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RESEARCH ARTICLE

Formulation and Evaluation of Self-microemulsifying drug delivery system of Curcumin for enhanced solubility and dissolution

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Abstract:

Curcumin is a poorly water-soluble drug and its oral bioavailability is very low. A new self- microemulsifying drug delivery system (SMEDDS) has been successfully developed to improve the solubility and oral absorption of curcumin. Suitable compositions of SMEDDS formulation were screened via solubility studies of curcumin and compatibility tests. Pseudoternary phase diagrams were used to evaluate the micro emulsification existence area. Formulation development and screening was done based on results obtained from phase diagram and characteristics of resultant microemulsion. The SMEDDS formulation showed complete release in 10 min as compared with crude drug.

Key Words: Curcumin, Dissolution, SMEDDS, Solubility

INTRODUCTION:

The fundamental step in the solubilisation of drug compounds is the selection of an appropriate salt form, or for liquid dosage forms, adjustment of pH of the solution. This is an especially important selection process for polar compounds as the majority of newer solubilisation techniques such as nanosuspensions and microemulsions utilize co-solvents when applied to a polar compound[1]. These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution, spray drying, addition of surfactants, inclusion in cyclodextrin-drug complexes, and the use of more novel mechanisms such as self- emulsifying systems, micronisation via nanoparticles, pH adjustment and salting-in processes [2,3].

Microemulsions and self-emulsifying systems have emerged as potential solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Traditionally, long and medium-chain triglycerides (LCTs and MCTs, respectively) have been employed with surfactants to incorporate drugs into self- emulsifying systems[4,5]. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances (HLB) are often used to ensure immediate formation of oil-in-water (o/w) droplets during production. Amphiphilic, non-ionic surfactants allow higher degrees of drug solubilisation to occur and may prevent the precipitation of drug out of the microemulsion in vivo. Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant in most self-emulsifying systems is required to be in excess of 30 per cent w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and poly ethylene glycol. Similar to the impact of introducing organic solvents elsewhere in drug product manufacture, the use of co- solvents increases processing complexity while improving the potential drug load of the emulsion [6]. Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hydroscopic contents from dehydrating or migrating into the capsule shell. Curcumin, a naturally active constituent extracted from the plants of the Curcuma longa, its structure shown in Figure 1. Curcumin is the principal curcuminoid of the popular Indian spice turmeric which belongs to the ginger family

(Zingiberaceae). It has a variety of biological activities and pharmacological actions, such as anti-tumor, anti-inflammatory, anti-virus, anti-oxidation and anti- HIV, and low toxicity with promising clinical application [7] which have low oral bioavailability i.e. 40-85 percent of an oral dose of Curcumin passes through the gastrointestinal tract unchanged, with most of the absorbed flavonoid being metabolized in the intestinal mucosa and liver[8]. In present study SMEDDS of curcumin was prepared for enhanced solubility and dissoloution of poorly soluble drug.

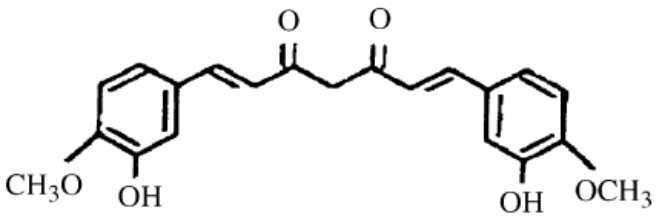

Figure1: The structure of curcumin.

MATERIAL AND METHODS:

Materials

Curcumin was received as a generous gift sample from Konark Herbals And Health Care, Daman, Gujarat. Capmul MCM C-8 were gifted by ABITEC Corporation LTD., India. Cremophore EL, Cremophore RH 40 were gifted by Sigma Aldrich PVT LTD. and Other chemicals and reagents used were of analytical grade.

Solubility Studies

The solubility of curcumin in various oils, surfactants, co-surfactants and Oil; surfactant mixture was measured using shake flask method [8 - 12]. An excess amount of curcumin was added into each vehicle followed by vortex mixing for 30 sec . Mixtures were shaken for 48 hr at 30^0 C in a thermostatically controlled shaking water bath, followed by equilibrium for 24 hr. Mixtures were then centrifuged at 3000 rpm for 10 min and the supernatant was filtered through a Millipore membrane filter (0.45µ). Samples were suitably diluted with methanol and drug concentration was obtained via UV validated method at 432 nm using hydro alcoholic

solvent (Methanol: Distilled Water. 3:7) as a blank. The experiment was repeated in triplicates. Results are represented as mean value (mg/ml) ± SEM.

