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"Formulation and evaluation of self emulsifying drug delivery system of herbal drug curcumin"

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Research Article

Abstract
Topical route of application has a great potential as an effective and safe way to administer curcumin for local anti-inflamatory effect. In vitro permeation study showed that menthol enhanced the transdermal absorption of curcumin from drug reservoir system. The topical gel formulations of curcumin developed in this study have great utility and are a viable option for effective and controlled management of inflammation. Further experiments are to be conducted in other animal models for anti-inflammatory effect.Various techniques are used to enhance oral bioavailability of poorly water soluble drugs[1-3]. Oral route has been the major route of drug delivery for the chronic treatment of many diseases as it offers a high degree of patient compliance. However, oral delivery of 50% of the drug compounds is hampered because of the high lipophilicity of the drug itself. Nearly 40% of new drug candidates exhibit low solubility in water, which is a challenge in development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products.

Keyword: anti-inflamatory effect, curcumin, Self-emulsifying drug delivery systems,lipid-based systems

Introduction

Various techniques are used to enhance oral bioavailability of poorly water soluble drugs[1-3]. Oral route has been the major route of drug delivery for the chronic treatment of many diseases as it offers a high degree of patient compliance. However, oral delivery of 50% of the drug compounds is hampered because of the high lipophilicity of the drug itself. Nearly 40% of new drug candidates exhibit low solubility in water, which is a challenge in development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products. Many strategies have been used to overcome these problems either by means of modifying the solubility or maintaining the drug in dissolved form throughout gastric transit time [4-5]. These strategies may include the use of surfactants, cyclodextrins, micronization, liquisolid techniques[6], salt formation, pH change, nano size delivery[7], solid dispersions[8-9] and permeation enhancers and [10-11]. Much attention has focused on lipid solutions, emulsions and emulsion preconcentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems[12].

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Among the lipid-based systems, Self-emulsifying drug delivery systems (SEDDS) is a promising strategy to improve the bioavailability of poorly water-soluble compounds. SEDDS are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers [13]. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. The size of the droplet formed is between 100 and 300 nm while self-micro-emulsifying drug delivery systems (SMEDDS) form transparent micro-emulsions with a droplet size of less than 50 nm [14].

In self emulsifying formulations, the formed emulsion increases membrane permeability as a result of surfactant presence and enhances lymphatic absorption (lymphatic transport) due to medium and long chain oils. These factor may contribute significantly to the better performance of the formulations[15-18].

Physico-Chemical Aspects Of Smedds

Formulation/ Composition of SMEDDS

The formulation generally consists of drug, oily vehicle, surfactant, co-surfactant and even co-solvents. The basic principle of this system is its ability to form fine oil-inwater (o/w) micro-emulsions under gentle agitation following dilution by aqueous phases (ie, the digestive motility of the stomach and intestine provide the agitation required for self-emulsification in vivo in the lumen of the gut). [20] This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. [21] Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption. [22] Selection of a suitable self-emulsifying formulation depends upon the assessment of (1) physicochemical properties of the drug, such as pKa, polarity and solubility in various components (2) physicochemical nature of oily phase, surfactant and co-surfactant (3) the area of the self-emulsifying region as obtained in the phase diagram, (4) the ratio of the components, especially oil to surfactant ratio and (5) the droplet size distribution of the resultant emulsion following selfemulsification. [23]

Mechanism Of Self-Emulsification

In SMEDDS, the free energy formed may either be positive or very low or it may even be negative as a result of which thermodynamic spontaneous emulsification takes place. The interface between the continuous aqueous phase and oil is formed on the addition of a binary mixture (non-ionic surfactant/ oil) to water. It has been found that self-emulsification take place due to the penetration of water into the Liquid Crystalline (LC) phase that is formed at the

water-oil/surfactant interface into which water can penetrate easily, assisted by gentle

agitation. After water penetration to a certain limit, it results in the disruption of interface and droplet formation takes place. According to the researches of Reiss, self-emulsification takes place when the entropy change favoring the dispersion is higher than the energy essential to increase the surface area of the dispersion. It can be expressed by:

$$\Delta G=\sum Ni\pi r2\sigma$$

Where,
ΔG – free energy accompanying the process (apart from the free energy of mixing),
N – Total number of droplets,
r – Radius of the droplets,
σ – Energy at the interface.

