IJPSR (2020), Volume 11, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 July 2019; received in revised form, 13 December 2019; accepted, 17 April 2020; published 01 June 2020

DESIGN AND CHARACTERIZATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF HERBAL DRUG COMPOUND

Niranjan Chivate [*1], Anuradha Chivate [2], Kiran Wadkar [3] and Rohit Shah [4]

Faculty of Pharmacy [1], Pacific Academy of Higher Education and Research University, Udaipur - 313003, Rajasthan, India.
Department of Pharmacology [2], Krishna Institute of Medical Sciences Deemed to be University Karad, Satara - 415539, Maharashtra, India.
Department of Pharmacognosy [3], Department of Pharmaceutics [4], Appasaheb Birnale College of Pharmacy, Sangli - 416416, Maharashtra, India.

Keywords:

Glycyrrhetinic acid, Self-emulsifying drug delivery system, Microemulsion, Diffusion

Correspondence to Author:
Mr. Niranjan D. Chivate

Senior Lecturer,
Department of Pharmaceutics,
KCT'S Krishna College of Pharmacy,
Karad - 415539, Maharashtra, India.

E-mail: niranjanbpharm@rediffmail.com

ABSTRACT: A glycyrrhetinic acid isolated from herbal plant *Glycyrrhiza glabra* (family Fabaceae), commonly known as licorice is used to formulate microemulsion as a self-emulsifying drug delivery system for oral administration using almond oil as the oil phase. Pseudoternary phase diagrams were constructed to determine the microemulsion existence region using surfactant (Tween 80) and co-surfactant (propylene glycol). Different formulations in the form of microemulsions were prepared to evaluate the effect of oil content, surfactant/co-surfactant concentration on *in-vitro* diffusion rates. *In-vitro* drug diffusion of glycyrrhetinic acid from the microemulsions was evaluated using the dialysis membrane. The amount of glycyrrhetinic acid permeated was analyzed by using the UV method. The permeability of the glycyrrhetinic acid incorporated into the microemulsion systems was considerably increased than that of the plain drug. These results indicate that the microemulsion system studied is a promising tool for increasing the solubility and oral absorption of glycyrrhetinic acid.

INTRODUCTION: The oral route is the most preferred method of administration of drugs. Unfortunately, this route is not possible for 50% of currently marketed drug compounds due to their low solubility in water and therefore, low oral bioavailability. The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability [1, 2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2761-66

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2761-66

Especially for class II substances, according to the Biopharmaceutics Classification System (BCS), bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids [3]. The poorly soluble drug having dissolution rate too slow therefore, uptake cannot be completed within the time at the absorption site. If it remains in GIT for a longer period may lead to decomposition of the drug.

Self-emulsifying drug delivery systems (SEDDS) are newly developed and are having a promising approach to improve the oral bioavailability of drugs. With these formulations slow and incomplete absorption of the drug is reduced, transportation *via* lymphatic system is increased and absorption from GI tract is facilitated [4, 5].

Microemulsions, on the other hand, are emulsion systems that have a droplet size of a few to hundreds of nanometers and are typical complex fluids that consist of three essential components: two immiscible fluids and a surfactant. Typically these are water-in-oil or oil-in-water micro-emulsions where the rheological properties of these two liquids and microstructure of the surfactant strongly affect the resulting microemulsion.

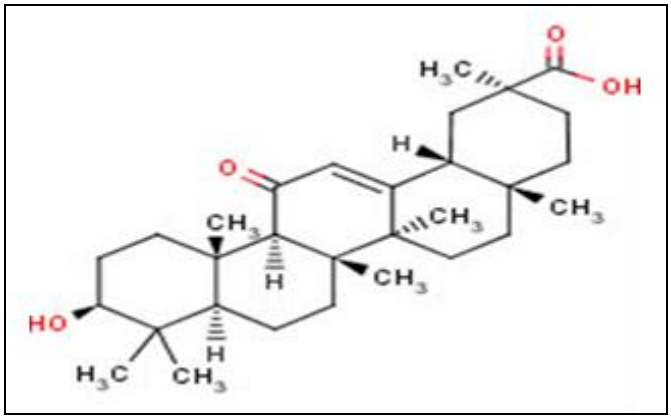

FIG. 1: GLYCYRRHETINIC ACID CHEMICAL STRUCTURE

In the present study, we have formulated and evaluated glycyrrhetinic acid in the form of microemulsion as a self-emulsifying drug delivery system (10 mg/ml) using almond oil as an oleaginous phase, tween 80 as surfactant and propylene glycol as a co-surfactant.

