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IN VITRO STUDY OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF POORLY WATER SOLUBLE DRUG SPIRONOLACTONE

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ABSTRACT

The main objective of study was to formulate SEDDS of Spironolactone in order to achieve a better dissolution rate which would further help in enhancing oral bioavailability. SEDDS are isotropic mixtures of oils and surfactants, sometimes containing cosolvents. The present research work describes a Self Emulsifying Drug Delivery System (SEDDS) of Spironolactone using oils (Arachise oil, Oleic Acid, Castor oil, Soyabean Oil, Neobee M5, Migloyol, Capmul), surfactants (Tween-80, Cremophor RH40,Cremophor EL) and adsorbents (Aerosil-200,Avicel PH101,Lactose, Dextrose, Mannitol and Talc). In case of SEEDS of Spironolactone, the release rates of all oils were very rapid in Avicel PH101(above 82%) because it has the best flow property among the other absorbents. It Self Emulsifying Drug Delivery System observed that the release pattern from Arachis oil (92.95%), Oleic acid (90.21%) and Castor oil (97.54%) were better in comparison to other oils. Besides, it can be comprehend that the release rate of the three oils were very rapid in Tween-80(above 85%) because it has the best emulsifying property than Cremophor RH40 and Cremophor EL. Besides the solubility of Spironolactone in various oils was determined to identify the oil phase of SEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify the selected oil. The formulation was found to show a significant improvement in terms of the drug release with complete release of drug within 60 minutes. Thus, Self microemulsifying formulation of Spironolactone was successfully developed.

INTRODUCTION: Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants, sometimes containing co-solvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds [1]. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation SEDDS can be orally administered in soft or hard gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution.[2] In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra and inter subject variability, and lack of dose proportionality.

In the oral formulation of such compounds, a number of attempts- such as decreasing particle size, use of wetting agents, co-precipitation, and preparation of solid dispersions have been made to modify the dissolution profile and thereby improve the absorption rate. Recently, much attention has focused on lipid-based formulations to improve the bioavailability of poorly water soluble drugs. Among many such delivery options, like incorporation of drugs in oils, surfactant dispersion, emulsions and liposomes, one of the most popular approaches are the self-emulsifying drug delivery systems (SEDDSs).

Self-emulsifying formulations spread readily in the gastrointestinal (GI) tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self emulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDSs are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles [3-4].

Spironolactone is a potassium-sparing diuretic (water pill) that prevents your body from absorbing too much salt and keeps your potassium levels from getting too low. Spironolactone also treats fluid retention (edema) in people with congestive heart failure, cirrhosis of the liver, or a kidney disorder called nephrotic syndrome. Spironolactone is also used to treat or prevent hypokalemia (low potassium levels in the blood).

Recently, due to good and reliable result, there is a great emphasis on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of lipophilic drugs [5-6].

Self-emulsifications is a phenomenon which has been exploited commercially for many years in formulations of emulsifiable concentrates of herbicides and pesticides [7]. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles [8], surfactant dispersions, self-emulsifying formulations [9], emulsions [10] and liposome [11] with every formulation approach having its special advantages and limitations.

There has been growing interest in the use of lipidic excipients in formulations and, in self-emulsifying lipid formulations (SELFs) because of their ability to solubilize poorly water soluble 'lipophilic' drugs and overcome the problem of poor drug absorption and bioavailability [12]. The lipophillic (poorly water soluble) drugs such as Nifedipine, Griseofulvin, Cyclosporin, Digoxin, Itraconazole Carbamazepine, Piroxicam, Fluconazole, Indomethacin, Steroids, Ibuprofen, Diazepam, Finasteroids, Difunisal, etc. are formulated in SEDDS to improve efficacy and safety [13].

MATERIALS AND METHODS:

Materials: Spironolactone (Zhejiang Shenzhou Pharmaceutical Comp. Ltd., China), Castor Oil, Arachis Oil (BDH Chemicals Ltd, Poole, England) Oleic Acid (Merk, Germany), Migloyol (Sasol, Germany), Capmul PG8 (ABITEC CORP., USA), Neobee M5 (STEPAN, USA), Soyabean Oil (Kuok oils & Grains Pte Ltd. Singapore), Talc, Mannitol, Tween- 8, Cremophor RH40 and EL (BASF, Germany), Dextrose, Lactose, Aerosil-200, Avicel PH101 (Gatefosse, France), Tween-20, Tween-40, Tween-80, Span-60, Span-80, PEG-400 and PEG-600 (Merk , Germany) and liquid Paraffin (MERCK, India).

