JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Enhancement of Solubility of Poorly Solubile Drug Tinidazole

Shah Harshil*[1], Hardeep Banwait[2], Nishith Patel[2]

1 Student of M.Pharm (Pharmaceutics) A-One Pharmacy College, Anasan, Ahmedabad, Gujarat, India-382330

2 Department of Pharaceutics, A-One Pharmacy College, Anasan, Ahmedabad, Gujarat, India-382330

ABSTRACT:

Tinidazole is nitro imidazole derivative, anti-parasitic drug used against protozoan infection. It is used as tissue amoebic ides for both intestinal and extra intestinal amoebiasis. It has broad spectrum cidal activity against protozoa including Giardia Lamblia many anaerobic bacteria such as fragilis, fusobacterium, clostridium perfrigens, cldifficile, helicobacter pylori. But as it is BCS Class-II drug, dissolution from its dosage forms is too low and is rate limiting step in absorption of drug. Poor aqueous solubility and poor dissolution rate poses difficulties in achieving predictable and reproducible in vivo/in vitro correlations and also bioavailability related problems. Further it also undergoes extensive first pass effect leading to low and variable bioavailability. Thus improvement in extent and rate of dissolution is highly desirable for such compounds, as this can lead to increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. In this research attempt was made to improve solubility of tinidazole by solid dispersion technique and prepared solid dispersions will be formulated in form of fast disintegrating tablets using various superdisintegrants to improve solubility, bioavailability and patient compliance and clinical efficacy of tinidazole.

KEY WORDS: Solid Dispersion, DoE, Factorial design, Tinidazole, Fast disintegrating Tablets.

Article history:

Received 14 April 2016
Accepted 28 April 2016
Available online 01 July 2016

Citation:
Shah H., Banwait H., Patel N. K. Enhancement of Solubility of Poorly Solubile Drug Tinidazole. **J Pharm Sci Bioscientific Res**. 2016 6(4):559-565

For Correspondence:
Harshil Shah
Student of M.Pharm (Pharmaceutics) A-One Pharmacy College, Anasan, Ahmedabad, Gujarat, India.

(www.jpsbr.org)

INTRODUCTION:

Oral solution transport is minimum troublesome and most easy technique for controlling medicines. In light of more important trustworthiness, more diminutive mass, definite estimations and straightforward creation, solid oral dosages structures are ideal over various sorts of oral dosage shapes. Therefore, most of new invention components (NCE) work in advancement these days are intended to use as solid measurement shape that start effective and reproducible in vivo plasma center after oral association. Honestly, most NCEs are deficiently water soluble drugs, not all around acclimatized after oral association, which can corrupt drug's innate feasibility. What's more, most reassuring NCEs, paying little respect to their high permeability, are all things considered just acclimatized in upper little digestive tract, absorption being diminished basically after ileum, showing up, in this way, that there is small absorption window. Consequently, if these prescriptions are not completely released in this gastrointestinal zone, they will have low bioavailability. In this way, one of major current troubles of pharmaceutical business is related to methods that improve water dissolvability of meds. Drug release is fundamental and compelling step for oral drug bioavailability, particularly for pharmaceuticals with low gastrointestinal dissolvability and high permeability1-5. By upgrading pharmaceutical release profile of these medicines, it is possible to enhance

their bioavailability and decrease manifestations. Solid scatterings are one of most powerful strategies to upgrade drug entry of deficiently dissolvable medicines. These can be described as nuclear mixes of ineffectually water dissolvable medicines in hydrophilic carriers, which present prescription release profile that is driven by polymer properties.[6]

Solubility

Dissolvability is champion amongst most essential properties influencing bioavailability in light of way that of its part in breaking down. Before happening to combinatorial science and high throughput screening in late 1980s and mid-1990s, most escalates that were considered incapably dissolvable had dissolvability in extent of 10-100 µg/ml. practically, no marketed drug had dissolvability underneath 10µg/ml. Today, blends with dissolvability range of 1-10 µg/ml and even < 1 µg/ml are incredibly consistent. Having OK understanding of components impacting dissolvability is fundamental to our ability to address deficiencies in formulation brought on by poor dissolvability.[7]

