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Design and evaluation of self micro-emulsifying drug delivery system of curcumin for solubility improvement

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ABSTRACT

The main purpose of the current study is to formulate a Self micro-emulsifying drug delivery system (SMEDDS) of a poorly water soluble drug curcumin to enhance solubility, dissolution rate which may improve therapeutic performance and drug loading capacity so as to develop alternative to traditional oral formulations to improve the bioavailability. The solubility of curcumin in individual microemulsion components viz. oil and surfactants was determined. The surfactants were screened for emulsification ability. Based on the solubility determinations and emulsification properties oleic acid and surfactants cremophor RH 40 and PEG 400 were selected for further study. The solubility of curcumin in different ratios of selected oil and surfactants was determined. The composition of oil:surfactants with maximum solubility for curcumin was used for SMEDDS formulation. Pseudo-ternary phase diagrams were used to evaluate the micro emulsification existence area. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsions. The microemulsions were evaluated for emulsion droplet size, self emulsification and phase separation, *In vitro* dissolution. The SMEDDS formulation showed complete release in 120 min. as compared with the plain drug, which showed a limited dissolution rate.

Keywords: Curcumin, Solubility enhancement, SMEDDS, pseudo-ternary phase diagram.

INTRODUCTION

Self Emulsifying Drug Delivery System

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. (Giri *et al*., 2013)

'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several microns. 'Self-micro emulsifying drug delivery system' (SMEDDS) indicates the formulations forming transparent emulsions with oil droplets ranging between 100 and 250nm. 'Self-nano emulsifying drug delivery system' (SNEDDS) is a recent term constructing the globule size range less than 100 nm. (Gupta *et al*., 2011)

MATERIALS AND METHODS

Drug, Excipients, chemicals/reagents used for various experiments

Material	Gifted/supplied by
Curcumin	Hindustan Herbals Limited, Haryana
Castor oil	RK Enterprises, Meerut
Oleic acid	RK Enterprises, Meerut
Cremophor RH40	RK Enterprises, Meerut
PEG 400	Central Drug House, New Delhi
PEG 200	Central Drug House, New Delhi
Tween 80	Central Drug House, New Delhi
Methanol	Qualigens fine chemicals, Mumbai

Formulation Development of Smedds

Curcumin 100 mg was dissolved in the varying quantity of surfactant in 500 ml beaker. Varying quantity of oil and co surfactant were accurately weighed and added to drug and surfactant mixture. Then, the components were mixed by gentle stirring and heated at 37^{o}C on magnetic stirrer with hot plate to obtain a homogenous isotropic mixture. The SMEDDS formulations were stored at room temperature in closed glass vials until used. (Grover, M., 2006)

Preformulation Studies

Identification And Characterization Of Curcumin

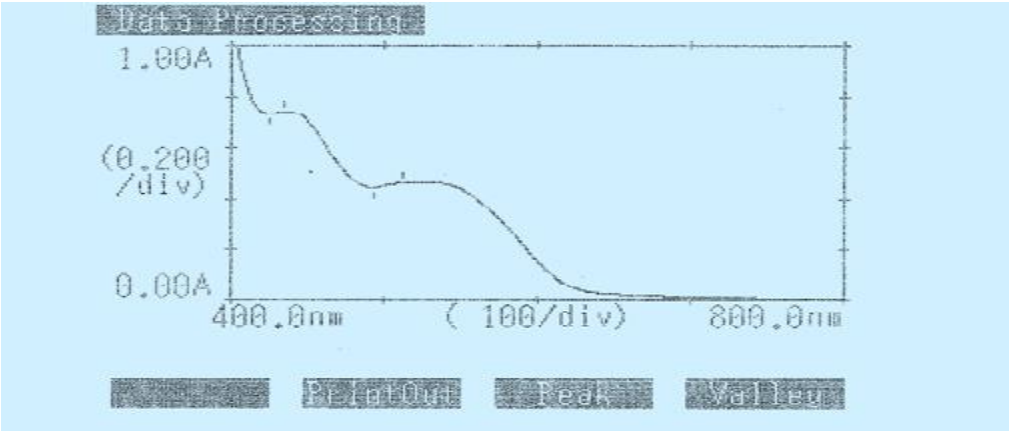
The characterization of drug was carried by conducting various physicochemical tests which include organoleptic properties, melting point determination, solubility analysis, clarity and color of solution, loss on drying, etc. for pure curcumin. Results are summarized in Table.

Table 1: Characterization of curcumin

Characters	Specifications	Result
Appearance	Yellowish orange	Yellowish orange
Taste	Tangy, a little sour	Tangy, a little sour
Melting range	178-181^{o}C	180^{o}C
Solubility	Practically insoluble in water, highly soluble in methanol, ethanol	Practically insoluble in water, highly soluble in methanol, ethanol
Loss on drying	NMT 2.0%	1.0%

The results of characterization of curcumin complied with the specifications given in certificate of analysis provided by the supplier.

