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Solubility Enhancement of Sunitinib Using PVP K-30 and Urea-Based Solid Dispersions: Comparative Formulation and Kinetic Evaluation

Sandeep Mukati[*1], Ravikant Gupta[2], Sachin K. Jain[2], Sudha Vengurlekar[2]

[*1]Research Scholar, Faculty of Pharmacy, Oriental University, Indore (M.P.), India.

[2]Faculty of Pharmacy, Oriental University, Indore (M.P.), India.

[*]**Corresponding author:**

Sandeep Mukati

Email ID: mukatisandeep1995@gmail.com

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ABSTRACT

Sunitinib is a poorly water-soluble, multi-targeted receptor tyrosine kinase (RTK) inhibitor used in the treatment of renal cell carcinoma (RCC) and gastrointestinal stromal tumours (GIST). Enhancing its solubility and dissolution is crucial for improving bioavailability. This study explores the solid dispersion technique as an effective approach for solubility enhancement. Solid dispersions of Sunitinib were prepared using the solvent evaporation method with hydrophilic carriers PVP K-30 and urea in different drug-to-carrier ratios. The formulations were evaluated through solubility studies, in vitro dissolution, and drug release kinetics. UV spectrophotometric analysis showed maximum absorbance at 457 nm, confirming suitability for quantitative determination. Among the formulations, the dispersion containing Sunitinib and urea in a 1:2 ratio F4 exhibited the highest drug release (249.38 µg/ml in 90 minutes), with the drug release following first-order kinetics. From the observation, urea proved more convenient for enhancing the solubility of Sunitinib. The results indicate that solid dispersion with appropriate carriers significantly improves dissolution behaviour. This study confirms that solid dispersion is a promising strategy to improve the aqueous solubility of hydrophobic drugs like Sunitinib, thereby enhancing their therapeutic efficacy and bioavailability.

Keywords: *Solubility Enrichment, Sunitinib, PVP K-30, Solid Dispersion, Urea, Bioavailability.*

1. INTRODUCTION

Solubility is a fundamental aspect of pharmaceutical formulation, playing a critical role in the design and development of various dosage forms. It refers to the capacity of a solute to dissolve in a particular solvent, forming a homogeneous system. In pharmaceutical sciences, solubility is defined as the concentration of a solute in a saturated solution at a specified temperature. This property significantly influences a drug's bioavailability, absorption rate, and therapeutic performance. Enhancing the solubility of poorly water-soluble drugs is essential to ensure effective drug delivery, consistent therapeutic outcomes, and formulation reliability across different dosage forms. [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]

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

b) **In this equation:**

S is the solubility of fine particles,

S_0 is the solubility of infinitely large (bulk) particles,

γ is the surface tension of the solid,

V is the molar volume,

R is the universal gas constant,

T is the absolute temperature, and

r is the radius of the fine particle.

This formula illustrates that solubility increases as the particle size (radius r) decreases. The inverse relationship shows that reducing the particle size enhances solubility due to increased surface energy, which promotes better dissolution. This principle is particularly important in improving the solubility of poorly water-soluble drugs in pharmaceutical formulations.

a) **Pressure:** Changes in pressure generally have negligible effects on the solubility of solid and liquid solutes. However, in the case of gaseous solutes, solubility is significantly influenced by pressure. An increase in pressure enhances gas solubility, while a reduction in pressure leads to decreased solubility. This behaviour aligns with Henry's Law, which states that the solubility of a gas in a liquid is directly proportional to the applied pressure. [2-5]

b) **Temperature:**The solubility of solutes is significantly influenced by temperature. An increase in temperature in endothermic dissolving processes supplies the energy required for interactions between the solute and the solvent, improving solubility. On the other hand, solubility tends to decrease with increasing temperature in exothermic reactions, where energy is produced during dissolution. Notably, because their dissolution is exothermic, some solid solutes become less soluble with higher temperatures. [2-5]

Molecular size: Higher molecular weight and size molecules are less soluble because it is more difficult to encircle larger molecules with solvent molecules to dissolve the material. The amount of carbon branching in organic compounds will increase their solubility since it will reduce their size (or volume) and make it easier to solvate them with a solvent. [2-5]

2. 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

1. **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]
2. **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 glassyform. [8,9]

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 tumour growth, pathologic angiogenesis, and metastatic progression of cancer.[11]

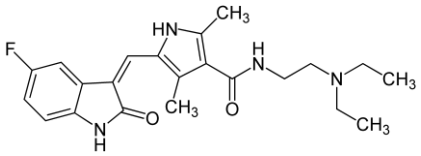

Fig. no. 1. Chemical Structure of Sunitinib[11,12]

3. MATERIALS AND METHODS

The raw material of Sunitinib (98%w/w) was obtained a gift sample, which was used as reference material throughout the experiment without any prior treatment.