Components Of Smedds
Lipid
Surfactant
Lipid Surfactant
Cosurfactant
Cosolvent
Characterizations of SMEDDS
The various ways to characterize SMEDDS are compiled below;
Visual assessment
The primary means of self-emulsification assessment is visual evaluation. This may provide key information about the self emulsifying and micro-emulsifying property of the mixture and about the resulting dispersion.
Equilibrium phase diagram
Comparison of different surfactants and their synergy with co-solvent is enabled using equilibrium phase diagram. The boundaries of one phase region can easily be assessed visually. The phase behavior of a three component system can be represented by a ternary phase diagram. Phase diagram helps in determining the optimum concentrations of different excipients necessary to obtain homogenous pre-concentrates, selfemulsifying ability and drug loading. Each corner of phase diagram represents 100% of particular components and when more than three components are used, closely related one are grouped together as one component and treated as such in the diagram.[25]
Turbidity measurement
This determines the efficiency of self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time[26]. These measurements are carried out using turbidity meters[27].
Droplet size
Microscopic techniques, Photon correlation spectroscopy or a Coulter Nanosizer are generally used to determine the droplet size of emulsion. Droplet size is an important factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the microemulsion[28].
Electron microscopic studies
Surface characteristics of micro-emulsion are studied using Freeze-fracture electron microscopy[29].
Zeta potential measurement
It is used to identify the charge of the droplets.
Determination of emulsification time
This process is used for estimation of the time taken for emulsification. In this efficiency of emulsification of various compositions of the surfactants and lipids is quantified using a rotating paddle to promote emulsification in a crude nephelometer.
Particle size distribution
Dynamic light scattering techniques is used for measurement of particle size distribution of the microemulsion. This utilizes the fluctuation in scattered light intensity to measure the velocity of the Brownian diffusion and consequently the dispersed droplets. Particle size distributions can be further verified by cryogenic transmission electron microscopy (cryoTEM). Cryo-TEM offers the advantage of visualizing the particle sizes and shapes.[30]
Conductivity measurements
Conductivity measurements are able to determine the point of aqueous phase addition where the system changes from having oil continuous to a water continuous phase. It also helps in monitoring of percolation or phase inversion phenomena[31].
Drug Profile
Curcumin
(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane, is the main natural polyphenol found in the rhizome of *Curcuma longa* (turmeric) and in others *Curcuma* spp. *Curcuma longa* has been traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties.
Curcumin, a polyphenol, has been shown to target multiple signaling molecules while also demonstrating activity at the cellular level, which has helped to support its multiple health benefits. It has been shown to benefit inflammatory conditions, metabolic syndrome, pain, and to help in the management of inflammatory and degenerative eye conditions. In addition, it has been shown to benefit the kidneys. While there appear to be countless therapeutic benefits to curcumin supplementation, most of these benefits are due to its antioxidant and anti-inflammatory effects. Despite its reported benefits via inflammatory and antioxidant mechanisms, one of the major problems with ingesting curcumin by itself is its poor bioavailability, which appears to be primarily due to poor absorption, rapid metabolism, and rapid elimination. Several agents have been tested to improve curcumin's bioavailability by addressing these various mechanisms. Most of them have been developed to block the metabolic pathway of curcumin in order to increase its bioavailability.
Biological activities of curcumin
Hypoglycemic effect
Curcumin and its analogs have been synthesized to improve its hypoglycemic efficacy which helps for the diabetic people. For an instance, a novel curcumin derivative (NCD) was developed through the covalent modification of the

curcumin molecule on sites remote from its natural functional groups.

This novel curcumin derivative (NCD) was tested on the diabetic rats to determine whether it exhibits a hypoglycemic effect. The results clearly showed that it lowered the plasma glucose by 27.5 percent and increased plasma insulin by 66.67 percent[62].

Anticancer effects

Curcumin has shown to display chemotherapeutic as well as the chemo preventive effects in different types of cancers. Mono carbonyl analog of curcumin is synthesized from several chemical modifications in the basic structure of the curcumin is to increase its biological activity and also the bioavailability of curcumin. In vitroassays showed that this curcumin derivatives had greater antiproliferative effects on colon cancer cells than curcumin[63].

Anti-inflammatory effects

A lipophilic derivative and hydrophilic derivatives of curcumin such as diacetyl curcumin and diglutaryl curcumin showed in vivo to have an analgesic and anti-inflammatory activities. A carrageenan induced paw edema model indicated anti-inflammatory activity to all curcumin derivatives. The percentage inhibition in the paw edema was higher in diacetyle curcumin than in curcumin[64].