Preliminary screening of surfactant

Different surfactants for the peroral use were screened for emulsification ability. Briefly, Excess amount of drug in 5ml of selected oils (Soya bean oil, Paraffin oil, Peanut oil, Ethyl Oleate) was taken in stopper vials and was then mixed by vortex mixer. The mixture vials were then kept at 37±2.0 0 C in an isothermal orbital shaker for 72 hr to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 5000 rpm for 15 min. The solubility profile of drug in oil was determined from the supernatant using UV-VIS spectrophotometer at 432 nm. Insoluble drug from the settled material was determined and mass balance was then found out. HLB value, drug solubility, biocompatibility and compatibility with drug are the parameters evaluated in the selection of surfactant. Since the formulation to be developed was o/w microemulsion, surfactants having HLB value ranges between 8 to15 were first screened followed by drug solubility as described earlier. Various surfactants (Tween-60, Tween-80, Cremophor EL, and Capmul MCM) were used for this study.

Along with drug compatibility, the main selection criterion for cosurfactant in the development of microemulsion is its ability to form clear and stable formulation with relevant surfactant at a minimum concentration. Cosurfactant is selected that is having no considerable interaction with drug. Various cosurfactant (PEG 400, Iso-propyl Alcohol, Ethanol, Methanol) were used for this study.

Phase diagram Study

In pseudotemary phase diagrams of curcumin based micro emulsion were prepared by CHEMIX software. The systems consisting of Ethyl Oleate as oil, Capmul MCM as surfactant, and PEG 400 as co-surfactant were titrated with water, and self-emulsifying formulations were selected observing regions of infinite dilution.

Formulation of SMEDDS

A series of SMEDDS formulations were prepared using Capmul MCM and PEG 400 as the Surfactant/cosurfactant combination and (Table 5). Briefly, accurately weighed curcumin was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components

were mixed by gentle stirring and vortex mixing on a magnetic stirrer, until curcumin was perfectly dissolved. The mixture was stored at room temperature until further use.

Evaluation of SMEDDS

Self Emulsification and Phase Separation:

Different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion [13, 14]. Visual assessment was performed by drop wise addition of the pre concentrate (SMEDDS) into 100, 250 and 1000 mL of distilled water, 0.1N HCl and pH 6.8 phosphate buffer. This was done in a glass beaker at room temperature, and the contents were gently stirred with glass rod. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours).

Droplet Size

Particle size of emulsion was determined by using dynamic light scattering technique by Malvern zetasizer (NANO ZS) [8, 15]. Samples were diluted to 50 times and 100 times with the Distilled water for the measurement

Drug Content

The SMEDDS containing curcumin was measured using UV visible spectroscopic method. The 2 µg/ml of aliquot was prepared using microemulsion formulation using diluting solvent. The samples were measured as 432 nm using UV-VIS spectroscopic method. [5,8 16].

In Vitro Dissolution

In vitro dissolution studies were carried out for all formulations using dissolution test apparatus USP Type II, at 37 ± 5^0C, 50 rpm paddle speed. The formulations were filled in a hard gelatin capsule and introduced into dissolution medium. Aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through whatman filter paper (No. 41), were analyzed spectrophotometrically at 432 nm for curcumin content. The data was analyzed using the software[17-19].

Stability Studies:

In order to evaluate the stability of the optimized SMEDDS the formulation was added into sealed glass vials and the vials were subjected to stability studies at $40^0C\pm2^0C/75\%\pm5\%$ RH for a period of three months. Samples were charged in stability chambers with humidity and temperature control. The samples were evaluated for clarity, phase separation, Drug content and in vitro drug release at predetermined intervals[20, 21].

RESULT AND DISCUSSION:

Solubility studies

Selection of right component is important prerequisite for formulation of stable SMEDDS. The drug should have good solubility in components of microemulsion so as the precipitation of drug during shelf life of formulation and after dilution in GI lumen can be avoided. Therefore, the solubility of Curcumin was determined in various oils, surfactants and cosurfactant mixtures. Among the various components studied Ethyl Oleate, Capmul MCM, PEG 400 showed maximum solubility. The solubility results are showed in Table 1 & Table 2. As the solubility of curcumin was maximum in Ethyl Oleate, Capmul MCM, PEG 400 these were selected as oil, surfactant and cosurfactant component for further development of SMEDDS. Final selection among different components would secondly be confirmed according to emulsification properties with other ingredients. Regarding surfactants and co-surfactants selection, drug solubility would come second to the main selection perspective: emulsification efficiency.

