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QUALITY BY DESIGN APPROACH FOR DEVELOPMENT AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF NITROFURANTOIN

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ABSTRACT
The Objective of present work is to develop a Solid Self Emulsifying Drug Delivery System (S-SMEDS) of poorly water soluble drug Nitrofurantoin (NFT). Nitrofurantoin is antibiotic or antimicrobial drug belongs to BCS Class II drug, having half-life 20 minutes. For formulation; solubility of NFT was determined in oil, surfactant and co-surfactant. The final components of micro-emulsion were found to be Cinnamon oil, Tween 20 as surfactant and PEG400 as a co-surfactant. Pseudoternary phase diagram NFT loaded micro-emulsion were prepared and optimized by using design of Experiments (DOE). By considering 2 factor globule size and emulsification time the 9 formulations were prepared. Batch No. 5 was selected on the basis of optimization of globule size 0.492 and emulsification time 75sec. According to the design of experiments, probability plots, pounter plots, pormal probability, Response surface plot 3D response curve it was observed that with increase in ratio of surfactant to co-surfactant and emulsification time leads to decrease in particle size. Formulated NFT SMEDDS was characterized for the various tests followed by formulated liquid microemulsions was converted into solid by Adsorption technique by using Neusilin US2. Solid SMEDDS formulation was tested for various test including FTIR DSC study and XRD study. Results showed that drug releases from S-SMEDDS formulation were found to be significantly higher compared to pure Nitrofurantoin. Stability study results showed that S-SMEDDS was found to stable. Thus study concluded that S-SMEDDS provides good solubility, dissolution rate and stability than Nitrofurantoin.

KEY WORDS: Nitrofurantoin, Solubility, DoE, S-SMEDDS, Dissolution rate.

INTRODUCTION
There are many ways to deliver drugs into the body like oral, sub mucosal, parental, transdermal and pulmonary etc.; but generally, the first choice is given to oral route of administration while taking the drug. It is the most preferred route of drug administration from children to old people because of its convenience, ease. During the selection of drug in the preparation of oral formulation; the most important parameter can be taken into consideration that is solubility of drug and poor water solubility of drug leads to incomplete absorption of drug which leads to low bioavailability.

Approximately 40% of a new drug or chemical entities exhibit poor solubility and present a major challenge to modern drug delivery system.[1] Currently there are various techniques available by which solubility of a drug can be enhanced but Self Emulsifying Drug Delivery System (SEDDS) is fetching attention of researchers due to its numerous characteristic benefits.

The Self Emulsifying Drug Delivery System (SEDDS) is an isotropic mixture of oils, surfactants, solvent, and cosolvent/ surfactant, which can be used for the design of formulation in order to improve the oral absorption of poorly water soluble drugs.[2] SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water soluble and lipophilic drugs.[4] An additional benefit of SEDDS over simple oily solution is that they offer a large interfacial area for partitioning of the drug between oil and water. Thus, SEDDS can be an efficient vehicle for class II to class IV molecules of biopharmaceutical classification system drugs.[5]

Nitrofurantoin is a medication used in the treatment of Urinary Tract Infections. It can be also used as antimicrobial or antibiotic agent. Nitrofurantoin is a poorly aqueous soluble drug. It is practically insoluble in water and belongs to BCS class II drug. It has low log P value 0.03 and half-life is 20 min. This drug is an example of solubility problem that is having poor

aqueous solubility. Although Nitrofurantoin is administered by oral route but it cannot be completely absorbed by digestive tract, and this incomplete absorption may result in undesirable side effect such as vomiting, diarrhoea, headache and rash. Oral bioavailability of such drug depends on its solubility and dissolution rate and it may be the rate determining step for the onset of therapeutic activity.

In order to overcome these problems, there is need to develop new formulation which is likely to achieve higher rate of solubility and extent of absorption of Nitrofurantoin leading to improved bioavailability. Recently much attention has been paid to lipid-based formulations with particular emphasis on Self Emulsion Drug Delivery System (SEDDS) to improve the oral bioavailability of lipophilic drugs. Hence it is needed to develop SEDDS of Nitrofurantoin to enhance solubility, dissolution rate which may improve therapeutic performance. SEDDS (Self Emulsifying Drug Delivery System) is promising approach for oral delivery of poorly water soluble drugs. The main objective of this study is to increase the solubility of poorely water soluble drug Nitrofurantion; which will ultimately improves its oral bioavailability.