Table 1 Solubility definition

Solubility definition	Part of solvent for one part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble	<1	>1000	1000
Freely soluble	From 1 to 10	100-1000	100
Soluble	From 10 to 30	33– 100	33
Sparingly soluble	From 30 to 100	10-33	10
Slightly soluble	From 100 to 1000	1-10	1
Very slightly soluble	From 1000 to 10,000	0.1-1	0.1
Practically insoluble	>10,000	<0.1	0.01

MATERIALS AND METHODS

Materials

Tinidazole was a generous gift from Balaji Pharmaceutical, Surat(India). PEG-6000 was a generous gift from Suvidhinath Laboratories, Vadodara. Crospovidone, Sodium Starch Glycolate, Cross Carmalose Sodium were purchased from Balaji Pharmaceutical, Surat(India). All chemicals used were of analytical grade. Double distilled water was used throughout the study.

Methodology

Preformulation of Drug

Preformulation study are mostly generate data which are useful to develop stable dosage forms that can be mass-produced for manufacturer.

Organoleptic Characteristics of Tinidazole

Physical examine was done to check Organoleptic Characteristics of Tinidazole like color, odor & physical appearance of pure drug.

Determination of Melting Point of Tinidazole

Melting point of Tinidazole was evaluated by capillary method.

Solubility study of Tinidazole

Studies six different commonly used nonvolatile solvents i.e. water, 0.1 N HCL, pH 6.4 Phosphate buffer, Acetone, Ethanol were used to carry out solubility studies of Tinidazole. Saturated solutions of Tinidazole were prepared by adding excess drug to vehicles and shaking on shaker for specific period of time under constant vibration. After this period solutions were filtered, diluted with distilled water and analyzed by UV-spectrophotometer at wavelength of 275 nm. Solvents with greater ability to solubilize drug was selected for formulation of Solid dispersion system for enhanced release.

Saturation Solubility of Tinidazole

Saturation solubility study was carried out by preparing saturated solution of drug in water & analyzing them by using spectrophotometer. Saturated solution was prepared by adding excess amount of drug to water and let it stay to achieve equilibrium state (e.g., by shaking, stirring) for specific time of period.

Identification of Wavelength max (λmax) of Tinidazole by Using 0.1 N HCL

Weigh 100mg of Tinidazole and dissolved in sufficient amount of methanol and make up volume up to 100 ml by using 0.1 N HCL. Take 1ml of this solution was pipette out in separate volumetric flask and diluted with 0.1 N HCL and subjected for UV scanning in range 200-400 using UV-visible spectrophotometer.

Preparation of Calibration Curve for Tinidazole by Using 0.1 N HCL (pH 1.2)

Sample Preparation of stock and standard solutions for Tinidazole by Using 0.1 N HCL (pH 1.2)

100 mg drug Dissolve in sufficient amount of Methanol than make up volume up to 100 ml by using 0.1 N HCL (pH 1.2) (Take 1 ml of above solution and make up it up to 100 ml to produce secondary stock solution (100 µg/ml). From secondary stock solution calibration curve standards (5, 10, 15 and 20 µg/ml) were prepared using 0.1 N HCL (pH 1.2). Absorbance were measured for all calibration curve standards at 275 nm and linear graph was plotted between concentrations versus absorbance.

Identification of Drug- Tinidazole by FT-IR Spectroscopy

Potassium bromide IR disc was prepared using 1mg of Tinidazole on Hydraulic Pellet press which was scanned of 4000-400 cm-1 re in FTIR and obtained IR Spectrum was compare with reference spectrum of Tinidazole.

Drug- Excipients Compatibility Studies by FT-IR

Potassium bromide IR disc was prepared using Tinidazole, Propylene glycol, poly ethylene glycol 200, Avicel PH 102, Arosile, sodium starch Glycolate, cross povidone, cross Carmalose sodium and mixture on Hydraulic Pellet press was be scanned 4000-400 cm-1 region in FTIR and obtained IR Spectrum was compared with reference spectrum of Tinidazole.

Drug-Excipients Compatibility Studies by DSC

Thermal analysis of Drug Tinidazole and carrier-coating material was studied employing differential scanning calorimetry which was done to check compatibility for Solid dispersion compact formulations.