METHOD:

Preparation of Spirinolactone SEDDS: Spironolactone SEDDS were prepared by using drug (Spironolactone), oils (Arachise Oil, Oleic Acid, Castor Oil, Soyabean Oil, Neobee M-5, Migloyol, Capmul), surfactants (Tween-80, Cremophor RH40, Cremophor EL) and adsorbent (Aerosil-200, Avicel PH101, Lactose, Dextrose, Mannitol and Talc) according to **table 1, 2 and 3** with proper stirring to make sure a homogenous mixing of the drug in the preparation. Then 1 gm of the formulation from each was placed into a clean 50 ml beaker with proper labeling and adsorbent was added with continuous stirring until free flowing powder formed. Formulations were kept in desiccators until the dissolution started.

Flow chart for the process of preparation of SEDDS:

Poorly water soluble drug (Spironolactone)
+
Molten dispersion carriers (Oils)
+
Surfactants
+
Adsorbents
↓
Free flowing powder

Prepared formulation of SEDDS

TABLE 1: FORMULATION FOR THE PREPARATION OF SPIRONOLACTONE SEDDS WITH SURFACTANT AND ADSORBENT USING DIFFERENT OILS

Ingredients	SPL-Arachise	SPL- Oleic	SPL-Castor	SPL-Soyabean	SPL-Neobee	SPL-Migloyol	SPL-Capmul
SPL	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
Tween-80	2 gm	2 gm	2 gm	2 gm	2 gm	2 gm	2 gm
Avicel PH101	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
Arachis Oil	1 gm						
Oleic Acid		1 gm					
Castor Oil			1 gm				
Soyabean Oil				1 gm			
Neobee M-5					1 gm		
Migloyol						1 gm	
Capmul							1 gm

TABLE 2: FORMULATION FOR THE PREPARATION OF SPIRONOLACTONE SEDDS WITH DIFFERENT ADSORBENTS USING DIFFERENT OILS

Ingredients	SPL-Arachise	SPL- Oleic acid	SPL-Castor oil	SPL-Soyabean oil	SPL-Neobee oil	SPL-Migloyol	SPL-Capmul
SPL	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
Tween-80	2 gm	2 gm	2 gm	2 gm	2 gm	2 gm	2 gm
Avicel PH101	400 mg						
Lactose		5 gm					
Dextrose			10 gm				
Mannitol				4 gm			
Talc					7 gm		
Avicel PH101						400 mg	
Arachis Oil	1 gm						
Oleic Acid		1 gm					
Castor Oil			1 gm				
Soyabean Oil				1 gm			
Neobee M-5					1 gm		
Migloyol						1 gm	
Capmul							1 gm

TABLE 3: FORMULATION FOR THE PREPARATION OF SPIRONOLACTONE SEDDS WITH AVICEL PH101 USING DIFFERENT OILS WITH DIFFERENT SURFACTANTS

Ingredients	SPL-Arachise oil	SPL- Oleic acid	SPL-Castor oil
SPL	300 mg	300 mg	300 mg
Tween-80	2 gm		
Cremophor EL		2 gm	
Cremophor RH40			2 gm
Avicel PH101	2 gm	2 gm	2 gm
Arachis Oil	1 gm		
Oleic Acid		1 gm	
Castor Oil			1 gm

***In vitro* dissolution study of SEDDS:** *In-vitro* dissolution was carried out in a USP XXX apparatus 2 (Paddle Apparatus) in 900 ml of distilled water for 1 hour at 37±0.5ºC and at a rotational speed of 50 rpm. Dissolution samples were withdrawn at predetermined intervals and were filtered through 0.45 µm filters. The drug content was determined spectrophotometrically at λ_{max} = 238 nm in the filtrate either directly or after appropriate dilution with the dissolution media.

Solubility Studies: The solubility of poorly soluble drug was study in different oils, surfactants and co-surfactants. The solubility of Spironolactone was determined by adding an excess amount of drug in 2 ml of different oils (Castor oil, Soya bean oil, Arachise oil, Capmul oil, Micloyol oil, Oleic acid and Neobee M 5) and surfactants (Tween-20, Tween-40, Tween-80, Span-60, Span-80, PEG-400 and PEG-600) in 5 ml stopper vials and mixed using a vortex mixer (Remi, India).Vials were stirred in a water bath at 40°C for 24 h and allowed to reach equilibrium at 30°C for 72 h. The equilibrated samples were removed from shaker and centrifuged at 3000 rpm for 10 minutes. The supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of Spironolactone was determined in oils using UV Spectrophotometer (Shimadzu, Tokyo, Japan) at 238 nm [14-15]. The experiment was repeated in twice and the results represent the mean value (mg/mL±SD) in **table 4 and 5.**

TABLE 4: SOLUBILITY OF SPIRONOLACTONE IN DIFFERENT OILS (CASTOR OIL, SOYA BEAN OIL, ARACHISE OIL, CAPMUL OIL, MICLOYOL OIL, OLEIC ACID AND NEOBEE M 5)