In the present study objective is to increase the solubility of poorly water soluble drug Nitrofurantion by SEDDS and design & optimize SEDDS formulation using lipids, surfactant and co-surfactant levels by Quality by Design (QBD) approach and in the end study of characterization of SEDDS formulation.

MATERIAL

Nitrofurantoin is purchased from Sigma Aldrich, Orange oil, Linseed oil, Olive oil, Clove oil, Nutmeg oil procured from Molychem lab, Mumbai. Propylene glycol, PEG 200, PEG 400 supplied by Gattefosse India Pvt. Ltd., Mumbai.

EXPERIMENTAL METHOD

➢ Pre formulation study of Nitrofurantoin

Nitrofurantoin was visually tested for Physical state, Colour and evaluated for Physical Characteristics like Odour and Taste. Melting point determination of the obtained sample of Nitrofurantoin was done by open capillary method. It is a good first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by lowering as well as widening in melting point range.
Solubility of Nitrofurantoin checked in different solvent like Methanol, Ethanol, Di-methyl Formamide etc.

➢ UV Spectroscopy

The UV spectroscopy is used to determine the wavelength maxima of drug also to determine the concentration of drug present in solution.

- **Determination of λmax:** The standard solution of Nitrofurantoin (10 µg/ml) was scanned in the range of 400-200 nm in 1.0 cm cell against standard blank solvent and spectra was recorded. A Shimadzu UV visible spectrophotometer (UV-1800) was used with 1cm, slit width of matched quartz cells.
- **Preparation of Standard Solution:** An accurately weighed quantity of Nitrofurantoin (10mg) was dissolved in appropriate quantity of Dimethyl Formamide and transferred in a 100.0 ml volumetric flask, and then volume was made up with dimethyl Formamide up to the mark to get standard stock solution of concentrated 100µg/ml. from this standard stock solution 1.0 ml was withdrawn and diluted up to 10 ml with dimethyl Formamide to get final solution of concentration 10µg/ml.

➢ Fourier transforms infrared (FTIR) spectroscopy

Infrared spectroscopy study is very important study for functional group determination. FTIR spectrum of drug sample was recorded for its identification and to study principle peaks using FTIR spectrophotometer (630 Agilent technologies). Spectrum was recorded in the wavelength region of 4000 to 650 cm-1. Infrared absorption spectrum was recorded and spectrum analysis was done for functional analysis. The identified peaks were compared with the principle peaks of reported IR spectrum and sample was identified.

➢ Differential scanning colorimetry

For the DSC study the Nitrofurantoin was sealed in an aluminum pan and heated at constant rate 100C/min, over temperature range of 350 to 3850C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min. the DSC curve was obtained using Differential Scanning Calorimeter instrument (TA Instruments SDT-2960, USA) equipped with an intercooler, Indium standard was used to calibrate the DSC temperature and enthalpy scale.

➢ Formulation Development

➢ Element of QbD for development of Nitrofurantoin Microemulsion is mentioned below

Quality Target Product Profile (QTPP) of Nitrofurantoin Microemulsion

As per ICH Guideline Q8 R2, QTPP is the first element of quality by design for development of Nitrofurantoin Microemulsion. QTPP encompasses the summary of quality characteristics that a finished drug product ought to possess so as to fulfill the objectives set in the target product profile as quantitative attributes. Considering the generic dosage form development, the quality target product profile (QTPP) based on the prior knowledge of and general consideration for oral Nitrofurantoin dosage was as proposed and are as follows;