X-ray diffraction (XRD) of optimized Formulation

XRD & SEM studies are recommended to control crystallinity of drug. Disappearance of characteristic peak or crystals of drug generally indicates that drug is converted into amorphous form or is solubilized in Solid dispersion formulation.

Particle Morphology of Optimized Formulation by SEM

For illustration of ultra-structure of prepared Tablets for morphology by using scanning electron microscopy

FT-IR and DSC Study of Optimized Formulation

It is used to determine any possible interaction between excipients used in formulation. There is indication that drug is in form of solution in Solid dispersion formulation if characteristic peak of drug is absent in FT-IR and DSC thermogram.

RESULT AND DISCUSSION

Melting point:

Melting point of Tinidazole was 126^0 C evaluated by capillary method.

Solubility study of Tinidazole

Studies six different commonly used nonvolatile solvents i.e. water, 0.1 N HCL, pH 6.8 Phosphate buffer, pH 7.4 Phosphate buffer were used to carry out solubility studies of Tinidazole. Saturated solutions of Tinidazole were prepared by adding excess drug to vehicles and shaking on shaker for specific period of time under constant vibration. After this period solutions were filtered, diluted with distilled water and analyzed by UV-spectrophotometer at wavelength of 307 nm.

Table 2 Solubility of Tinidazole

SL. NO.	SOLVENTS	INTERPRETATION
1.	Water	Insoluble
2.	pH 6.8 Phosphate buffer	Insoluble
3.	pH 7.4 Phosphate buffer	Insoluble
4.	0.1 N HCL	Slightly Soluble
5.	Acetone	Freely soluble
6.	Methanol	Sparingly soluble

Saturation Solubility of Tinidazole

Saturation solubility study was carried out by preparing saturated solution of drug in water & analyzing them by using spectrophotometer. Saturated solution was prepared by adding excess amount of drug to water and let it stay to achieve equilibrium state (e.g., by shaking, stirring) for specific time of period.

***Table 3*: Saturation solubility of Tinidazole**

SL. NO.	SOLVENT	SATURATION SOLUBILITY (mg/mL)
1.	Water	2.35± 0.82

Identification of Wavelength max (λmax) of Tinidazole by Using 0.1 N HCL

Weigh 100mg of Tinidazole and dissolved in sufficient amount of methanol and make up volume up to 100 ml

by using 0.1 N HCL. Take 1ml of this solution was pipette out in separate volumetric flask and diluted with 0.1 N HCL and subjected for UV scanning in range 200-400 using UV-visible spectrophotometer.

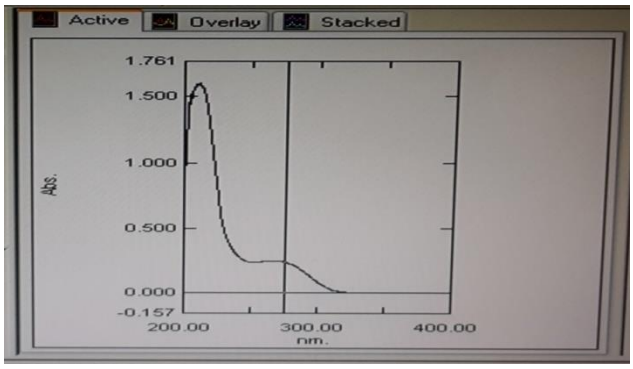


Figure1 **λmax Spectrum for Tinidazole using 0.1 N HCL**

Table 4 **Wavelength $_{max}$ (λ_{max}) of Tinidazole using 0.1 N HCL**

Drug Name	Actual λ_{max}	Observed λ_{max}
Tinidazole	278nm	275nm

Preparation of Calibration Curve for Tinidazole by Using 0.1 N HCL

Sample Preparation of stock and standard solutions for Tinidazole by Using 0.1 N HCL (pH 1.2)

100 mg drug Dissolve in sufficient amount of Methanol than make up volume up to 100 ml by using 0.1 N HCL (pH 1.2) (Take 1 ml of above solution and make up it up to 100 ml to produce secondary stock solution (100 µg/ml). From secondary stock solution calibration curve standards (5, 10, 15 and 20 µg/ml) were prepared using 0.1 N HCL (pH 1.2). Absorbance were measured for all calibration curve standards at 275 nm and linear graph was plotted between concentrations versus absorbance.