Ultra-Violet Absorption Maxima (Determination of Λ_{max})



The λ_{max} was obtained at 415 nm, which is very near with the official value of 416 nm.

Fig 1: λmax of curcumin using UV Spectrophotometer

Solubility of Drug in Oils, Surfactants and Co-surfactants

The concentration of curcumin in various oils, surfactants and co-surfactants was determined by UV spectroscopy at room temperature and results are shown in Table

Table 2: Solubility of Curcumin in various oils

S. No.	Oil	Solubility (mg/ml)
1	Soya bean oil	0.142±0.018
2	Paraffin oil	0.127±0.017
3	Peanut oil	0.257±0.026
4	Ethyl Oleate	0.368±0.035
5	castor oil	0.51±0.05
6	oleic acid	1.04±0.02

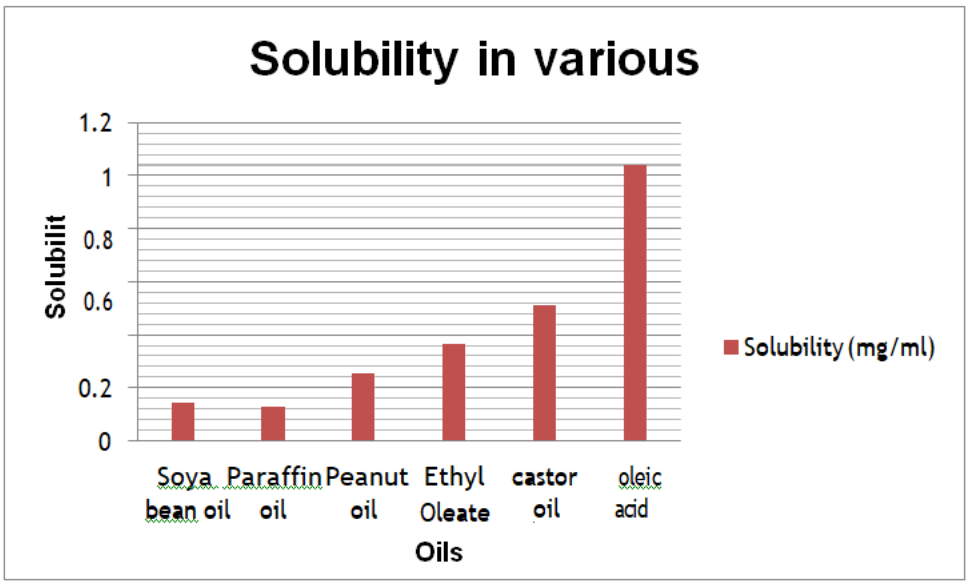


Fig 2: solubility of curcumin in various oils

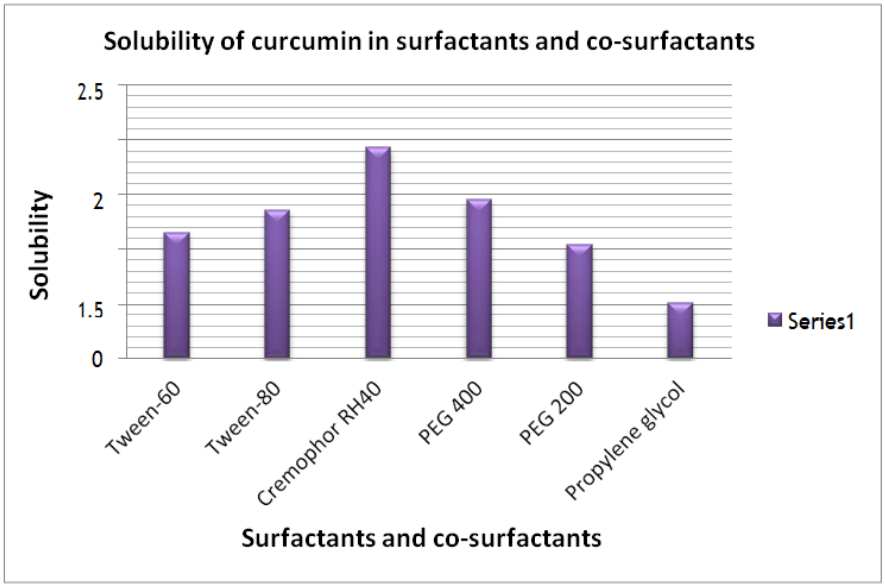


Fig 3: Solubility of curcumin in various surfactants and co-surfactants

From the results of solubility study of curcumin in different oils, surfactants and co- surfactant, it was found that curcumin was more soluble in Oleic acid, ethyl oleate, cremophor RH40, Tween 80and PEG 400 than other vehicles. Hence Oleic acid was selected as oil and from Tween 80, Propylene glycol, cremophor RH40 and PEG 400 might be selected as surfactant and co-surfactant after screening their emulsification ability with Oleic acid so that optimal SMEDDS will be formed with improved drug loading capabilities.