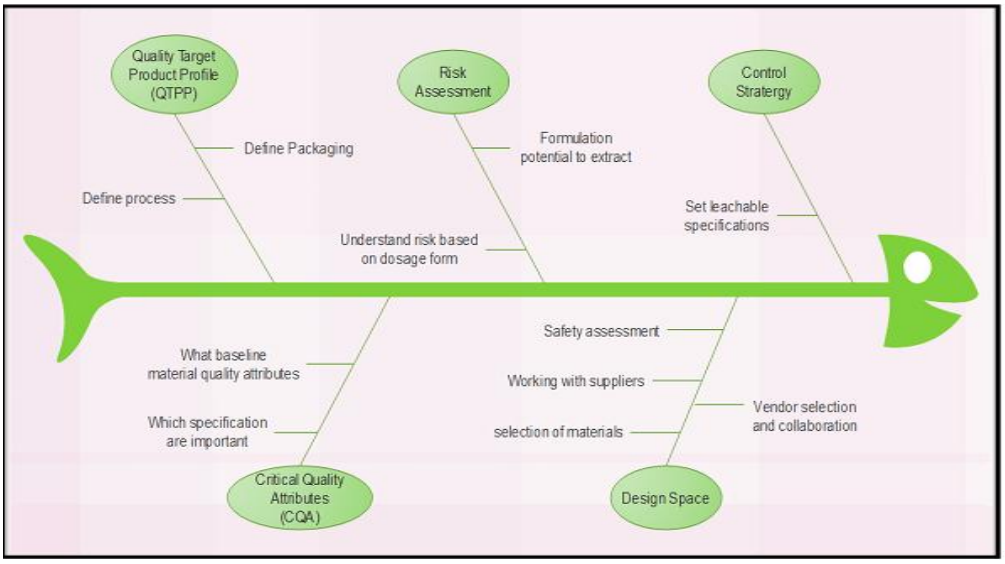

Figure No 1: Fishbone Diagram of Quality by Design.

- **Solubility determination of drug in the oils, surfactant and co-surfactant**

It is the first step in the rational development of dosage forms of a drug substance alone and when combined with excipients, to form dosage form. The different oils, surfactants, co-surfactants as mentioned in the table no 8.5 and 8.6,below were supposed to test out for solubility study, 5.00 ml of different oils, surfactants, co-surfactants were taken in small vials separately and excess amount of the drug was added to each vial. The vials were tightly closed and were continuously stirred for 24 hrs and various revolution speed like 150, 300 and 350 rpm used in mechanical shaker at 25^0C and after that, oils, surfactant, co-surfactant were centrifuged at 10,000 rpm for 10 min. the supernatant was separated and dissolved in methanol and solubility was quantified with UV-spectroscopy (Shimadzu 1800) at 367 nm after appropriate dilution with methanol.

- **Selection and screening of potential micro emulsion component (oil, surfactant and co-surfactant)**

Depending upon the hydrophobic lipophilic balance (HLB) system for surface active agents, the selection of surfactant for micro emulsion will be done. The HLB concept is based on the relative percentage of hydrophilic to lipophilic groups in the surfactant molecule. w/o microemulsion is formed using emulsifier within the HLB range 3 to 6. while o/w microemulsion is formed using emulsifier within the HLB range of 8 to 18. The HLB value for each component (single and in combination) will be determine wherever necessary. The surfactant in combination with co-surfactant was tried for screening a stable microemulsion system which could incorporate the optimum amount of internal phase. Various combinations of surfactant and co-surfactant, which leads to the formation of micro emulsion, were determined. The combination of surfactant and co-surfactant which shows higher micro emulsion region i.e. the combination which solubilized greatest amount of water on titration was sealed for micro emulsion formulation. For screening, a fixed ratio of surfactants and co-surfactants: water, for different ratios of surfactant/co-surfactant was tried.

- **Construction of pseudo ternary phase diagram**

Phase diagram is needed to be established for systemic study of microemulsion composition. From these, the extent of microemulsion region can be identified and its relation to other phases can be carried out. The pseudo ternary phase diagrams were constructed by drop wise addition of double distilled water to homogeneous liquid mixture of oil, surfactant and co-surfactant, at ambient temperature by water titration method.

From the result of solubility studies and screening of excipients, Cinnamon Oil, Tween 20, PEG 400 was selected as oily phase, surfactant and co-surfactant respectively. A ratio of surfactant over co-surfactant (Km) i.e. S/Co was chosen and the corresponding mixture (Smix) was made. At desired Km value (1:1, 2:1, 3:1) Smix and oil were mixed at ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 in pre-weighed volumetric flask. To the resultant mixtures, distilled water was added drop wise till the first sign of turbidity and then clear solution in order to identify the end point and after equilibrium, if the system became clear then the water addition was stopped. After complete equilibrium was reached, the mixture was checked visually for phase clarity and flow ability.