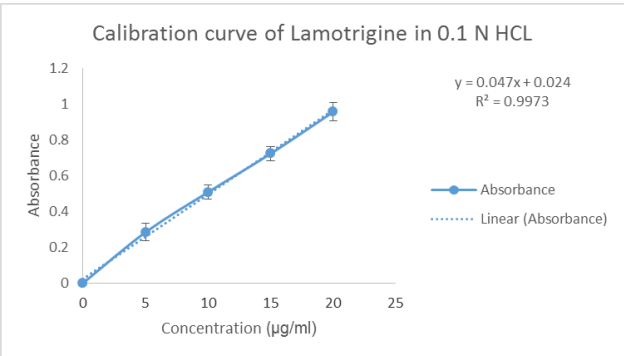


Figure 2 **Calibration curve of Tinidazole in 0.1 N HCL**

Table 5: Summery Report of calibration curve for Tinidazole Using 0.1 N HCL (pH 1.2)

Parameters	Tinidazole
Wavelength (λmax)	**275**
Beer's limit (µg/ml)	**0-20**
Corrélation coefficient (R^2)	**0.9973**
Slope	**0.047**
Obeys Beer law in conc. range of 0-20 µg/ml	
R^2 value shows linearity	

Calibration curve for Tinidazole was obtained by using 0-20 µg/mL solution of Tinidazole in methanol. Absorbance was measured at 257 nm. Calibration curve for Tinidazole was shown in figure 4.5. Absorbance obtained for given concentrations was shown in Table 4.11. Calibration curve (Table 4.12) shows regression equation Y= 0.047x and R^2value 0.9973. Result revealed that drug concentration between 0 – 20 µg/mL follows Beer Lambert's law as regression coefficient was 0.9973.

Statistical Analysis:

Design expert software version 9.0.2.0. Was used for Statistical analysis and produced first order polynomial equations. From preliminary results, 3^2 full factorial design was utilized in which two factors were evaluated, separately at three levels and possible nine combinations were formulated. Three level factorial studies were carried out using two different variables. In first factorial design, amount of concentration of PEG 6000(X1) and concentration of Poloxamer 188 (X2) were taken as independent variables while drug content (Y1), solubility (Y2) and % CDR in 40 min (Y3) were selected as dependent variables for both factorial designs.

Effect on drug content (Y1) - Surface Response Study:

Positive value for coefficient of X1- concentration of PEG 6000 in equation indicates increase in Drug content. Positive value of coefficient of X2- concentration of poloxamer 188 indicates increase in response of Y1 i.e. drug content. It indicates linearity of surface response and contour plot as shown in figure. Reduced linear model was significant. Therefore, it was applied for all two independent variables and detailed ANOVA, Response Surface Counter Plot and 3 D plot are as follows:

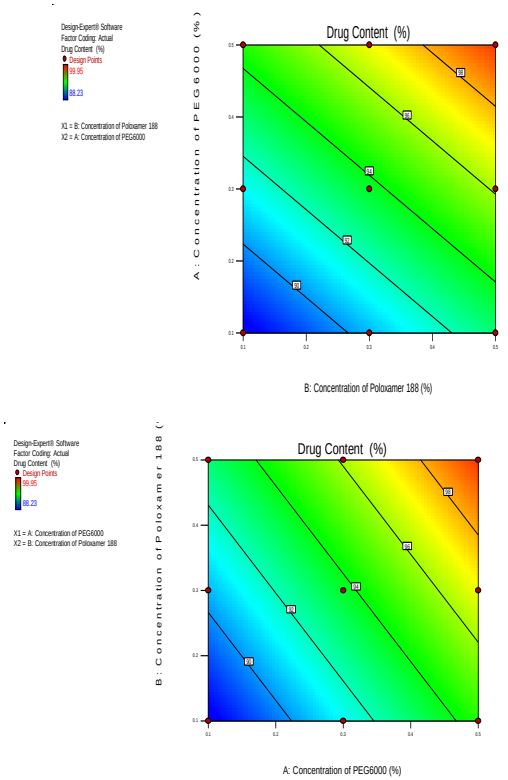
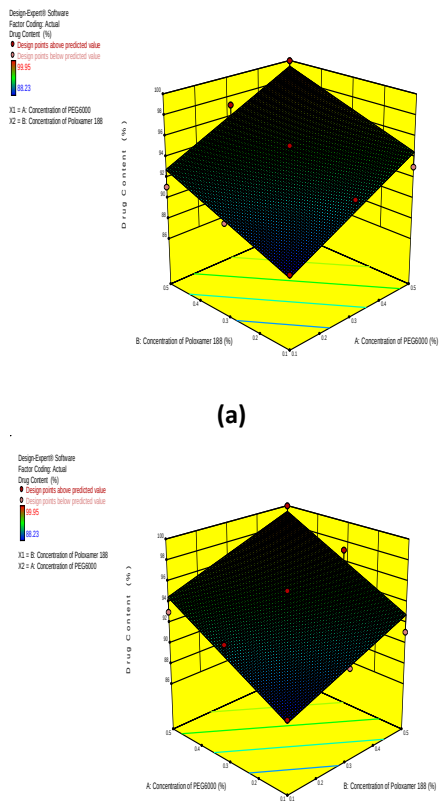


Figure 6: Response Surface Plot

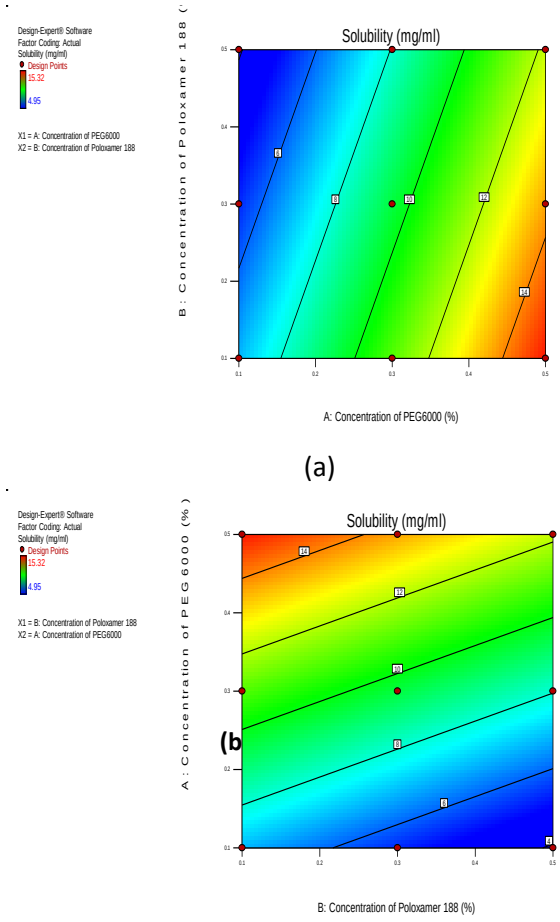


(a)

Figure 7: **3D Surface Plot**

Effect on solubility (Y2) - Surface Response Study:

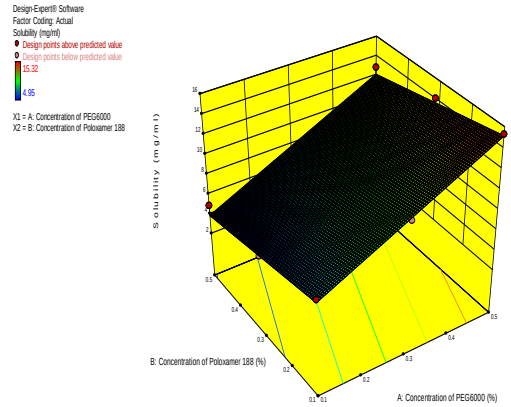
Positive value for coefficient of X1- Concentration of PEG 6000 in equation indicates increase in solubility. Negative value of coefficient of X2-concentration of Poloxamer 188 also indicates decrease in response of Y2 i.e. solubility. It indicates linearity of surface response and contour plot as shown in figure.