Infra Red spectrum

The IR spectrum of the pure drug was found to be similar to the reference standard IR spectrum of the curcumin. The IR spectrum of curcumin (Fig.)

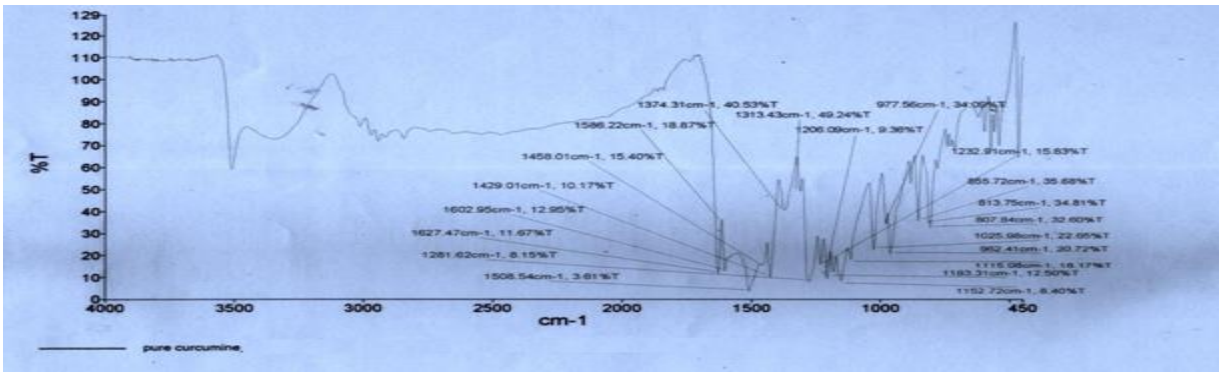


Fig 4: IR spectrum of curcumin

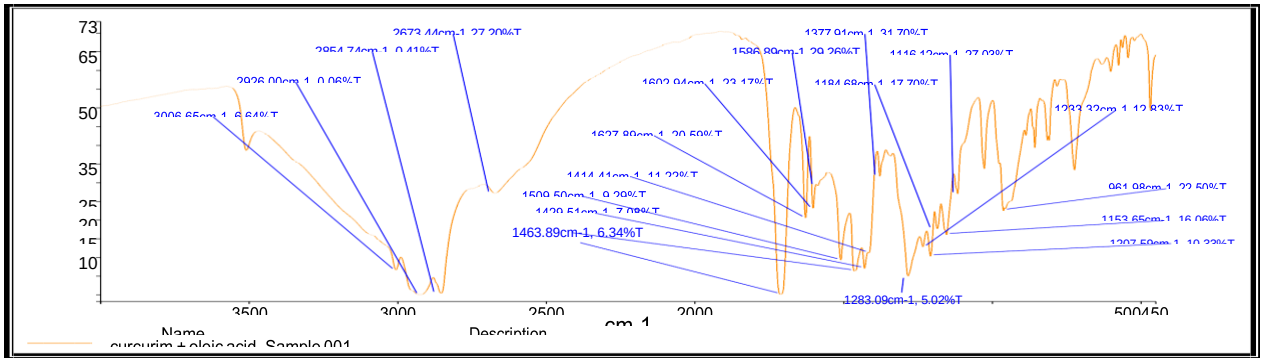


Fig 5: IR spectrum of curcumin + oleic acid

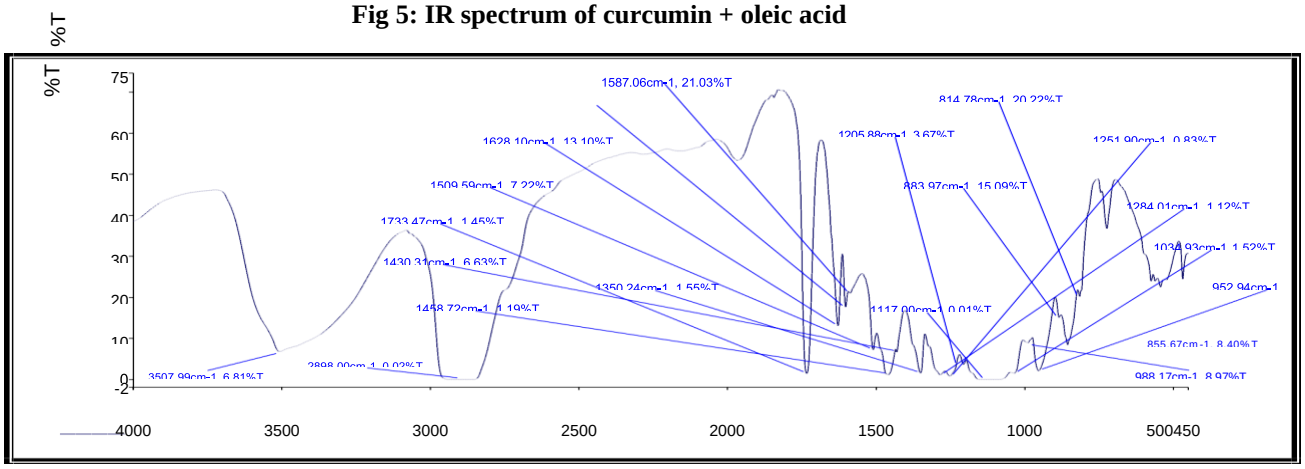


Fig 6: IR spectrum of curcumin + Cremophor RH40