Table No: 1. tentative components for Nitrofurantoin Microemulsion.

Ingredients	Function	Quantity
Nitrofurantoin	Active	20/40 mg capsule
Surfactant	Emulsifier	As per optimization
Co-surfactant	Emulsifier	As per optimization
Oil	Emulsifier	As per optimization
Water	Medium	As per optimization

- **Preparation of liquid self microemulsifying drug delivery system (SMEDDS)**

The phase diagram were constructed at which high microemulsion region obtained was selected for further studies. The % content of water, oil and surfactant/co-surfactant in each selected formulation was determined. Then, the components were mixed by gentle stirring and vortex mixing at 370C until Nitrofurantoin was completely dissolved. Then the mixture was sealed in glass vial and stored at room temperature until used.

Table No: 2. Composition of L-SMEDDS.

Batch Code	Drug (mg)	% Composition (w/w)				
		Cinnamon oil	Tween 20	PEG 400	Smix	Water
LS1	20 mg	55	30	30	60	40
LS2	20 mg	60	35	35	70	30
LS3	20 mg	65	40	40	80	20

- **Optimization of Liquid Nitrofurantoin Microemulsion**

Based on studies, the two independent critical factors identified for this study were globule size and emulsification time. These factors were operated at three levels (+1, 0 and -1). The response factor was identified as particle size and emulsification time for all the batches undertaken.

A 3^2 factorial design was used in this study where 2 factors, Globule size (X1) and Emulsification time (X2) were evaluated at 3 levels. The independent variables and their levels (selected based on preliminary evaluation) are depicted in table no. 3, Experimental trials were performed at all 9 possible combinations. The formulation design of 3^2 factorial batches 1 to 9 are given below,

Table No: 3. 3^2 Factorial Designs.

Sr. No	Factor	Levels		
		-1	0	+1
1	Concentration of oil	62.5	65	67.5
2	Concentration of surfactant/co-surfactant	77.5	80	82.5

Initially QTPP element like dosage form, type, strength, microbiological evaluation, content uniformity, *in vitro* release was identified and documented. On the basis of fishbone diagram, CQA parameters such as content uniformity, drug release, microbiogical evaluation, pH of solution were identified. The various surfactants, co-surfactants and oils were screened; and preformulation study on the procured sample of drug Nitrofurantoin was carried out. The phase diagram was constructed with help of screened surfactant, co-surfactant and oil and high microemulsions region was obtained used for further studies. The % content of water, oil and surfactant/ co-surfactant in each selected formulation was determined. Then, the components were mixed by

gentle stirring and vortex mixing at 37^0C until Nitrofurantoin was completely dissolved. Then the mixture was sealed in glass vial and stored at room temperature. For optimization of formulation development a 3^2 factorial design was used; where 2 factors, Globule size (X1) and Emulsification time (ET) (X2) were evaluated at 3 levels with help of 9 different formulation batches.

RESULT AND DISCUSSION

The Preformulation study was carried out by the organoleptic properties, melting point determination, solubility analysis, pH, clarity, colour solution, UV spectroscopic study, FTIR study and DSC study; at end drug Nitrofurantoin was confirmed.