Table1: Solubility of Curcumin in various oils, , ,

Sr No.	Oil	Compatibility	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

Table 2: Solubility of Curcumin in various surfactants

Sr No.	Surfactant	Compatibility	Solubility (mg/ml)
1	Tween-60	++	1.145±0.084
2	Tween-80	+++	1.353±0.115
3	Cremophor EL	++	1.447±0.168
4	Capmul MCM	++++	1.924±0.238

Preliminary screening of surfactants

The surfactants were compared for their emulsification efficiencies using different oily phases. It has been reported that well formulated SMEDDS is dispersed within seconds under gentle stirring conditions. Transmittance values of different mixtures are demonstrated in Table 3. Results inferred that among all the surfactants employed the oily phase Ethyl Oleate exhibited the highest emulsification efficiency with Capmul MCM ranking first. It was observed that the solubility of Curcumin was found to be highest in Ethyl Oleate as compared to other oils. This may be attributed to the polarity of the poorly water soluble drugs that favor their solubilization in small / medium molecular volume oils such as medium chain triglycerides or mono- or diglycerides. The solubility of Curcumin was found to be highest in Capmul MCM as compared to other surfactant.

Table 3: Preliminary Screening of Surfactants

Surfactant	% Transmittance			
	Soya bean oil	Paraffin oil	Peanut oil	Ethyl Oleate
Tween-60	54.8	40.1	60.0	45.7
Tween-80	40.7	35.1	52.1	50.0
Cremophor EL	44.9	43.2	45.8	43.0
Capmul MCM	43.5	45.7	55.0	97.9

Preliminary screening of co-surfactants

The PEG 400 was selected and used as cosurfactant due to the fact that transient negative interfacial tension and fluid interfacial film can only be achieved by the use of single surfactant along with a cosurfactant. The presence of PEG 400 enhances the stability of the formulation by reducing the interfacial tension and hence transparent formulation obtained.

Pseudoternary phase diagrams:

From the result it was observed that microemulsion existence zone was relatively more profound with S mix 1:1 and 2:1. The result was given in Table 4. In figure 2 the ternary graphs are shown. Figure 2 (B) and (D) show the maximum microemulsion zone. Both ratios show stability upon infinite dilution with water. While the other ratios were become cloudy on dilution with water and became unstable.

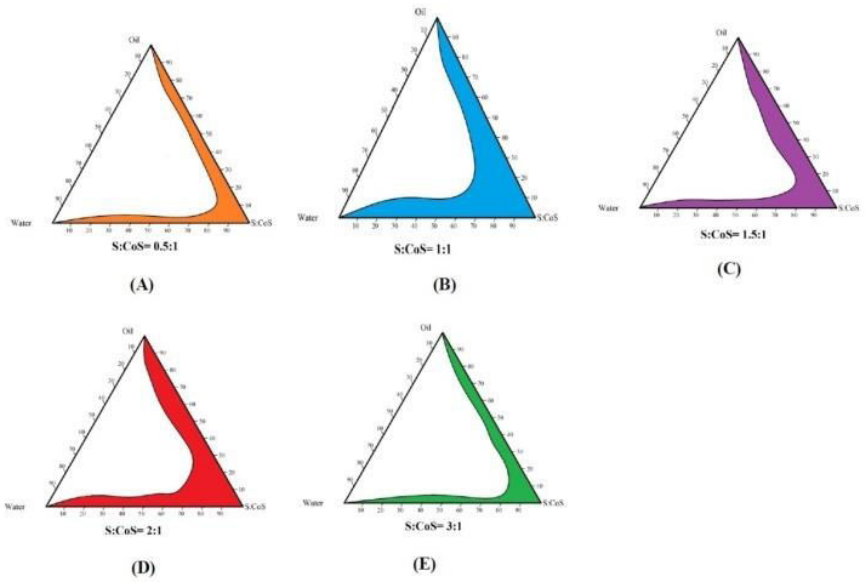

Figure 2: Pesudoternary phase diagrams (A) Smix=0.5:1 (B) Smix=1:1 (C) Smix=1.5:1 (D) Smix=2:1 (E) Smix=3:1

EVALUATION OF SMEDDS:

Self emulsification, phase separation study and Globule Size

The concentration of oil, surfactant and co-surfactant was optimized by preparing different batches of two selected Smix (2:1&1:1) and one optimized formulation from each ratio was selected based on globule size, zeta potential, % transmittance and physical stability (centrifugation) characterization. Results were given in Table 5.

Drug content

ME08 and ME17 were showing drug content 98.1% ±0.85 and 98.7%± 1.03 respectively. Drug content of the developed formulation was found near to 100% showing the chemical stability.

Centrifugation

As showed in figure 3 that no phase separation on centrifugation indicating physical stability of formulations.