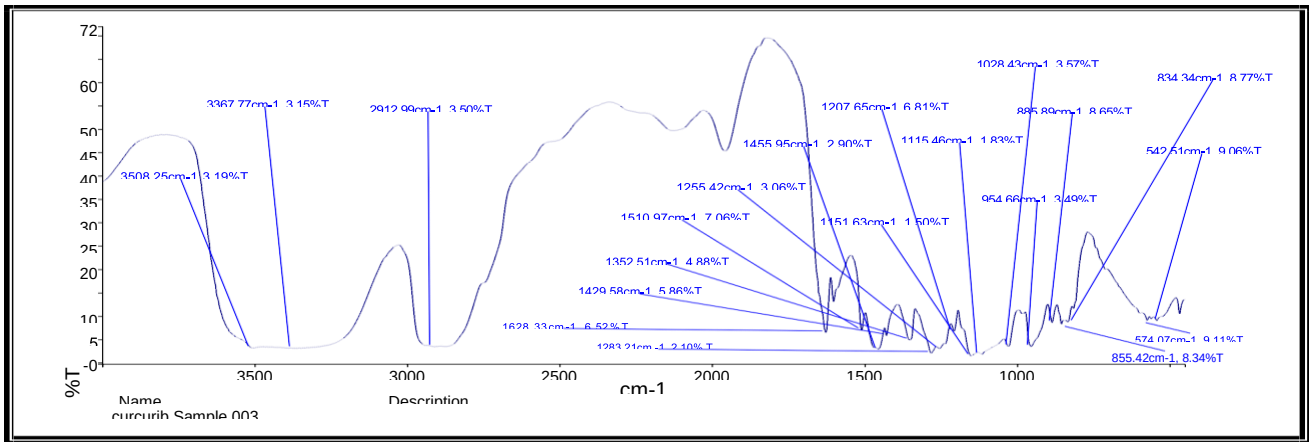


Fig 7: IR spectrum of curcumin +PEG 400

Calibration Curve of Curcumin by UV Spectrophotometric Method

Calibration curve of curcumin in methanol

Below Table and Fig. represent the absorbance data and standard plot of curcumin in methanol respectively. Beer-Lambert's law was obeyed over the range of 2-10 µg/ml and the data was found to fit the equation.