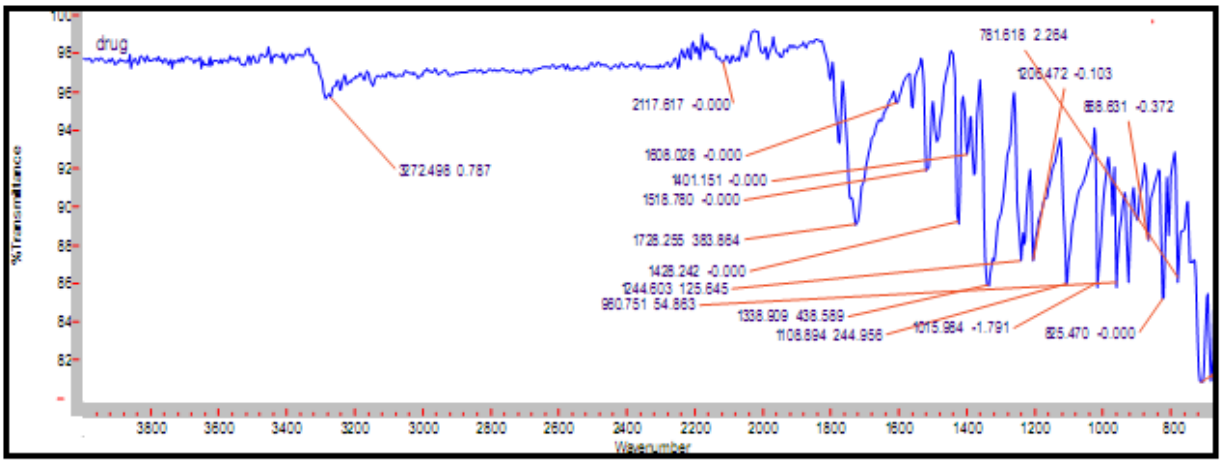

Figure 01: FTIR of Nitrofurantoin.

Solid state characterization of solid SMEDDS (SA3) was done with Differential Scanning Calorimetry (DSC) study reveals that decrease in the crystalline i.e. amorphous nature of solid SMEDDS than that of pure drug.

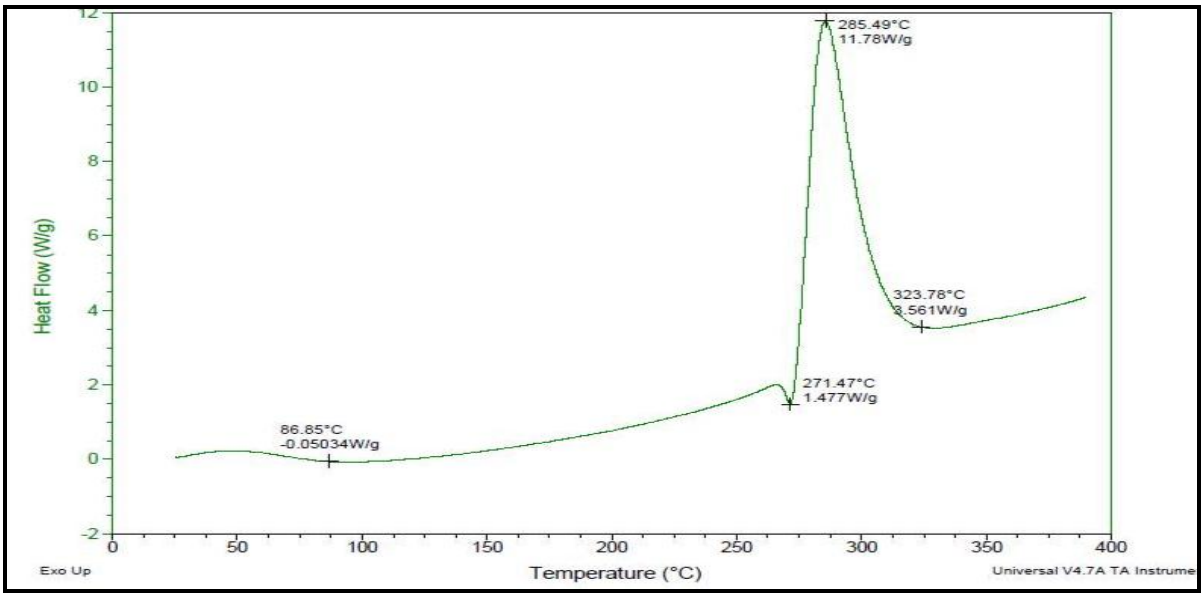

Figure 02: DSC of Nitrofurantoin.

Cinnamon oil was used as oil; Tween 20 was used as surfactant while PEG 400 was used as a co-surfactant on the basis of solubility study.

The phase diagram Km = 1 Shows better micro-emulsion region as compared to Km value 2 and 3 hence, the phase diagram of Km=1 was selected as optimized batch for liquid micro emulsion and further solid- SMEDDS formulation.

