	F3	78.6(µg/ml)	0.916	0.954	0.827	0.728
4	F4	249.38(µg/ml)	0.991	0.969	0.886	0.847

Discussion

Solid dispersions were prepared. Solid dispersions are set of products which comprises of two different components namely a hydrophilic matrix and a hydrophobic drug. The matrix may be in a crystalline or amorphous form. Here, the possible reason for increase in solubility is that, in solid dispersion Sunitinib can be dispersed molecularly, in amorphous particles or in crystalline particles. In this work PVP K-30 and Urea were used to prepare solid dispersion. PVP K-30 and Urea were used in four formulations in a ratio of Sunitinib: PVP K30 to be 1:1 and 1:2 &Sunitinib : Urea to be 1:1 and 1:2. From the observation Urea proved more convenient for enhancing the solubility of Sunitinib.

Conclusion

Sunitinib malate is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST).Sunitinib malate is a UV-absorbing molecule with specific chromophores in the structure that absorbs at a particular wavelength and this fact was successfully employed for their quantitative determinations using the UV Spectroscopic method and validating the same. The λmax was observed at 431, 457 and 489 nm in D0 , D1 and D2 order derivative modes respectively.

In this work, From the observation Urea proved more convenient for enhancing the solubility ofSunitinib.

REFERENCES-

1. Kumar R, Singh A, Salwan R, Bhanot R, Rahar S and Dhawan RK,GSC(2023)Bilogical and pharmaceutical sciences,22(01),114-121.
2. Amidon GL, Lennernas H, Shah VP and Crison JR (1995). Theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res., 12(3): 413-420.
3. Savjani K, Gajjar A, Savjani J.(2012) Drug solubility: Importance and enhancement Technique. ISRNP. 1-10.
4. Lobenberg R, Amidon GL.(2000) Modern bioavailability, bioequivalence and biopharmaceutical classification system.New scientific approaches to international regulatory standards. Eur J Pharm Sci. 50(1):3–20.
5. Singh et al,(2011) A review on solid dispersion, IJPLS, 2(9), 1078-1095.
6. Chaudhary A, Nagaich U, Gulati N, et al.(2012) Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications. J Adv Pharm Technol Res. 2(1):32–67.
7. Dixit AK., Singh RP,(2012) solid dispersion – A strategy for improving the solubility of poorly soluble drugs, IJRPBS, 3(2), 960-966.
8. Blagden N, Gavan P, York P. Crystal(2007) engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Del Rev. 59(30):617–630.
9. Dhirendra K, Lewis S, Udupa N, et al.(2009) Solid Dispersions: A Review. Pak J Pharm Sci., 22(2):234–246.
10. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use ICH Guideline:(1994) Validation of Analytical procedures text and methodology Q2(R1);
11. Edwin P Rock, Vicki goodman, Janet X Jiang, KoorosMahjoob, S Leigh Verbois, David Morse, et al.(2007) Food and drug administration drug approval summary: sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist;12:107-13.
12. Val R Adams, Markos Leggas.(2007) Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Clin Ther;29:1338-53.
13. Sandhya B, Chinnari Harika V, Bikshal Babu Kasimalla, Reshma Syed, Kalpana Pammi.(2011) RP-HPLC method development and validation for the analyisis of Sunitinib in pharmaceutical dosage forms. Int J Sci Innovations Discoveries;1:441-50.
14. De Bruijn P, Sleijfer S, Lam MH, Mathijssen RH, Wiemer EA, Loos WJ. (2010) Bioanalytical method for the quantification of Sunitinib and its n-desethyl metabolite SU12662 in human plasma by Ultra performance liquid chromatography/tandem triple quadrupole Mass spectrometry. J Pharm Biomed Anal;51:934-41.
15. Marie Christine Etienne-Grimaldi, Nicole Renée, Hassan Izzedine, Gérard Milano.(2009) A routine feasible HPLC analysis for the anti- angiogenic tyrosine kinase inhibitor, Sunitinib, and its main metabolite, SU12662, in plasma. J Chromatogr;877:3757-61.
16. Benoit Blanchet, Carole Saboureau, Anne-Sophie Benichou, Bertrand Billemont, Fabrice Taieb, Stanislas Ropert, et al.(2009) Development and validation of an HPLC-UV-visible method for sunitinib quantification in human plasma. Clin Chim Acta ;404:134-9.
17. Hsu CH, Cui Z, Mumper RJ, et al.(2023) Micellar Solubilization of Some Poorly Soluble Antidiabetic Drugs. AAPS Pharm Sci Tech. , 9(2):431–436.

18. Huang Y, Dai WG.(2014) Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm Sin B. 4(1):18–25.