$$Y = 0.0161x + 0.0004 \quad R^2 = 0.9931$$

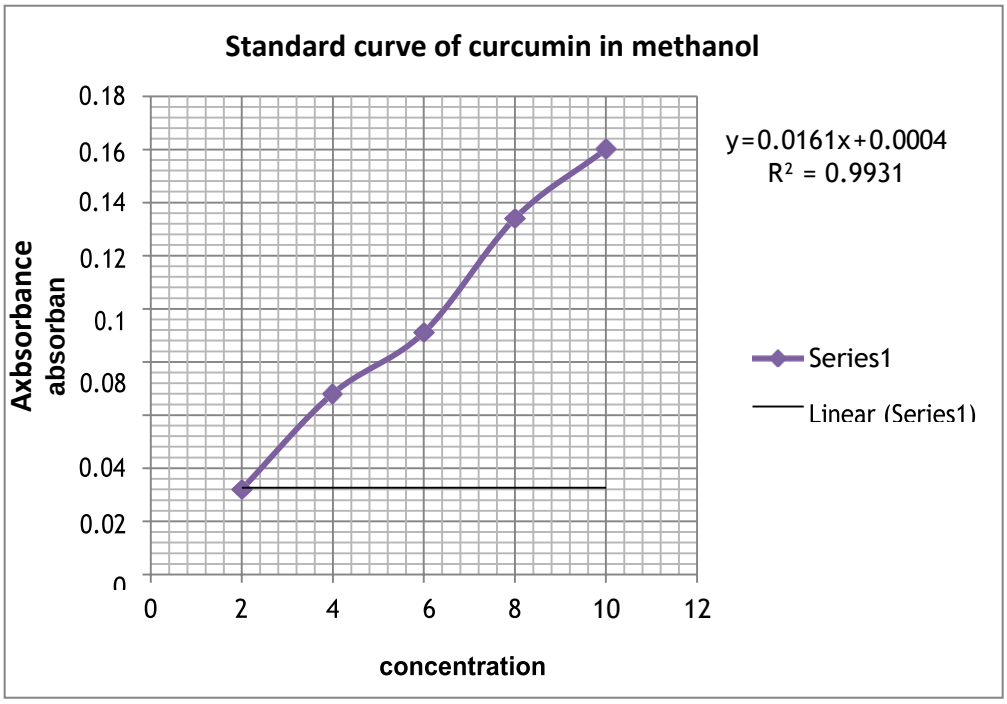


Fig 8: Standard curve of curcumin in methanol

Calibration curve of curcumin in phosphate buffer pH 8

Below Table and Fig. represent the absorbance data and standard plot of curcumin in phosphate buffer pH 8 respectively. Beer-Lambert's law was obeyed over the range of 2-10 µg/ml and the data was found to fit the equation.

$Y = 0.048x + 0.0373$ $R^2 = 0.9987$

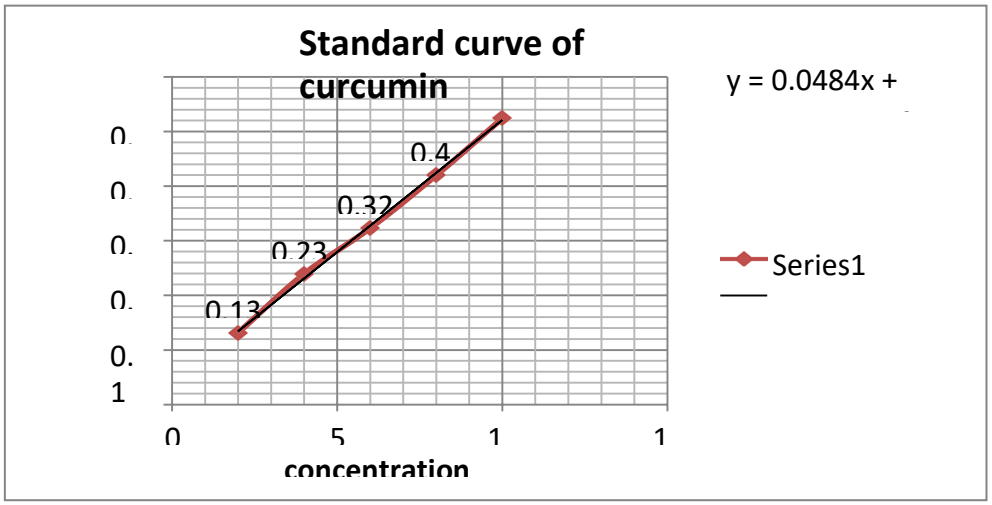


Fig 9: Standard curve of curcumin in phosphate buffer pH 8

Screening of Surfactant and Co-surfactant

The percent transmittance values required for uniform emulsion of various dispersions are given in Table

Table 3: Emulsification efficacy of surfactant and co-surfactant with oleic acid

Surfactant/co surfactant	% transmittance
PEG 400	98.8
Ethyl oleate	94.3
Cremophor RH40	99.5
Tween 80	95.6

Oleic acid has good solubilizing capacity for curcumin hence it was selected as oil component. At the same time cremophor RH40 has more emulsification ability so it was selected as surfactant. Co-surfactants were also selected in same way, i.e. PEG 400 was selected as co-surfactant.

Preparation Of Self Micro-Emulsifying Formulation

Various formulations were prepared with a constant amount of curcumin (100 mg) and varying ratios of oil, surfactant and co-surfactant. In brief, curcumin was dissolved in oleic acid in stoppered glass vials. Required amounts of cremophor RH40 and PEG400 were added to the mixture and mixed well. These systems were warmed to 40°C using a water bath for 30 min with intermittent shaking to ensure complete mixing. The prepared formulations were then stored until further use. The compositions of different SMEDDS formulations are shown in Table.