Antioxidant effects

Synthetic sugar derivative in the curcumin has more powerful antioxidant properties. Curcumin decreases the amyloid-β and tau peptide aggregation at micromolar concentrations, whereas the sugar–curcumin conjugate inhibits this aggregation at concentrations as low as the nanomolar level. 5-chloro curcumin which is obtained from natural curcumin, has free radical scavenging activity. CNB-001, a pyrazole derivative of curcumin, protects neuronal cells against toxicity by decreasing free radical formation, and reduces apoptosis by its action onmitochondria. Semi carbazone derivative of curcumin has also shown efficient antioxidant and antiproliferative activity, although its antiradical activity was less than that of curcumin. The probable site of attack for CRSC is both the OH phenolic group and the imine carbonyl position[65].

Excipient Profile

Carbopol

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor.

Nonproprietary names

BP: Carbomers

PhEur: Carbomers

USP-NF: Carbomer

Synonyms: Carbopol; carboxy polymethylene; polyacrylic acid; carboxyvinyl polymer; Pemulen; Tego Carbomer.

Chemical Name: Carbomer

Empirical Formula and Molecular Weight: Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. It contains 52% and 68% of carboxylic acid (COOH) groups on dry basis. The BP 2009 have a single monograph which describing carbomer. The USP32–NF27 contains various monographs describing separate carbomer grades that differ in aqueous viscosity, polymerization solvent and polymer type. The molecular weight of carbomer is theoretically estimated at 7 X 10^5 to 4 X 10^9. In an effort to measure the molecular weight between crosslinks, MC, researchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and MC. Estimated MC values of 237 600 g/mol for Carbopol 941 and of 104 400 g/mol for Carbopol 940 have been reported.

Materials and Methods

Preformulation study

Preformulation studies include studies of:-

- The physiochemical properties of drug, and an assessment of their relevance to the final formulation.
- The physical and chemical stability of drug.
- Chemical /physical compatibility of the drug with excipients.

These studies give clues as to how to achieve the desired performance of the finished products.

Physiochemical Properties of Curcumin

a)Physical evaluation:

b) Solubility: Solubility of drug,obtained by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5ml of the solvent (water, ethanol, methanol, 0.1 N HCl, 0.1 N NaOH and chloroform). Shake vigorously and kept for some time.Note, the solubility of the drug in different solvents (at room temperature) [78].

c) Melting point: It is one of the parameters to judge the purity of drugs.

Procedure for determine melting point:

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus(Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

d) Identification test using FTIR Spectroscopy:

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the molecular structure of an organic compound. Identification of Curcumin was done by FTIR Spectroscopy with respect to marker compound. Curcumin was identified as yellow powder[79]. It was identified from the result of IR spectrum as per specification.

e) Loss on drying: The term loss on drying is an expression of moisture content on a wet weight basis.

Procedure:

Loss on drying is directly measured by IR moisture balance. Firstly calibrated the instrument by knob, then taken 5 gram of sample (powder) and fixed the temperature at 100°C to 105°C for 15 minutes and constant reading, and fixed the knob and check percent moisture.

f) Moisture content determination:

Procedure

Karl Fischer volumetry is used for samples with high water content, *i.e.* 1-100 mg per sample. An iodine-containing

solution serves as titrating agent. The water content of the sample is calculated using titration volume and titer of the titrating agent. One-component reagents conveniently contain all reactants (iodine, sulfur dioxide and a base) dissolved in a suitable alcohol in one solution, whereas two-component reagents contain all necessary reactants separated in two different solutions to enhance the rapidity of the Karl Fischer reaction.

Karl Fischer coulometry is a micro-method and is particularly suitable for samples with small quantity of water content, from 10 µg up to 10 mg. Here, the required iodine is electrochemically obtained in the titration vessel by anodic oxidation from iodide contained in the coulometric reagents. The amount of consumed electric charge is used to compute the utilization of iodine and therefore the quantity of water in the sample.

g) Determination of λ_{max} and Calibration curve of Curcumin

The λ_{max} of Curcumin was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer[80].