MATERIALS AND METHODS: Glycyrrhetinic acid was purchased from Yucca Enterprises Mumbai. Tween 80, propylene glycol, almond oil were purchased from Bangalore Chemicals. All other chemicals used were of AR grade and used without further purification.

Screening of Microemulsion Components: For selecting different components for formulating microemulsion of glycyrrhetinic acid, the solubility of glycyrrhetinic acid was checked in different oils, surfactants and co-surfactants like Tween 80, Tween 20, Cremophore, Ethanol, Propylene Glycol, Polyethylene Glycol, *etc*. [6, 7]

Excess of the drug was added to 5 ml each of oils, surfactants, co-surfactants and aqueous phase in screw-capped tubes and shaken on orbital flask shaker at 100 RPM for 24 h at ambient temperature. The resultant solution was then centrifuged at 5000 RPM and the clear supernatant liquid was decanted and filtered through Whatman 0.45µ nylon membrane filter. The amount of drug dissolved was estimated by using UV spectro-photometer after suitable dilution with methanol. The solubility study was done in triplicate. The result of the analysis is reported in **Table 1**.

TABLE 1: SOLUBILITY STUDIES FOR GLYCYRRHETINIC ACID IN VARIOUS OILS AT ROOM TEMPERATURE

Phase Type	Excipient	Solubility (mg/ml)
Oil	Soyabean oil	-
	Olic acid	-
	Arachis oil	-
	Castor oil	0.004 ± 0.036
	Olive oil	0.303 ± 0.045
	Almond oil	0.823 ± 0.029
Surfactant	Tween 80	0.076 ± 0.078
	Tween 20	0.015 ± 0.065
	Cremophore	0.065 ± 0.038
Co-surfactant	Ethanol	0.585 ± 0.083
	Propylene glycol	0.691 ± 0.072
	Polyethylene glycol	0.153 ± 0.064
Water	Distilled water	Insoluble

(Mean ± S.D., n=3)

In order to formulate microemulsion for poorly water-soluble drugs, keen attention should be given on solubilising capacity of oil, surfactant & co-surfactant. The solubility of glycyrrhetinic acid in the various oils, surfactant & co-surfactant are listed in **Table 2**. The solubility of glycyrrhetinic acid was found to be highest in almond oil (0.823 ± 0.029) amongst the oils investigated and followed by olive oil and castor oil. Tween 80 (0.076 ± 0.078) showed maximum solubility followed by cremophor among the surfactants, while propylene glycol (0.691 ± 0.072) showed the highest solubility among the co-surfactant followed by ethanol and polyethylene glycol. Almond oil, Tween 80 and Propylene glycol were selected for formulating microemulsions based on the solubility studies and the preformulation studies as oil, surfactant and co-surfactant.

Construction of Pseudo-Ternary Phase Diagrams: Pseudo ternary phase diagrams were constructed to determine the microemulsion existence region [8]. The compositions of the phase diagrams of various weight ratios of tween 80/ propylene glycol are depicted in **Fig. 2-4** for Km values 1.0, 2.0 and 3.0 respectively. The translucent region presented in the phase diagram represents the microemulsion existence region.

No distinct conversion form water-in-oil (w/o) to oil-in-water (o/w) microemulsion was observed. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual inspection.

The procedure employed was as follows; a ratio of surfactant to co-surfactants was fixed as 1:1, 2:1, 3:1, *etc*. and such mixtures were prepared. This ratio was termed as a fixed value Km. These mixtures (S/CoS) were mixed with oil phase to give weight ratio of 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80 and 10:90.

The phase study clearly revealed that as surfactant: co-surfactant ratio increases, the existence area of microemulsion also enlarges.