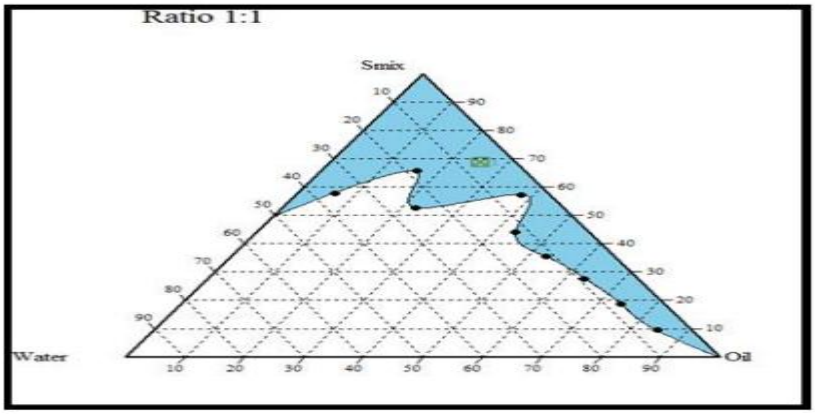

Figure No 03: Pseudo-ternary phase diagram of Cinnamon oil / Tween 20 / PEG 400 / Water at Km = 1(1:1).

The factors were operated at three levels (+1, 0 and -1) globule size and emulsification time were selected as dependent variables. 9 batches were performed according to design of experiments. Batch no 5 was selected on the basis of optimisation of globule size 0.492 and emulsification time 75sec.

Table No.4: Batches for Design-Expert.

Batch No.	Globule Size(m)	Emulsification time (sec)
1.	0.921	128
2.	0.674	90
3.	0.825	100
4.	0.810	128
5.	**0.492**	**75**
6.	0.751	120
7.	0.799	121
8.	0.811	127
9.	0.736	118

According to the design of experiments, Probability Plots, Counter Plots, Normal probability, Response surface plot 3D response curve it was observed that with increase in ratio of surfactant to co-surfactant and emulsification time leads to decrease in particle size.

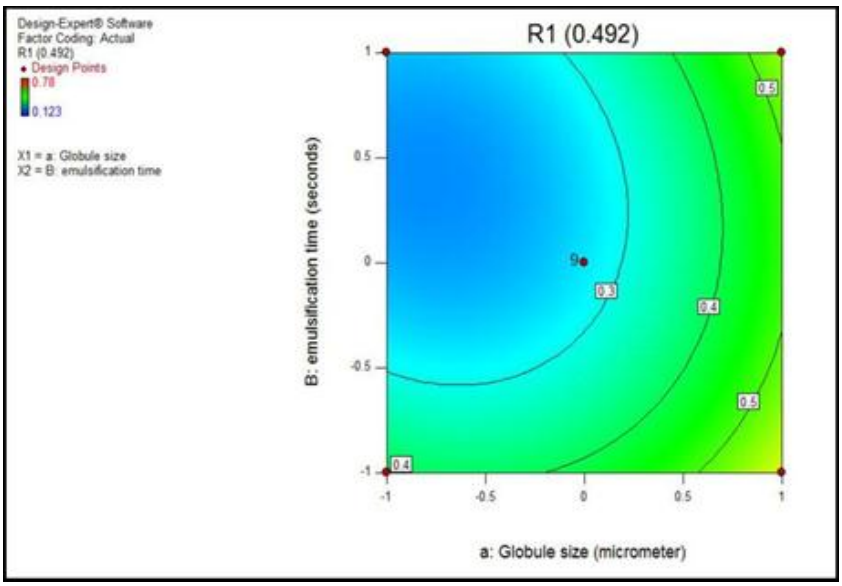

Figure No 04: Counter plot graph for Globule size.

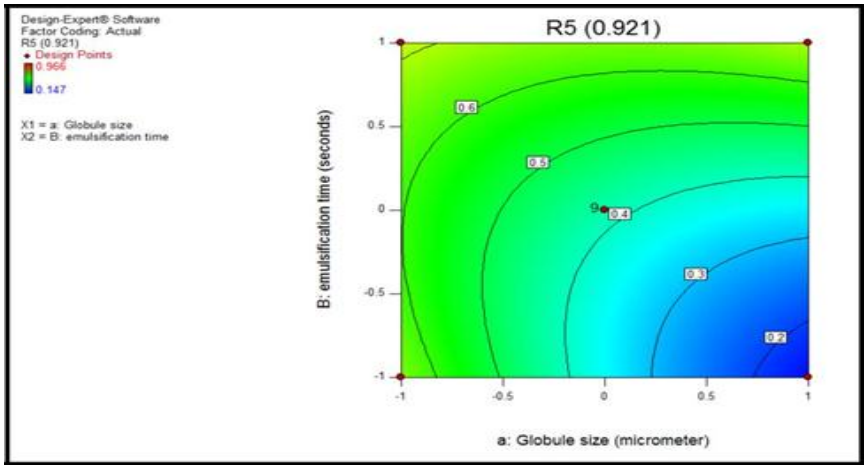

Figure No 05: Counter plot graph for ET.