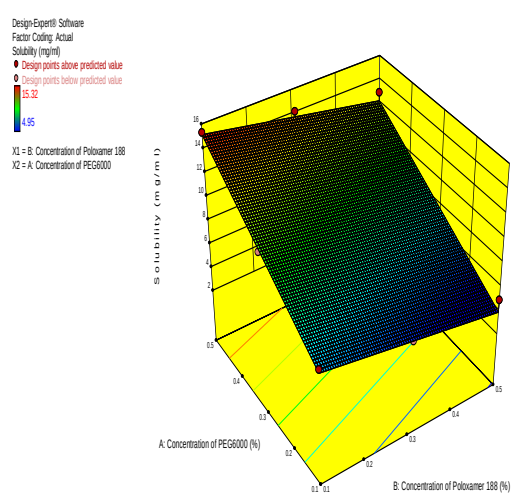
(a)

(b)

Figure 8: Response Surface Plot



(a)

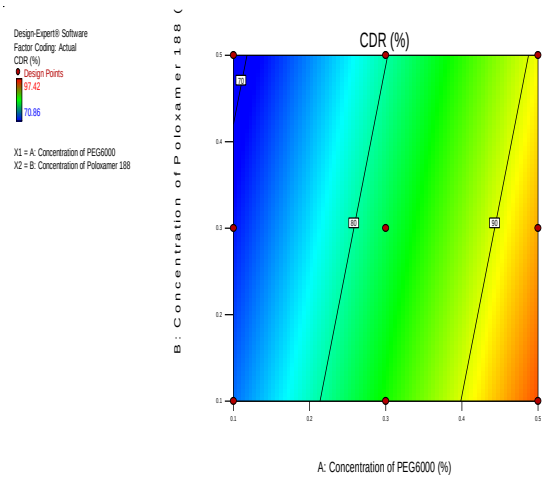


(b)

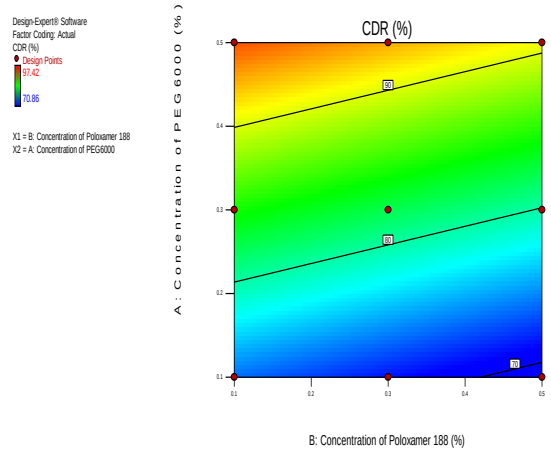
Figure 9: 3D Surface Plot

Effect on % CDR (Y3) - Surface Response Study:

Positive value for coefficient of X1-Concentration of PEG 6000 in equation indicates increase in Drug release. Negative value of coefficient of X2- Concentration of Poloxamer indicates decrease in response of Y3 i.e. drug release. It indicates linearity of surface response and contour plot as shown in figure. Reduced model was applied for all two independent variables and detailed ANOVA, Response Surface Counter Plot and 3D plot are as follows:

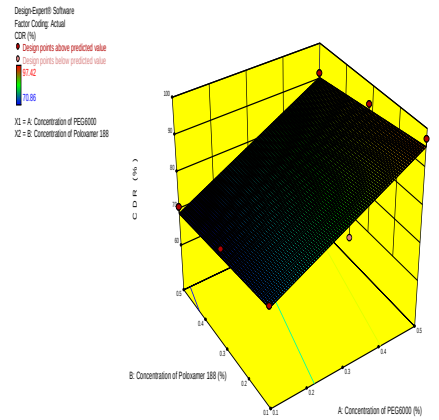


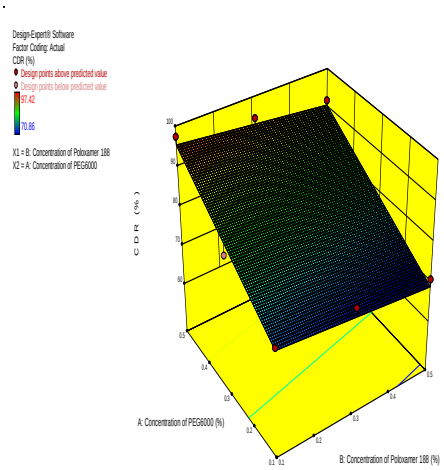
(a)