Table 4:Composition of different SMEDDS formulations

Formulation	Components		
	Drug (gm)	Oil (gm)	Smix
F1	100	0.96	9.04
F2	100	1.92	8.08
F3	100	2.88	7.12
F4	100	3.84	6.16
F5	100	4.8	5.10
F6	100	5.7	4.20
F7	100	6.66	3.34
F8	100	7.62	2.38
F9	100	8.58	1.42

Fig 10: SMEDDS formulation of curcumin

Evaluation Of Smedds

Determination of Self Emulsification Time and Visual Assessment

Formulations were graded for self emulsification time, according to the visual assessment criteria for self micro emulsion formation listed in Table 4.4. The results of this visual assessment study are depicted in Table 5.14

Table 5: Visual assessment of various SMEDDS

Formulation	Grade based on visual observation	Time of emulsification (sec)
F1	B	37
F2	A	32
F3	A	26
F4	B	43
F5	B	37
F6	B	41
F7	A	27
F8	B	54
F9	B	67

The assessment of emulsification time showed that with the increase in surfactant concentration the time of emulsification increases. Formulations F1, F4, F5, F6, F8, and F9 were found to be of grade B but all other formulations were found to be of grade A.

Robustness to Dilution

Robustness to dilution was studied by diluting the system 100 and 1000 times with various dissolution media viz. 0.1N HCl and phosphate buffer (pH 8). The diluted micro emulsions were stored for 12hrs. The formulations did not show any signs of phase separation or drug precipitation after 12 hrs.

IR Spectrum of SMEDDS Formulation

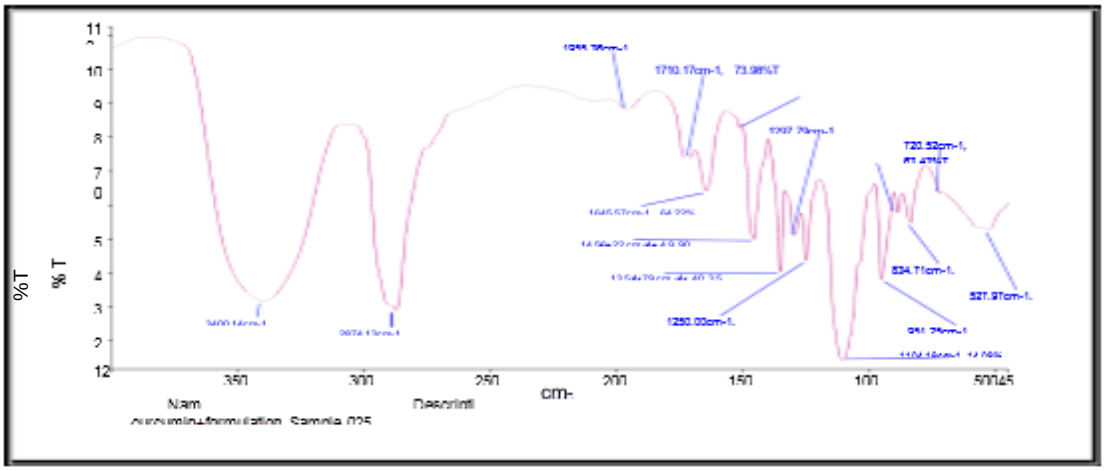


Fig 11: IR spectrum of SMEDDS formulation of curcumin

FTIR spectra as given in fig. 5.4 to 5.7 and fig. 5.16 showed that there was no interaction between curcumin and selected Excipients. Therefore, all the Excipients were found to be compatible with the drug.