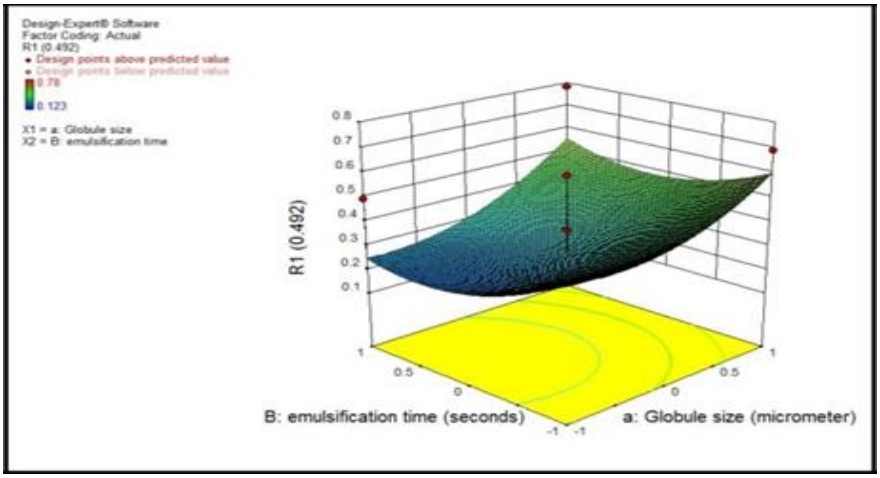

Figure No 06: 3D Response surface plot for Globule Size.

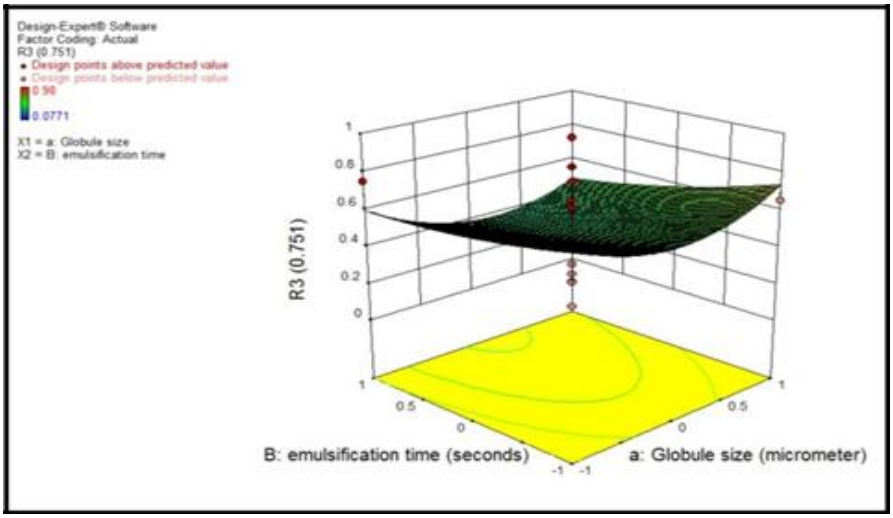

Figure No 07: 3D Response surface plot for ET.

This can be attributed to the high impact at the ratio of surfactant to co-surfactant curve for globule size. The Drug release time is 75 min is optimised.

Nitrofurantoin has the ionisable group and thus its solubility and dissolution is pH dependent. Solid SMEDDS formulations shows more than 85% drug release in 120 min in all dissolution media whereas Nitrofurantoin shows less than 50% drug release in Phosphate buffer pH 6.8. There is high drug release in 0.1 N HCl than 6.8 pH Phosphate buffer, so we can also conclude that in case of solid SMEDDS formulation solubility, dissolution of Nitrofurantoin is pH dependent.