Procedure:

Accurately weighed 10 mg of drug was dissolved in 10 ml of 7.4 pH phosphate buffer in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and make up the volume with 7.4 pH phosphate buffer prepared suitable dilution to make it to a concentration range of 5-25 µg/ml. The spectrum of this solution was run in 200-800 nm range in U.V. spectrophotometer (Labindia-3000+). The spectrum peak point graph of absorbance of Curcumin versus wave length was shown in figure:

i) Optimization of Smix ratio

Surfactant and co-surfactant (Smix) in each group were mixed in different volume ratios Tween 80: Ethanol (1:2 1:3, 1:4, 2:1, 3:1: 4:1) and Span: n Butanol (1:2 1:3, 1:4, 2:1, 3:1: 4:1) mix separately and the stock of 100 mL of each groups was prepared. These (Smix) ratios were chosen in increasing concentration of cosurfactant with respect to surfactant and increasing concentration of surfactant with respect to cosurfactant for detailed study of the phase diagrams for the SEDDS formation.

Result:

A) Solubility of Curcumin in different oil, surfactants and co surfactants

On the basis of above study it was concluded that the solubility in the combination of surfactant and co surfactant was found to be favourable for the SEDDS preparation of Curcumin. The maximum solubility was obtained in mixture of Ethanol and Tween 80, Span 80 and n Butanol was selected as for further formulations optimization.

ii) Solubility studies in various ratio of Smix

Construction of pseudo-ternary phase diagrams different ratio of oil and Smix was taken (oil) Oleic acid: Span 80 + n Butanol (Smix) and prepared the SEDDS. The different conc. of oil and mixture of surfactant and cosurfactant were taken and Ternary mixtures were formed in this ratio and quantity of water forming transparent solution was plotted in the pseudo-ternary phase diagram.

B) Stability studies

Curcumin loaded nanoemulsion gel was prepared and stored for 2 months first at cold condition (2ºC-8ºC), room temperature and at elevated temperature (50º±2ºC) and evaluated by visual inspection (phase separation). The prepared gel was found to be stable in 2ºC – 8º.

Conclusion

In Present investigation self emulsifying drug delivery system of Curcumin was developed, Solubility of Curcumin in different oil, surfactants and co surfactants was determined. On the basis of above study it was concluded that the solubility in the combination of surfactant and co surfactant was found to be favourable for the SEDDS preparation of Curcumin. The maximum solubility was obtained in mixture of Ethanol and Tween 80, Span 80 and n Butanol was selected as for further formulations optimization.

In-vitro drug release data for optimized formulation F2 was carried out by modified Franz diffusion cell, the drug release of formulation was found 23.32 after 30 min and 98.74 after 8 hrs. The in vitro release kinetics of optimized formulation was carried out for zero order and first order release kinetics. The release kinetics was found maximum for zero order 0.973indicate the optimized formulation F-2 follow zero order release kinetics.

Topical route of application has a great potential as an effective and safe way to administer curcumin for local anti-inflamatory effect. In vitro permeation study showed that menthol enhanced the transdermal absorption of curcumin from drug reservoir system. The topical gel formulations of curcumin developed in this study have great utility and are a viable option for effective and controlled management of inflammation. Further experiments are to be conducted in other animal models for anti-inflammatory effect.

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S. No.	Melting Point of Curcumin	Average Melting Point of Curcumin
1.	182-184ºC	183-185ºC
2.	183-185ºC	
3.	183-185ºC	

Table 1: Solubility studies of Curcumin in different solvent

S. No.	Solvent used	Solubility
1.	Water	---
2.	0.1 N HCl	---
3.	Ethanol	++++
4.	Methanol	++++
5.	Chloroform	---
6.	0.1 N NaOH	+++
7.	7.4 pH Phosphate Buffer	+++

Table 2: Melting point of Curcumin

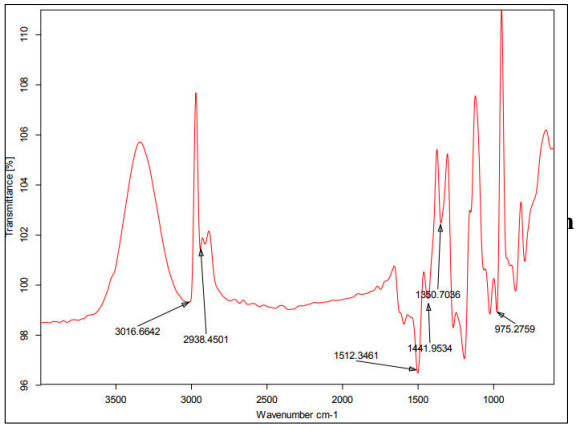

Figure 1: FT-IR Spectrum of Pure Drug (Curcumin)