Solubility studies

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

- Very freely soluble in Dimethyl Sulfoxide (DMSO).
- Very freely soluble in Methanol
- Soluble in alcohol.
- Slightly Soluble in 0.1N HCl.
- Slightly Soluble in 0.1N NaOH. [13,14]

Selection of solvent

Sunitinib drug is very freely soluble in Methanol. Hence, Methanol was chosen as thesolvent to solubilize Sunitiniband to carry out further analysis.

Preparation of standard stock solution of Sunitinib

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

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

Formulation of solid dispersions

Solid dispersions were 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: In order to determine the potential solubilizing effect of the carrier, solubility studies of sunitinib were conducted by adding 20 mg of the drug to 10 ml of aqueous solutions containing increasing concentrations of the carrier (1:0, 1:1, 1:2). Glass containers were sealed and kept under stirring at a constant temperature (20°C) for two days. The prepared solid dispersions were also subjected to solubility studies; the drug concentration was measured spectrophotometrically at 457 nm.[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:

$$Q_0 - Q_t = K_0 T$$

Reposition the above equation,

$$Q_t = Q_0 + K_0 T$$

Were,

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 model is based on the hypotheses that:

1. Initial drug concentration in the matrix is much higher than drug solubility.
2. Drug diffusion takes place only in one dimension (edge effect must be negligible).
3. Drug particles are much smaller than system thickness.
4. Matrix swelling and dissolution are negligible.
5. Drug diffusivity is constant and 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:

1. 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.
2. Drug release occurs in a one-dimensional way.
3. 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]

4. RESULT

(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 was shown in the fig. 2, 3 & 4 respectively

