CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Avalable online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF SPIRONOLACTONE

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Article Received: November 2020 **Accepted:** December 2020 **Published:** January 2021

Abstract:

The objective of present study was to develop self-emulsifying drug delivery system (SEDDS) of model drug Spironolactone. Self-emulsified formulations are in focus of recent research due to its advantages like it enhances the bioavailability of oral lipophilic drugs, reduced dosing frequency and the tendency to load both hydrophilic and lipophilic drugs.

The self-emulsions were prepared by using different ratios of oil and surfactant/co- surfactant with water. The prepared self-emulsions were evaluated for emulsification time, preliminary stability indicating study, % transmission measurement and drug content. Drug content of all the prepared self-emulsions was ranged from 91.43% to 96.76 %. In-vitro permeation results revealed that 82.03%- 95.00% of drug permeate from the formulations in 80 mins. study period. The F6 was selected as the best optimised formulation.

Hence it was concluded that poorly soluble drugs such as Spironolactone can be effectively formulated as SEDDS this may improve bioavailability followed by patient compliance.

Keywords: *Self emulsifying drug delivery system (SEDDS), Oil, Co-surfactant, Surfactant.*

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Please cite this article in press Prakhar Gupta et al, ***Formulation And Evaluation Of Self Emulsifying Drug Delivery System Of Spironolactone.,*** *Indo Am. J. P. Sci, 2021; 08(1).*

INTRODUCTION:

Self-emulsifying drug delivery systems (SEDDS) are lipid-based formulations that encompass isotropic mixtures of natural or synthetic oils, solid or liquid surfactants and co-surfactants.

Lipid formulations may be oils, dispersions of surfactants, emulsions, solid lipid nanoparticles and liposomes. SEDDS are isotropic mixtures of drugs, lipids and surfactants, generally with one or more hydrophilic co-solvents or co-emulsifiers. In case of mild agitation followed by dilution with aqueous media, these systems can instantly form a fine emulsion (oil in water). "SEDDS" is a generic term, which generally produces emulsions with a droplet size that varies from a few nanometers to several microns. "Self-emulsifying drug delivery systems" (SEDDS) indicate formulations that form transparent microemulsions with oil droplets between 100 and 250 nm. "Auto nanoemulsifying drug delivery systems" (SMEDDS) is a recent term with blood cell sizes below 100 nm. [1] It has been suggested that self-emulsifying drug delivery systems can be prepared which, after oral administration in gelatin capsules, will be emulsified within the gastric content. [2] The advantage of self-emulsifying formulations over solid dosage formulations is that it prevents slow dissolution of the drug. The distribution of the emulsion within the GIT helps prevents irritation.

Spironolactone is a potassium sparing diuretic like eplerenone that competitively inhibits mineralocorticoid receptors in the distal convoluted tubule to promote sodium and water excretion and potassium retention.

METHODOLOGY:

A series of SEDDS formulations for Spironolactone were prepared based on solubility studies, pseudo ternary phase diagram and visual observation. Here, Castor oil was used as oil phase and Tween 80 and PEG 400 were used as surfactant and cosurfactant respectively. The compositions were given in the (Table 1**)**. [3] In brief, Spironolactone (100mg) was added in accurately weighed amount of oil into screw capped glass vial and heated in a water bath at 40ºC. The surfactant and co-surfactant were added to the oily mixture using positive displacement pipette and stirred with magnetic bar at 500 rpm. The formulation was further sonicated for 15 mins and stored at room temperature until its use in subsequent studies. [4]

To obtain a dose of 100mg of Spironolactone, 4ml of liquid formulation was required.

Table 1: Formulation Ratio

Smix (Surfactant:Co-Surfactant)	Oil: Smix	Code	Drug (mg)	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)
3:1	1:5	F1	100	0.640	2.488	0.828
	1:6	F2	100	0.568	2.572	0.856
	1:7	F3	100	0.500	2.624	0.872
	1:8	F4	100	0.426	2.664	0.888
	1:9	F5	100	0.400	2.700	0.900
2:1	1:8	F6	100	0.426	2.368	1.184
	1:9	F7	100	0.400	2.400	1.200
	1:6	F8	100	0.568	2.284	1.140
	1:5	F9	100	0.664	2.220	1.108

RESULT AND DISCUSSION:

Emulsification time:

To determine emulsification time, 0.5 ml of the SEDDS formulations was introduced into 250 ml of water in 500 ml conical flask under action of magnetic stirrer rotating at constant speed. Emulsification was done at room temperature. After 5 min, the surface of emulsion was examined for turbidity. [5]