In-vitro Dissolution Studies

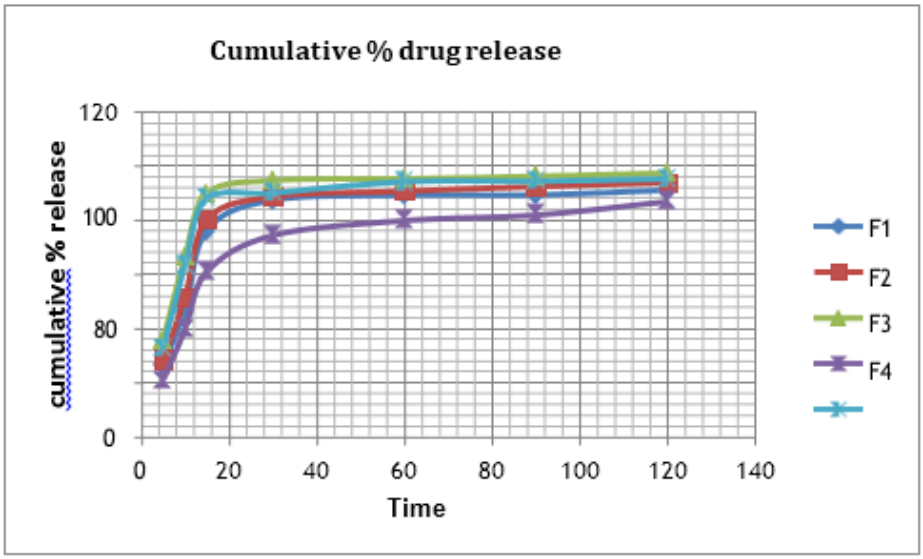


Fig 12: Cumulative % drug release of SMEDDS formulation F1 to F5

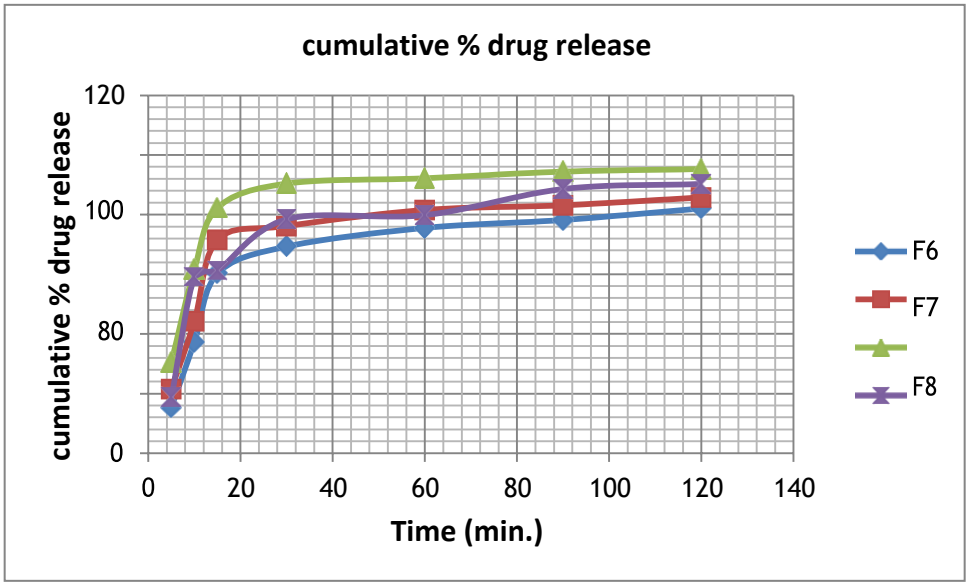


Fig 13: Cumulative % drug release of SMEDDS formulations of F6 to F9

Drug Content

Curcumin content in the extract was analyzed spectrophotometrically (UV spectrophotometer) at 415 nm.

Table 6: Drug content of various formulations

Formulation	Drug Content (%)
F1	91.22±1.01
F2	91.89±1.33
F3	**95.64±1.03**
F4	93.86±1.15
F5	97.43±1.34

F6	90.42±1.97
F7	92.22±2.12
F8	96.54±1.15
F9	94.67±1.17

The drug content of the best formulation F3 was found to be 95.64±1.03 which lies under the range of 95.0% to 96.8% w/w as per given in the specifications of the drug.

Globule Size and Zeta Potential Determination

The globule size and zeta potential were observed with the help of Malvern Zetasizer. The average globule size was taken into consideration. The average diameters of vesicles were in nano size range. The zeta potential of the liquid systems is of considerable importance from the stability point of view. The systems having the zeta potentials in the range of+30 to -30 show poor stability profiles. In this study the zeta potentials of the optimized formulation was less then –30 mV, indicating good stability. Droplet size distribution is one of the most important characteristics of emulsion for stability evaluation and *in vivo* absorption. Poly dispersity index below 0.3 indicates good uniformity in the droplet size distribution after dilution with water. In this study the poly dispersity index below 0.3 was obtained for F8 formulation.