In vitro dissolution study was done in 0.1N HCl, 6.8 pH Phosphate buffer shows that the formulated S-SMEDDS (SA3) shows higher drug release than pure Nitrofurantoin drug. *In vitro* dissolution study carried out solid SMEDDS, pure Nitrofurantoin in 1.2 HCL, pH 6.8 phosphate buffer. Results showed that drug releases from S-SMEDDS formulation were found to be significantly higher as compared to pure Nitrofurantoin.

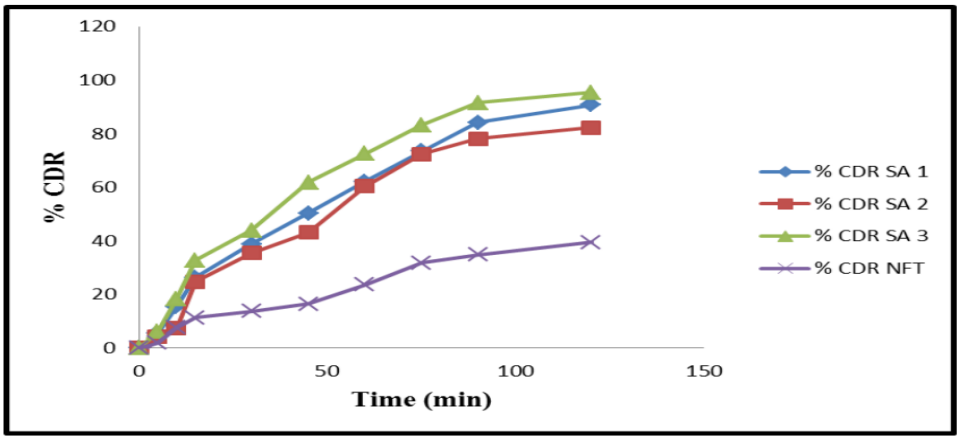

Figure No 08: In-vitro dissolution study of SA batches, Nitrofurantoin in 6.8 Phosphate buffer solution.

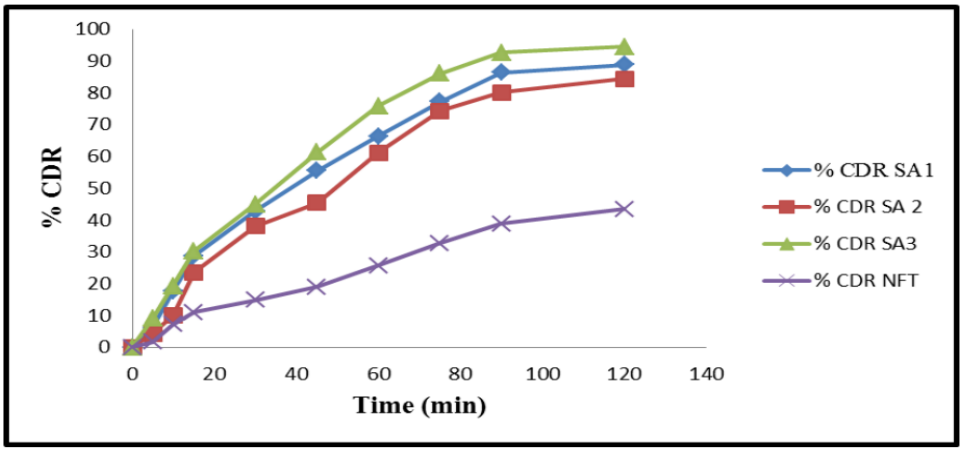

Figure No 09: In-vitro dissolution study of SA batches, Nitrofurantoin in 0.1N HCl.

There is high drug release in 0.1 N HCl than 6.8 pH Phosphate buffer, so we can also conclude that in case of solid SMEDDS formulation solubility, dissolution of Nitrofurantoin is pH dependent.

CONCLUSION

It can be presumed that the system of SMEEDS was effectively connected in plan of Nitrofurantoin which caused expanded dissolvability and bioavailability notwithstanding Nitrofurantoin being an inadequately water solvent medication. In this manner this investigation closes with strong SMEDDS as medication conveyance framework disintegration rate and soundness of Nitrofurantoin can be enormously improved.

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