Preliminary stability indicating study:

Centrifugation was performed at 3000 rpm for 30 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies. [6]

% Transmittance measurement:

The percent transmittance of various SEDDS formulations was measured at 235 nm using UV spectrophotometer using water as a blank. [7]

Determination of drug content:

SEDDS equivalent to 50mg of Spironolactone were weighed accurately and dissolved in 100 ml of 0.01 N HCl buffer pH 7.4. The solution was filtered, diluted suitably and drug content was analysed at λmax 235 nm against blank by UV spectrometer. The actual drug content was calculated using the following equation. [8]

% Drug content = Actual quantity of drug in SEDDS/ Theoretical quantity of drug in SEDDS X 100

Table 2: Evaluation observation of prepared formulation

S. No.	Formulation code	Emulsification Time (sec.)	Centrifugation	% Transmittance	% Drug Content
1.	F1	50	+	96.36	91.43
2.	F2	70	-	97.55	92.16
3.	F3	100	+	97.77	92.50
4.	F4	130	-	98.30	94.11
5.	F5	120	-	98.53	94.84
6.	F6	160	+	99.77	96.76
7.	F7	100	+	99.04	95.98
8.	F8	80	+	98.24	93.64
9.	F9	70	-	98.87	95.31

(+) Formulation passed, (-) Formulation failed

***In-vitro* dissolution studies:**

The release of drug from SEDDS formulations was determined using a USP Type II dissolution apparatus. The SEDDS formulations were directly placed into the medium water, maintained at 37ºC operated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined intervals 10, 20, 30, 40, 50,60, 70 and 80 mins and filtered through 0.45-µm pore size membrane filters. The volume was replaced each time with 5ml of fresh medium. The concentrations were assayed spectrophotometrically at 235nm. [9,10]

Table 3: *In-vitro* release profile study

Time (min)	Dissolution media –Water (% drug release) Formulation Code									
	Pure drug	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
10	4.15± 0.03	9.05± 0.07	10.20± 0.03	11.21± 0.04	12.36± 0.05	13.66± 0.02	14.05± 0.04	11.46± 0.05	9.4± 0.04	7.54± 0.02
20	12.64± 0.05	21.19± 0.05	22.80± 0.04	22.96± 0.02	23.39± 0.04	24.50± 0.02	26.68 ± 0.02	22.49± 0.03	20.3± 0.02	20.98± 0.04
30	16.02± 0.06	33.2± 0.07	33.82± 0.05	33.92± 0.05	44.16± 0.02	35.36± 0.03	48.78 ± 0.03	44.31± 0.04	42.6± 0.05	40.64± 0.05
40	22.15± 0.05	44.57± 0.05	45.35± 0.02	45.93± 0.08	56.19± 0.05	46.24± 0.01	50.26 ± 0.02	57.46± 0.07	55.7± 0.01	52.02± 0.06
50	25.08± 0.03	56.33± 0.02	57.31± 0.04	57.97± 0.05	68.46± 0.06	58.62± 0.01	62.73 ± 0.02	69.03± 0.02	68.9± 0.02	64.66± 0.07
60	32.28± 0.02	67.21± 0.01	68.76± 0.02	69.46± 0.04	79.23± 0.03	60.99± 0.02	74.21 ± 0.02	71.71± 0.04	70.1± 0.03	76.22± 0.05
70	34.56± 0.06	70.42± 0.05	70.86± 0.06	71.66± 0.03	82.21± 0.02	72.50± 0.01	86.70 ± 0.01	83.78± 0.03	82.4± 0.05	80.63± 0.03
80	40.37± 0.04	82.03± 0.03	82.06± 0.04	84.05± 0.08	90.23± 0.07	89.19± 0.01	95.00 ± 0.02	91.88± 0.04	90.4± 0.06	89.02± 0.05