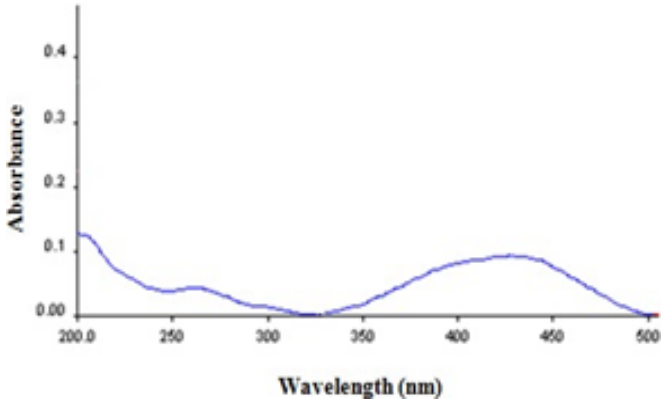

Fig no. 2. UV spectra showing maximum absorbance at D0 mode

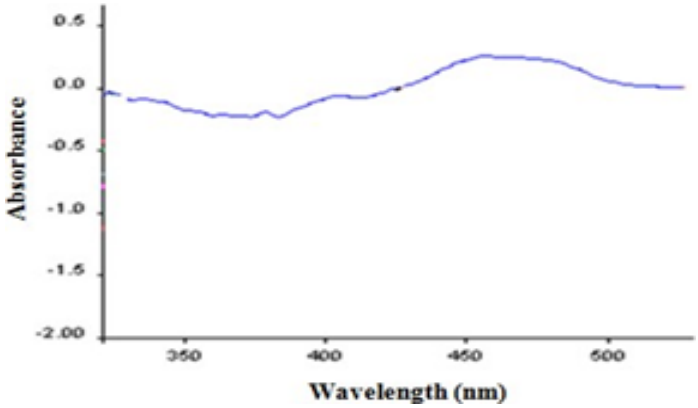

Fig. no. 3. UV spectra showing maximum absorbance at D1 mode

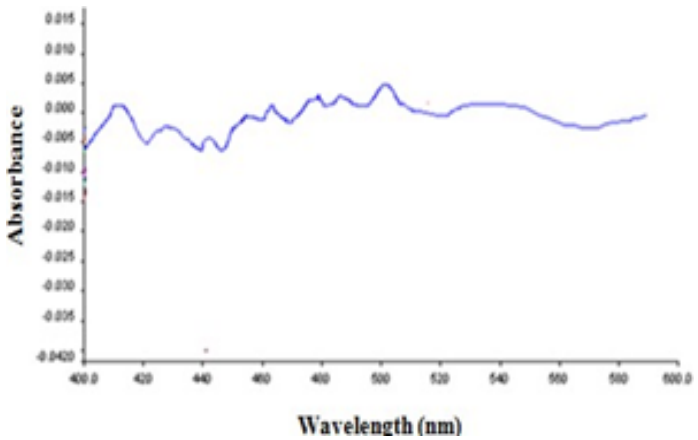

Fig. no. 4. UV spectra showing maximum absorbance at D2 mode

2. Solubility Profile of Sunitinib in Various Solvents

Table no. 2 Solubility Profile of Sunitinib in Various Solvents

S. No.	Solvent	Solubility of Sunitinib
1	Dimethyl Sulfoxide (DMSO)	Very Freely Soluble
2	Methanol	Very Freely Soluble
3	Ethanol	Soluble
4	0.1 N HCl	Slightly Soluble
5	0.1 N NaOH	Slightly Soluble

3. Calibration curve of Sunitinib:

Table no. 3 Calibration curve of Sunitinib

Mode	D0			D1			D2		
Concentration (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