Figure 3: Centrifugation study of ME08 and ME17

Table 5: Various SMEDDS formulation

Batch No.	% Transmittance	Globule Size (nm)	Centrifugation
(S:CoS- 2:1)			
ME01	91.2±0.1	82.7±1.3	×
ME02	95.9±0.5	70.1±1.6	×
ME03	92.7±0.3	78.3±2.7	×
ME04	86.9±0.5**	---	√
ME05	90.9±0.4	122.3±2.9	√
ME06	97.9±0.6	61.1±1.6	×
ME07	98.6±0.4	57.3±1.9	×
ME08	98.9±0.3	53.7±1.7	×
ME09	95.1±0.5	99.3±1.2	×
(S:CoS- 1:1)			
ME10	99.8±0.2	48.3±2.2	×
ME11	89.2±0.3	86.8±2.2	×
ME12	84.9±2.1	116.1±1.6	√
ME13	94.5±2.1	72.7±1.3	×
ME14	98.8±0.2	48.3±2.2	×
ME15	96.2±0.3	67.8±2.5	×
ME16	95.3±1.2	75.7±1.3	×
ME17	99.8±0.2	48.3±2.2	×
ME18	96.2±0.4	68.8±2.7	×

(- Becomes hazy)(√- phase separation, ×- no phase separation)**

In Vitro dissolution

Release of curcumin crud drug powder and SMEDDS was compared in figure 4. Curcumin was released completely from SMEDDS at 10 minutes, where as the release percentage of curcumin crud drug powder was limited to 41.22% within 60 minutes because of its hydrophobic property. it could be suggested that curcumin dissolved perfectly in SMEDDS form could be released because of small globular size which permits a faster rate of drug release into aqueous phase, and it could affect the bioavailability.

Stability Studies

Samples of SMEDDS were charged on accelerated and long term stability conditions. Chemical and visual observations of samples were done. No significant change in the drug content in the formulations was observed over the period of 3 months at accelerated and long term stability conditions. The drug release in both the mediums for all two formulations studied remained unchanged.

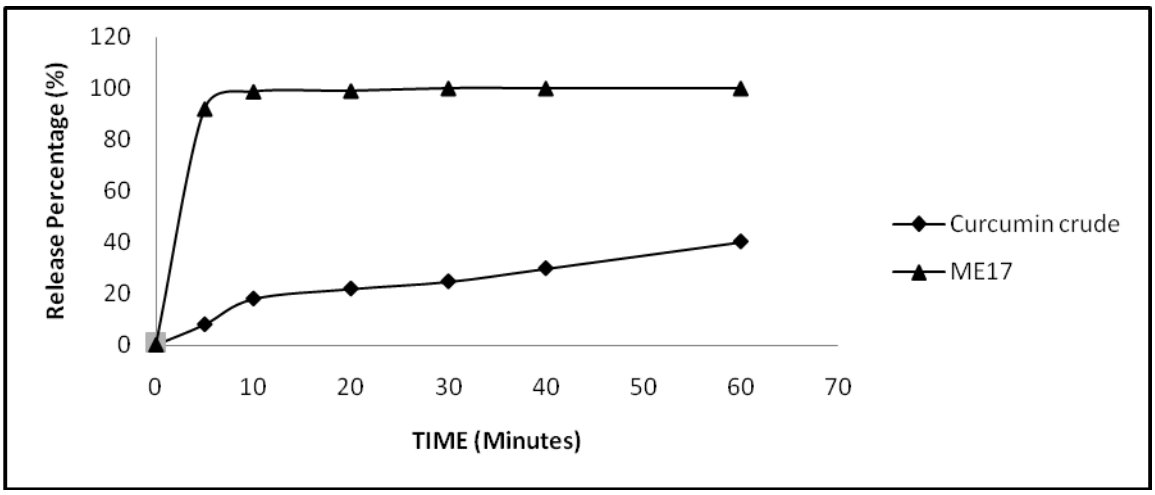

Figure 4: Release percentage of curcumin SMEDDS and curcumin powder.

CONCLUSION:

An optimized curcumin loaded formulation consisting of Ethyl Oleate Capmul MCM, and PEG 400 offers the advantage of good solubilization of Curcumin. Thus our studies confirmed that SMEDDS can be used as a possible alternative to conventional oral formulation of curcumin. Results further conclude that SMEDDS can be explored as a potential drug carrier for dissolution enhancement of curcumin and other insoluble drugs.