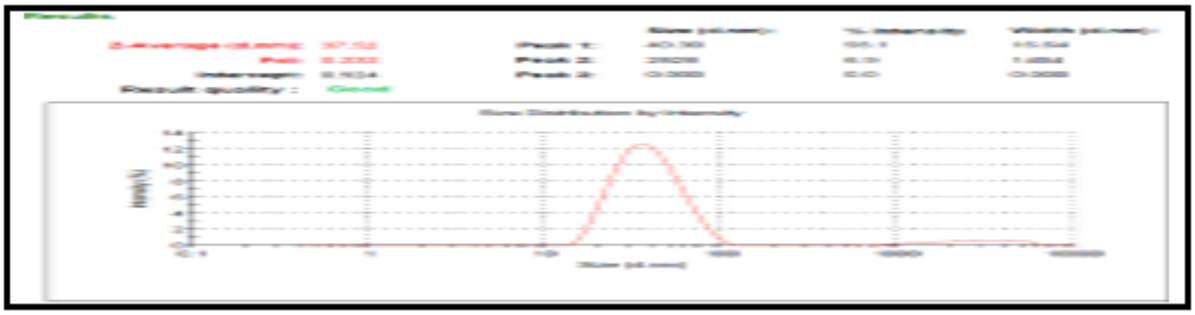


Fig 14: Globule size distribution

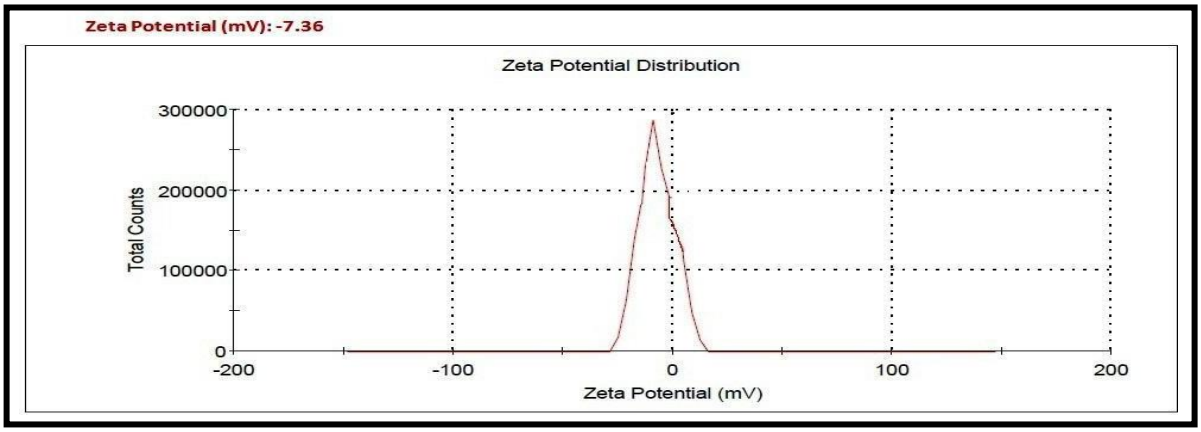


Fig 15: Zeta potential

SUMMARY

Self micro-emulsifying Drug delivery System (SMEDDS) is one of the most popular system and commercially available viable approaches for delivery of "solubility problem" drugs that exhibits dissolution-rate limited absorption. SMEDDS are isotropic mixtures of oils and surfactants that form fine oil-in water micro emulsions upon mild agitation in aqueous media such as GI fluids SMEDDS present the solubilized drugs in oil-in water micro emulsions of small droplet size (nm), and this therefore ultimately results in increased drug absorption. Curcumin is a polyphenolic compound present in the rhizomes of turmeric (*curcuma longa* Linn.). Due to its lower oral bioavailability, curcumin

could be considered as a good candidate self micro emulsifying drug delivery system.Curcumin was identified and characterized as per requirements of official monograph (Herbal Pharrmacopoeia, 2002). The λ_{max} was obtained at 415 nm. The drug was also identified by IR spectroscopy. The IR spectrum of drug sample was found to be in agreement with the standard IR spectra of pure drug given in the official monographs. A calibration curve of curcumin was prepared in methanol in the concentration range of 2-20 µg/ml by measuring absorbance at 415 nm. Correlation coefficient of calibration curve was found to be 0.998 indicating good linearity.

The existence of self micro emulsifying oil formulation fields that could self-emulsify under dilution and gentle agitation was identified from pseudo ternary phase diagram of systems containing oil surfactant-cosurfactant. A series of self micro emulsifying systems were prepared in the formula with varying concentrations of castor oil, cremophor RH40 and PEG 400. Droplet size distribution of suitably diluted SMEDDS with water was determined using Photon correlation spectrometer. The zeta potentials of the optimized formulation was less then –30 mV, indicating good stability. Poly dispersity index below 0.3 indicates good uniformity in the droplet size distribution after dilution with water. Increase in turbidity was measured using a turbidimeter (digital turbidimeter). Time required to disperse the system completely and uniformly was determined by observing change in turbidity was recorded as emulsification time and it was found 2 minutes.

1 ml of SMEDDS was dissolved in excess methanol, and curcumin content in the extract was analyzed spectrophotometrically (UV spectrophotometer) at 415nm. Drug content of various formulations was found to be in range of 90.22 - 97.43%.

In-vitro release profiles of SMEDDS of curcumin were studied using USP XXIII apparatus at 37±0.5ºC with a rotating speed of 100 rpm in buffer pH 8 with 900 mL of the dissolution media. In vitro drug dissolution study of SMEDDS shows 28.48±0.34 to 90.01±0.22% drug release within 15 minutes for all the formulations.

CONCLUSION

An optimized SMEDDS formulation consisting of oleic acid, cremophor RH40, PEG 400 and curcumin was successfully developed with an increased dissolution rate, increased solubility, and ultimately increased bioavailability of a poorly water-soluble drug. Results from stability studies confirmed the stability of the developed formulation. Thus, study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of curcumin to improve its bioavailability.

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