(b)

Figure 10: Response Surface Plot





(b)

Figure 11: 3D Surface Pl

Establishing Design Space and Control Strategy

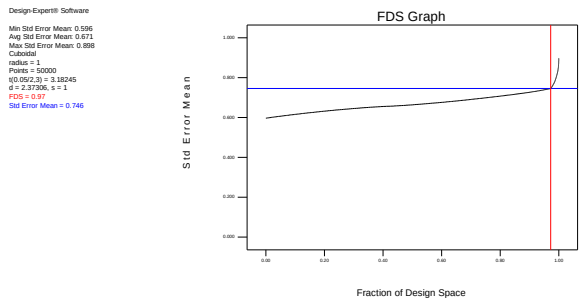


***Figure 12*: FDS Graph**

FDS curve indicates what % fraction of design space has given prediction error or lower. Good design will have flatter and lower curve than poor design as shown in figure 4.35. Flatter means overall prediction error will be constant. Lower means overall prediction .error will be smaller. FDS should be at least 0.84 or 80% for exploration, and 100% for robustness testing.

CONCLUSION

Compounds with poor solubility are increasingly posing challenges in development of new drugs, since large number of drugs coming directly from synthesis or from high throughput screening have very poor solubility. It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in gastrointestinal tract after oral administration hence comprising oral bioavaibility.

Biopharmaceutical Classification system divides drugs into four classes depending on in vitro and in vivo permeability data. For class II drugs dissolution /solubility and for Class III drug permeability limits oral drug absorption. It is obvious that class II drugs low ability to dissolve is more important limitation to their overall rate and extent of absorption than their ability to permeate through intestinal epithelia. There are several pharmaceutical strategies available to improve aqueous solubility of poorly soluble drugs

Among all technique solid dispersion (SD), is most efficient technique from dispersion in carrier more especially poloxamer have been recently widely used as wetting and solubilizing agents as well as surface adsorption excipients. They have been employed to enhance solubility, dissolution and bioavailability of many hydrophobic drugs using various techniques, for some drugs, improvement in solubility using poloxamer was higher compared to other meltable polymers such as PEGs and complex forming agents such as cyclodextrin. In present study, poloxamer was thus empirically selected as hydrophilic carrier for its excellent surfactant properties and oral safety.

REFERENCES

1. Dhirendra K, Lewis S and Atin K, “Solid dispersions: A review”, *Pak. J Pharm. Sci*, **2009**, 22(2), 234-46.
2. Dressman J.B, Amidon G.L, Reppas C and Shah V.P, “Dissolution Testing As a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Form”, *Pharm Res*, **1998**, 15, 11-22.
3. Sekiguchi and Obi, “Crystal engineering of active pharmaceutical ingredients to improve solubility & dissolution rates”, *Adv Drug Deliv Rev,* **2007**, 59(7), 617-30.
4. Wadke DA, Serajuddin AT and Jacobson H, “Preformulation testing. In : Lieberman HA, lachman L. Schwartz JB. eds. Pharmaceutical Dosage Forms: Tablets” New York, Marcel Dekker **1989**: 1-73.
5. Available from: http://www.drugbank.org
6. Lipinski CA, Lombardo F, Dominy BW and Feeney PJ, “Experimental and Computational approaches to estimate solubility and permeability in drug discovery and developmental settings”, *Adv. Drug Deliv*, **1997**, 23, 3-25.
7. Yalkowsky N, “Estimation of aqueous solubility I : Application to organic non-electrolytes.” *J Pharm Sci.*, **2000**, 90, 234-52

Journal of Pharmaceutical Science and Bioscientific Research Publication
www.jpsbr.org, www.jpsbr.com
jpsbronline@rediffmail.com, publish@jpsbr.com