Formulation Code	Centrifugation	% Drug Content in SEDDS *

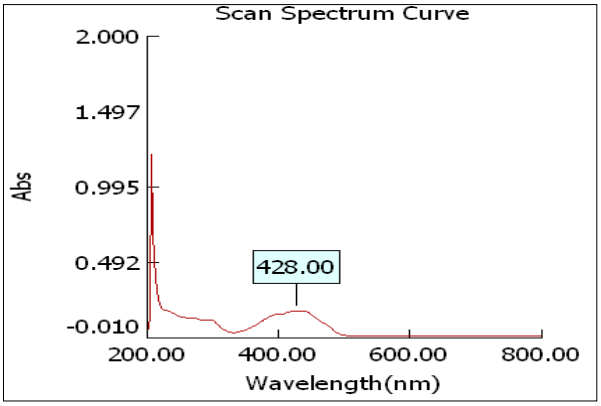

Table 3: Calibration curve of Curcumin at 428nm

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.146
2	10	0.278
3	15	0.427
4	20	0.556
5	25	0.704

Table 4: Formulation of SEDDS

Formulation code	Drug	Oil (Ratio)	Surfactant: Co-surfactants (Smix ratio)
F1	10	1	1:2
F2	10	1	1:3
F3	10	1	1:4
F4	10	1	1:5
F5	**10**	**1**	**1:6**
F6	10	1	1:7
F7	10	1	1:8
F8	10	1	1:9

Table 5: Solubility of Curcumin in different oil, surfactants and co surfactants

S. No.	Component	Solubility
1	Span 40	Soluble
2	Span 80	Soluble
3	Tween 20	Soluble
4	Tween 80	Soluble
5	Pluronic F-127	Soluble
6	Castor Oil	Soluble
7	Sunflower Oil	Slightly soluble
8	Oleic acid	Slightly Soluble
9	Ethanol	Freely soluble
10	n Butanol	Freely soluble

Table 6: Results of pH of Curcumin loaded SEDDS

S. No.	Formulation code	pH*
1	F1	6.98±0.02
2	F2	7.01±0.01
3	F3	6.99±0.02
4	F4	7.01±0.02
5	F5	6.98±0.02
6	**F6**	**6.99±0.03**
7	F7	6.65±0.01

F1	Translucent	75.65±0.45
F2	Translucent	74.56±0.36
F3	Translucent	69.98±0.21
F4	Transparent	71.45±0.25
F5	Transparent	75.65±0.14
F6	Transparent	83.32±0.15
F7	Transparent	80.14±0.25
F8	Transparent	75.01±0.32

Table 7: Results of Centrifugation and % Drug Content in SEDDS

Fig 3: **Result of Zeta Potential of Optimized Batch F6 (-37.5mV)**

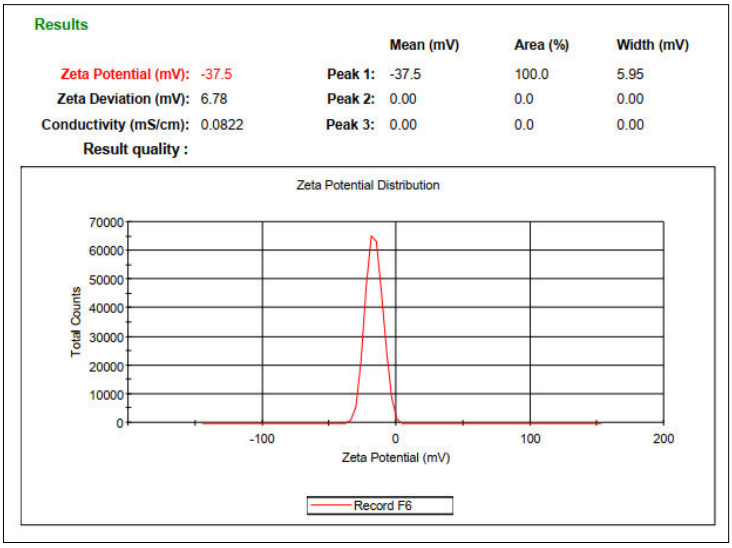

Table 8: In-vitro drug release data for formulation F1

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	30.25	1.481	69.75	1.844
1	1	0	46.65	1.669	53.35	1.727
2	1.414	0.301	59.98	1.778	40.02	1.602
4	2	0.602	79.95	1.903	20.05	1.302
6	2.449	0.778	98.85	1.995	1.15	0.061
8	2.828	0.903	98.92	1.995	1.08	0.033