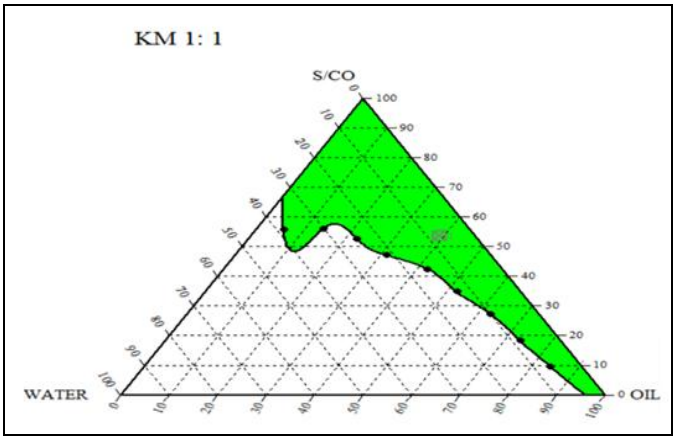

FIG. 2: PSEUDOTERNARY PHASE DIAGRAM OF AMOND OIL-TWEEN 80-PROPYLENE GLYCOL-WATER AT Km-1:1

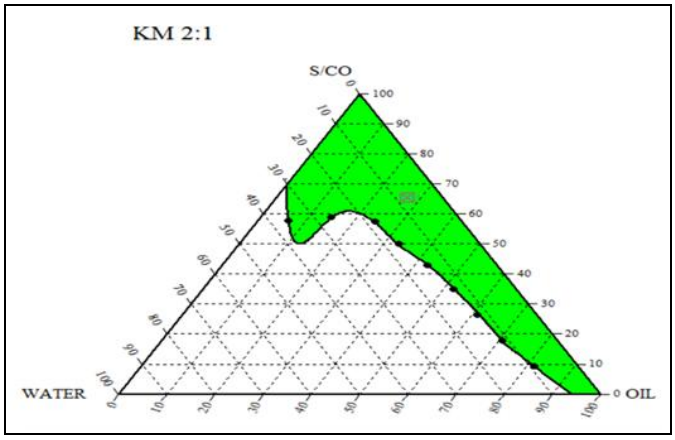

FIG. 3: PSEUDOTERNARY PHASE DIAGRAM OF AMOND OIL-TWEEN 80-PROPYLENE GLYCOL-WATER AT Km-2:1

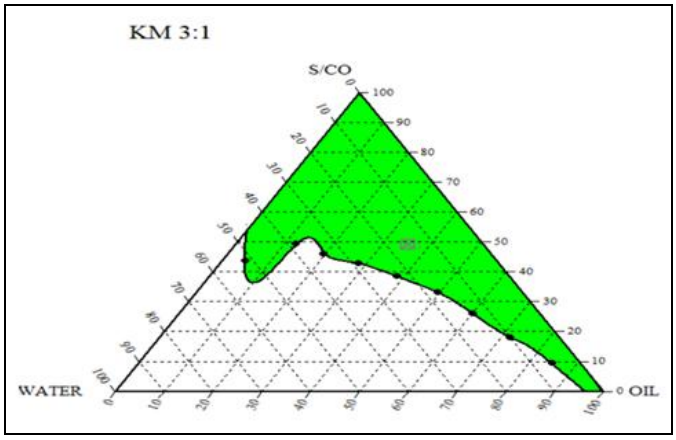

FIG. 4: PSEUDOTERNARY PHASE DIAGRAM OF AMOND OIL-TWEEN 80-PROPYLENE GLYCOL-WATER AT Km-3:1

Preparation of Glycyrrhetinic Acid Micro-emulsions: Almond Oil - Tween 80 – Propylene Glycol - Water Based System.

The phase study clearly reveals that with increase in the weight ratio of surfactant (Km = 1-3), the microemulsion existence region also increased. The maximum proportion of oil was incorporated in weight ratio 3:1 of Tween 80 to Propylene Glycol. Based on the phase diagram varying proportions of surfactant - co-surfactant (35-60%), oil (60-10%) and water (5-30%), six different formulations were prepared using Almond oil / Tween 80 / Propylene Glycol / Water (ATP) **Fig. 5**.