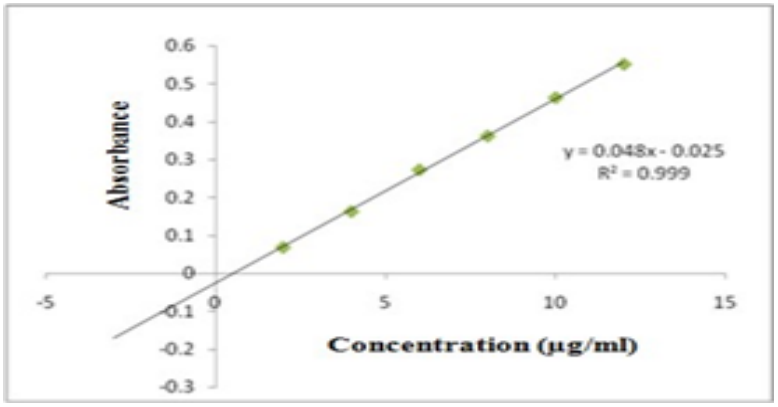

Fig. no. 5. Calibration graph of D0 mode

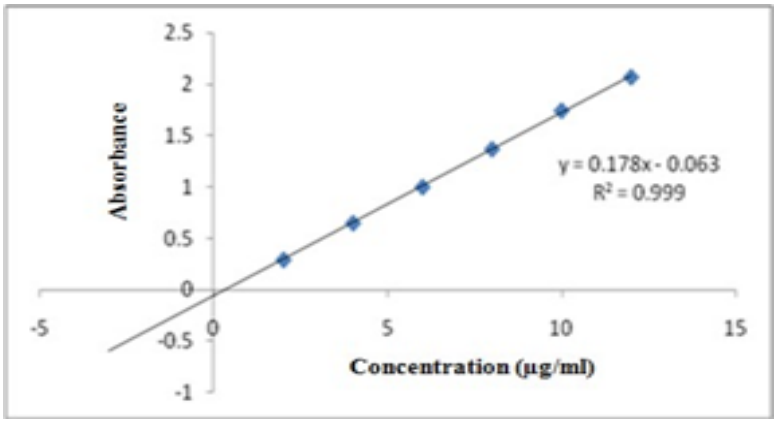

Fig.no. 6. Calibration graph of D1 mode

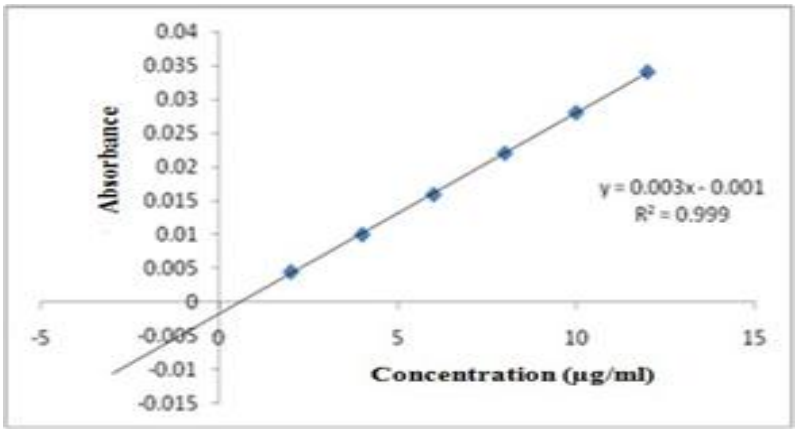

Fig. no. 7. Calibration graph of D2 mode

(B) Evaluation of solid dispersion

(i) Solubility studies

Table no. 4 Solubility studies of solid dispersion

Concentration (in µg/ml)	Absorbance(F1)	Absorbance(F2)	Absorbance(F3)	Absorbance(F4)
5	0.0052	0.0542	0.0832	0.0091
10	0.0104	0.1084	0.1664	0.0182
15	0.0208	0.2168	0.3328	0.0364
20	0.0416	0.4336	0.6656	0.0728
25	0.0832	0.8672	1.3312	0.1456

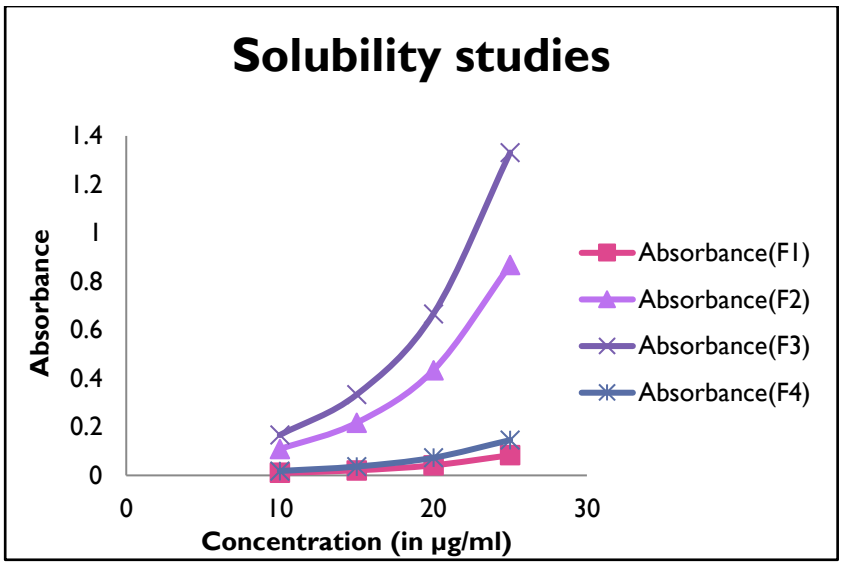

Fig. no. 8. Phase solubility study

(ii) Dissolution Studies and Kinetic Models for Drug Release

Table no. 5 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

5. 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 aratio ofSunitinib: 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.

6. CONCLUSION

Sunitinib 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 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 comparative study, from the observation Urea proved more convenient for enhancing the solubility of Sunitinib.

Future Directions/Insights: The current work shows how solid dispersion methods, specifically the use of urea as a hydrophilic carrier, can improve sunitinib solubility and dissolution profile. To confirm its therapeutic efficacy, future investigations might concentrate on scaling up the improved formulation (F4) for stability testing, in vivo evaluation, and clinical correlation studies.

Conflicts of Interest: The authors declare no conflict of interest.

Author Contributions: Mr. Sandeep Mukati conceptualized and conducted the research as part of his doctoral work. Mr.

Ravikant Gupta and Dr. Sudha Vengurlekar provided technical guidance and supervised the experimental work. Dr. Sachin K. Jain contributed to analytical standardization and data interpretation. All authors reviewed and approved the final manuscript.

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