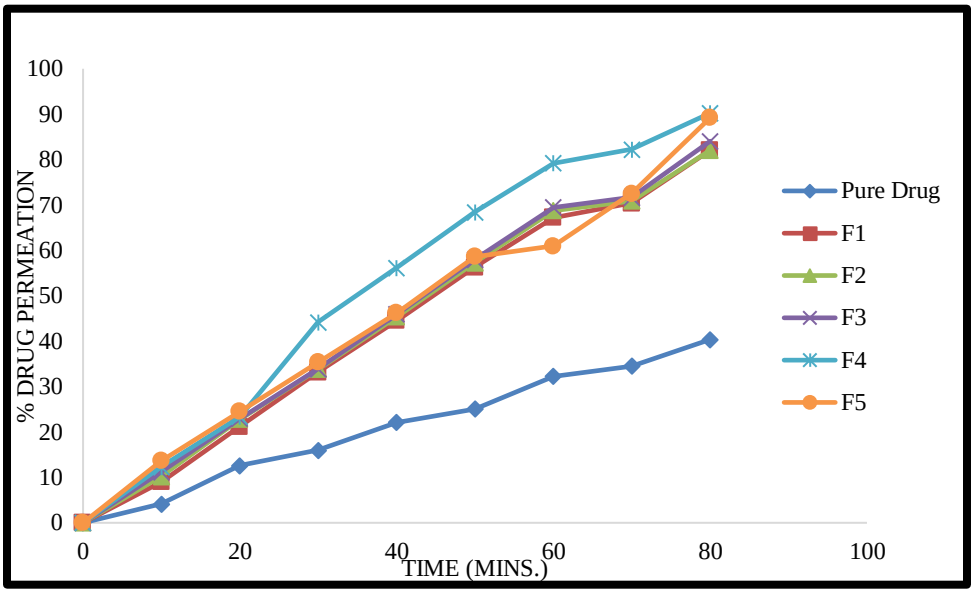

Figure 1(a): *In-vitro* release profile for formulation F1-F5

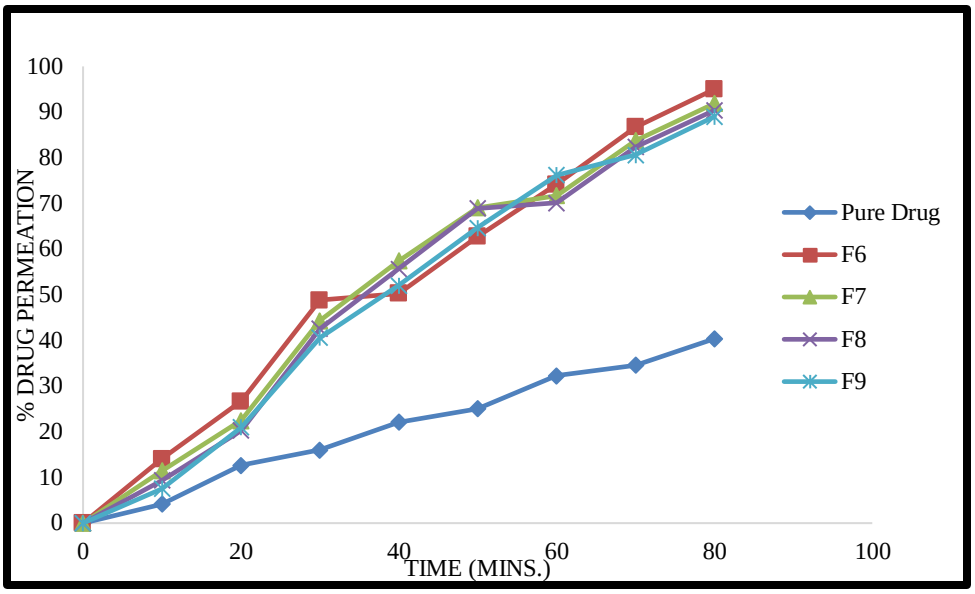

Figure 2(b): *In-vitro* release profile for formulation F6-F9

CONCLUSION:

In this work a SEDDS formulation of a poorly water-soluble drug, Spironolactone was developed by using excipients like Castor oil, Tween 80, PEG 400 and Neusilin US2. In preliminary stability study, no phase separation was observed and there was no change in the visual description of all formulations after centrifugation freeze-thaw cycles. From % transmittance measurement, the clarity of the emulsions was observed. From all the formulations F6, F7, F9 were found to be clear and transparent. The drug content of all the formulations was performed. Maximum drug content was found in the formulation **F6** (96.76%). The *in vitro* dissolution studies were performed for all the nine SEDDS formulations. The release from liquid SEDDS formulation **F6** was faster than SEDDS formulations F1, F2, F3, F4, F5, F7, F8 and F9 indicating the influence of droplet size on the rate of drug dissolution.

Based on visual observation test and faster dissolution rate, formulation **F6** was finalized as optimized formulation. From above experimental study it was concluded that SEDDS of spironolactone increase its solubility followed *in-vitro* release rate. Hence, this may improve bioavailability followed by patient compliance.

Acknowledgement:

Author is thankful to Mr. Sayantan Mukhopadhyay, Assistant Professor in Pharmaceutics, S.G.R.R.U., Dehradun, Uttarakhand for his continuous support and encouragement.

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