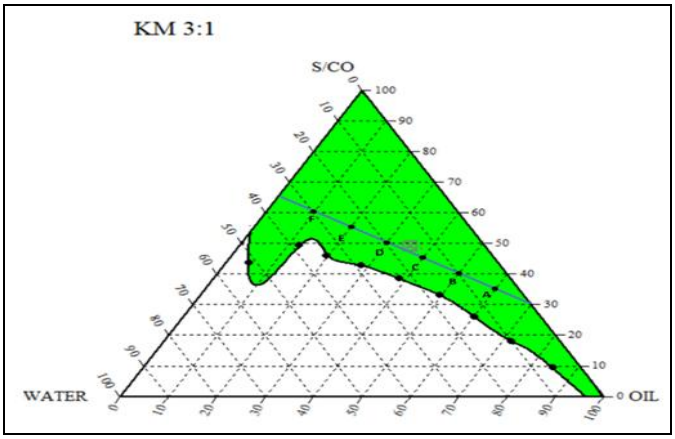

FIG. 5: FORMULATIONS OF GLYCYRRHETINIC ACID MICROEMULSION

10 mg/ml of glycyrrhetinic acid was added to the mixtures of oil, surfactant and co-surfactant with varying component ratios, as described in **Table 2**. An appropriate amount of water was added to the mixture drop by drop, followed by stirring the mixtures at ambient temperature to obtain glycyrrhetinic acid microemulsion. All micro-emulsion formulations were stored at ambient temperature.

TABLE 2: FORMULATIONS OF GLYCYRRHETINIC ACID MICROEMULSION

Ingredients % w/v	Formulation A	Formulation B	Formulation C	Formulation D	Formulation E	Formulation F
Almond Oil	60	50	40	30	20	10
Tween 80 : Propylene Glycol	35	40	45	50	55	60
Water	5	10	15	20	25	30

RESULTS AND DISCUSSION:

Determination of pH: The pH value of a solution was determined using the pH meter (Model El 101 Equiptronics, India). The prepared ME was taken and immersed glass electrode and allowed to stabilize. After stabilization, the pH of the formulation was recorded.

TABLE 3: pH OF DIFFERENT FORMULATIONS

Formulation	A	B	C	D	E	F
pH	5.82	5.88	5.93	5.95	5.97	5.87

Optical Birefringence: The optical birefringence of the prepared microemulsions, as well as the blank formulations, was done to evaluate the isotropy of the phases. All the formulation, when viewed through the cross polarizer through a polarizing microscope, revealed darkness indicating that the prepared microemulsions are optically isotropic and non-birefringent.

Determination of Viscosity: [9-15] The viscosities of microemulsions were measured with a Brookfield viscometer (LV2, Brookfield Inc., USA) equipped with spindle no. 4. The measurement was done at ambient temperature. Viscosities were determined in triplicate.

TABLE 4: VISCOSITY OF DIFFERENT FORMULATIONS

Formulation	A	B	C	D	E	F
Viscosity (cP)	0.8872	0.8872	0.8872	0.8872	0.8872	0.8872

Drug Content: The drug content of the prepared glycyrrhetinic acid MEs was determined by the HPLC method to evaluate the uniformity of the dose in the formulation. HPLC system used was a JASCO system equipped with a model PU 2080 Plus pump, Rheodyne sample injection port (20 µl), JASCO UV 2075 Plus detector and Borwin chromatography software (version 1.5). A chromatographic column HiQ Sil C_8 (250 × 4.6 mm, 5 µm) was used for separation at a flow rate of 1 ml/min using 10 mM KH_2PO_4 buffer: Acetonitrile (5:95 v/v) as mobile phase and detection at 250 nm. The retention time of the drug found to be 3.620 min [16].

The drug content in different glycyrrhetinic acid MEs are listed in **Table 5**. All the results obtained reveal that the drug loading efficiency of MEs varied from 94.844% to 99.011%. All the results indicate that the drug was uniformly distributed amongst the different ME formulations. All the formulation meets the Pharmacopoeial requirement that permits ± 5% deviation.

TABLE 5: DRUG CONTENT OF DIFFERENT FORMULATIONS

Formulation	Area	Conc. (µg/ml)	% Content*
A	460796.4	9.63	96.35±0.32
B	454658.9	9.48	94.84±0.42
C	471653.9	9.90	99.01±0.74
D	465926	9.76	97.61±0.13
E	457801.7	9.56	95.61±0.20
F	468582.8	9.83	98.26±0.63

*All values indicate average value ± SD, n=3

***In-vitro* Drug Diffusion Study:** The *in-vitro* diffusion study of glycyrrhetinic acid from various microemulsion formulations were determined to evaluate the effect of oil content & surfactant/co-surfactant. The permeation studies were performed using a dialysis membrane at 37 ± 0.1 °C.