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REFERENCES:

1. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. Int. J. Pharm. 27: 335-348 (1985).
2. Singh A., Chaurasiya A., Singh M., Upadhyay S., Mukherjee R., and Khar R., ExemestaneLoaded Self-Microemulsifying Drug Delivery System (SMEDDS): Development andOptimization AAPS PharmSciTech, Vol. 9, No. 2, (2008)628-634.
3. Robinson, J.R., 1996. Introduction: Semi-solid formulations for oral drug delivery. B. T.Gattefosse. 89, 11-13.
4. Yuksel, N., Karatas, A., Ozkan, Y., Savaser, A., Ozkan, SA., Baykara, T., 2003. Enhanced bioavailability of piroxicam using Gelucire 44/14 and labrasol: in vitro and in vivo evaluation.Eur. J. Pharm. Biopharm. 56,453-459.

5. Charman, S.A., Charman, W.N., Rogge, M.C., Wilson, T.D., Pouton,C.W., 1992. Selfemulsifying drug delivery systems: formulation and biopharmaceutical evaluation of aninvestigational lipophilic compound. Pharm Res. 9, 87-93.
6. Li, P., Ghosh, A., Wagner, R.F., Krill, S., Joshi, Y.M., Serajuddin, A.T.M.,2005. Effect ofcombined use of nonionic surfactants on formation of oil in-water emulsions. Int. J. Pharm. 288,27-34.
7. Jing Cui,Bo yu,Yu Zhao,Weiwei Zhu,Houli Li, Hongxiang Lou and Guangxi Zhai, Enhancement of oral absorbtion of curcumin by self microemulsifying drug delivery systems, DOI:10.1016/j.ijpharm.2008.12.009.
8. Patil, P., Joshi, P., Paradkar, A., 2004. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. AAPS PharmSciTech. 5(3), E 42.
9. Kanga,K.B. Lee,S.J .Chona, K.S. Jeong,Y.S., Yuk,H.S. Khanga,G, Development of Selfmicroemulsifying drug delivery systems for oral bioavailability enhancement of Simvastatin in Beagle Dogs Int.J.Pharm,(2004)274,6573
10. Subramanian, N., Ray, S., Ghosal, S., Bhandra, R., Moulik, S. P., Formulation design of Self-Microemulsifying drug delivery systems for improved oral bioavailability of Celecoxib, Bio,Pharm, Bull., (2004) 27(12),1993-1999.
11. Bora, D., Borude,P.,Bhise, K.,Formulation and evaluation of self emulsifying drug delivery system of low solubuility drug for enhanced solubility and dissolution,Asian journal of biomedical and Pharmaceutical Sciences.,2(15),(2012),7-14.
12. Wei Wu, Yang Wang, Li Que Enhanced bioavailability of silymarin by selfmicroemulsifying drug delivery system, European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 288–294
13. Eman A., Albert AB, Formulation and in vitro and in vivocharacterization of a phenytoin self-emulsifying drug delivery system(SEDDS), European journal of pharmaceutical sciences 35 (2008) 257–263
14. Kim, J. Y., Young, S. K.,(2000), Enhanced absorption of Indomethacin after oral or rectal administration of Self emulsifying system containing Indomethacin torats, Int.J.Pharm,194, 81- 89.
15. Grove, M., Mullertz, A., Nielsen, J. L and Pedersen, G. P., (2006), Bioavailability of seocalcitol II: Development and characterization of self microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides, Eur. J.Pharm.Sci,28(3), 233-242.

16. Nazzal, S., Nutan, M., Palamakula, A., Shah, R., Zaghloul, A.A., Khan,M.A., 2002. Optimization of self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int. J. Pharm. 240, 103-114.
17. Pouton, C.W., Charman, W.N., 1997. The potential of oily formulations for drug delivery to the gastro-intestinal tract. Adv. Drug Del. Rev. 25, 1-2.
18. Yu, X. L., wang, T.J., Hussain, S.A., (2002), Evaluation of USP apparatus 3 for dissolution testing of immediate release products, AAPS Pharmsci., article 4(1).
19. Odeberg, J. M., Kaufmann, P., Kroon, K.G., and Hoglund P., (2003),Lipid drug delivery and rational formulation design for Lipophilic drugs with low oral bioavailability, applied to Cyclosporine, Eur. J.Pharm.Sci,20, 375-382.
20. Patel A. and Vavia P. , Preparation and In Vivo Evaluation of SMEDDS (Self - Microemulsifying Drug Delivery System) Containing Fenofibrate, The AAPS Journal 2007; 9(3) Article 41.
21. Jing C., Bo Y., Yu Z., Weiwei Z., Houli L., Hongxiang L., Guangxi Z., Enhancement of oralabsorption of curcumin by self microemulsifying drug delivery systems, Int.J.Pharm, (2008),doi:10.1016/j.ijpharm.2008.12.0090