1.0 ml sample was withdrawn from the receptor fluid at a predetermined time interval for upto 6 h after the application. The first two hours the medium used was the 0.1N HCl and later on phosphate buffer pH 6.8 is used for four hours. All the samples collected were analyzed by UV method, and % CDR is calculated [17-21].

TABLE 6: *IN-VITRO* DRUG DIFFUSION STUDIES FOR DIFFERENT MICROEMULSION FORMULATIONS

Time in h	% CDR					
	A	B	C	D	E	F
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	38.79	36.06	38.66	59.83	40.66	44.30
1	50.90	50.12	40.23	70.59	51.47	54.90
1.5	62.75	58.57	44.08	77.50	57.87	61.15
2	66.14	61.64	62.58	85.73	77.44	76.51
3	87.13	83.18	78.92	102.37	89.60	88.07
4	81.94	87.19	75.94	102.23	83.98	88.25
5	74.21	86.57	76.28	100.54	83.46	87.36
6	73.98	85.60	75.43	100.03	83.95	87.94

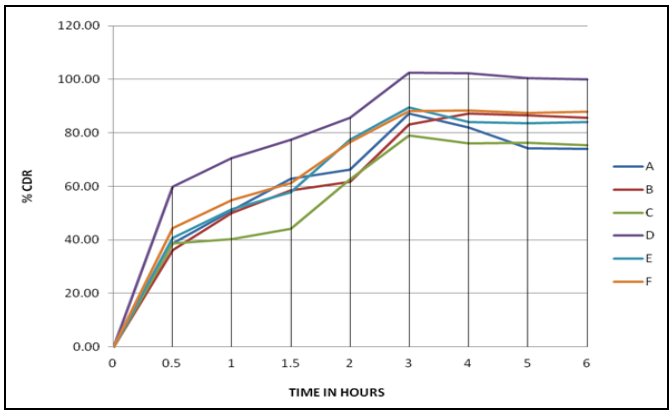

FIG. 6: *IN-VITRO* DRUG DIFFUSION STUDIES FOR DIFFERENT MICROEMULSION FORMULATIONS

The cumulative drug release rates through various microemulsion formulations are illustrated in the above **Fig. 6**. Amongst the formulations tested, the formulation D showed the highest % CDR. The high % CDR of microemulsion might attribute to several factors. Firstly, the high concentration of glycyrrhetinic acid in microemulsion resulted in a high concentration gradient, which might be the main mechanism of drug permeation through the membrane from microemulsion. Microemulsions act as a drug reservoir where the drug is released from the dispersed phase to the continuous and then further on to the membrane.

The glycyrrhetinic acid permeation rate was significantly affected by the content of the surfactant mixture in the microemulsion. This may be due to an increase in the thermodynamic activity of the drug in the microemulsion at the lower content of surfactant, as glycyrrhetinic acid is poorly water-soluble and yet solubilized in the surfactant mixture.

As the surfactant concentration increases, drug permeation also increases due to increased contact of drug and membrane. This might be due to the reduction in surface tension and increased wetting of drugs. From the permeation studies, it clearly reveals that the permeation rate increased for formulation D containing almond oil 30%, Tween 80/Propylene Glycol 50% (3:1) and water.

CONCLUSION: Microemulsions containing glycyrrhetinic acid were formulated for oral administration. Pseudoternary phase diagrams were constructed to determine the components and their concentration ranges for the formation of the microemulsion. Their concentrations were optimized by evaluating *in-vitro* permeation rates of glycyrrhetinic acid. The optimum formulation of the microemulsion consisted of almond oil 30%, Tween 80/ Propylene glycol 50% (3:1) and water.

ACKNOWLEDGEMENT: Authors are grateful to AISSM College of Pharmacy Pune for providing the necessary facilities to carry out this work. Also thankful to KCT'S Krishna College of pharmacy Karad for providing necessary library facilities and support.

CONFLICTS OF INTEREST: The authors declared no conflict of interest.

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How to cite this article:
Chivate N, Chivate A, Wadkar K and Shah R: Design and characterization of self emulsifying drug delivery system of herbal drug compound. Int J Pharm Sci & Res 2020; 11(6): 2761-66. doi: 10.13040/IJPSR.0975-8232.11(6).2761-66.

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