Oils	Solubility (mg/ml)
Castor oil	120.61±1.13
Soyabean oil	77.61±1.23
Oleic Acid	60.48 ± 2.89
Capmul	55.24 ± 3.11
Arachis oil	48.24 ± 3.11
Migloyol oil	40.78 ± 3.23
Neobee M 5	35.65 ± 1.78

TABLE 5: SOLUBILITY OF SPIRONOLACTONE IN DIFFERENT SURFACTANTS AND CO-SURFACTANTS (TWEEN-20, TWEEN-40, TWEEN-80, SPAN-60, SPAN-80, PEG-400 AND PEG-600)

Surfactants	Solubility (mg/ml)
Tween 20	50.61±1.13
Tween 40	60.61±1.23
Tween 80	80.48 ± 2.89
Span 60	35.24 ± 3.11
Span 80	70.24 ± 3.11
PEG 400	121.78 ± 3.23
PEG 600	160.65 ± 1.78

RESULT AND DISCUSSION:

Percent (%) Release study of Spironolactone SEEDS with different adsorbents using Different Oils: According to **table 6**, it can be said that the release rate of all oils were very rapid in Avicel PH101 because it has the best flow property among the other adsorbents. Whereas the other adsorbents like Aerosil-200, Lactose, Dextrose, Mannitol and Talc show slow release rate.

TABLE 6: PERCENT (%) RELEASE OF SPIRONOLACTONE SEDDS WITH DIFFERENT ADSORBENTS USING DIFFERENT OILS

Oil	Aerosil-200	Avicel PH101	Lactose	Dextrose	Mannitol	Talc
Neobee M-5	72.76	82.35	79.86	77.57	80.51	68.66
Capmul	75.41	84.98	76.05	77.86	83.78	72.19
Oleic Acid	84.24	90.21	90.57	89.98	88.37	85.8
Migloyol	77	86.53	82.22	76.49	72.78	70.64
Arachis Oil	87.36	92.95	91.10	91.88	91.12	78.71
Castor Oil	90.29	97.54	96.75	93.87	92.95	94.94
Soyabean Oil	82.41	92.95	85.89	87.26	81.95	77.25

Avicel PH101 can be used in the formulation of poorly water-soluble drug as it causes the rapid release of Spironolactone. This test was performed to choose an adsorbent for further use in some other formulations. It was observed from **figure 1 and 2** that the release pattern from Castor Oil, Arachise Oil and Oleic Acid were better in comparison to other oils.

Percent (%) Release of Spironolactone SEDDS with different oils using different surfactants: From **figure 3**, it can be figure out that the release rate of the three oils was very rapid in Tween-80 because it has the best emulsifying property among the other surfactants. Whereas the other surfactants like Cremophor RH40 and Cremophor EL showed slow release rate. Tween - 80 can be used in the formulation of poorly water-soluble drug as it has the solubilizing property for a variety of substances, including essential oils and oil-soluble vitamins, and as a wetting agent in the formulation of oral and parenteral suspensions. This test was performed to choose a surfactant for further use in some other formulations.

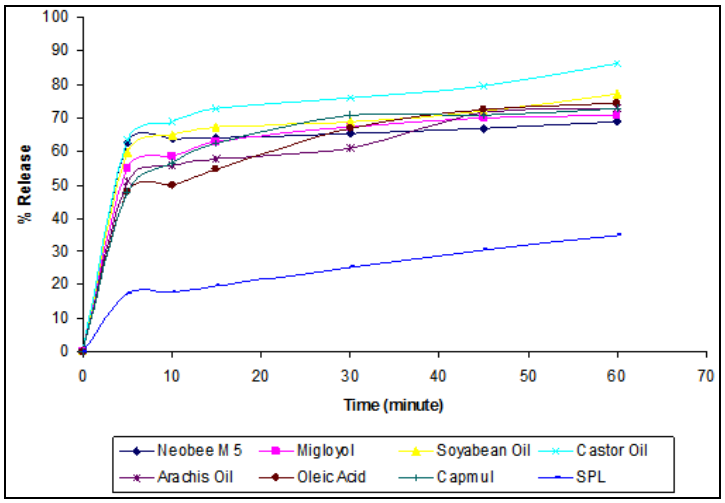

FIGURE 1: PERCENT RELEASE (OR DISSOLUTION STUDY) OF SPIRONOLACTONE SEDDS WITH DIFFERENT ADSORBENTS USING DIFFERENT OILS (CASTOR OIL, SOYA BEAN OIL, ARACHISE OIL, CAPMUL OIL, MICLOYOL OIL, OLEIC ACID AND NEOBEE M 5)

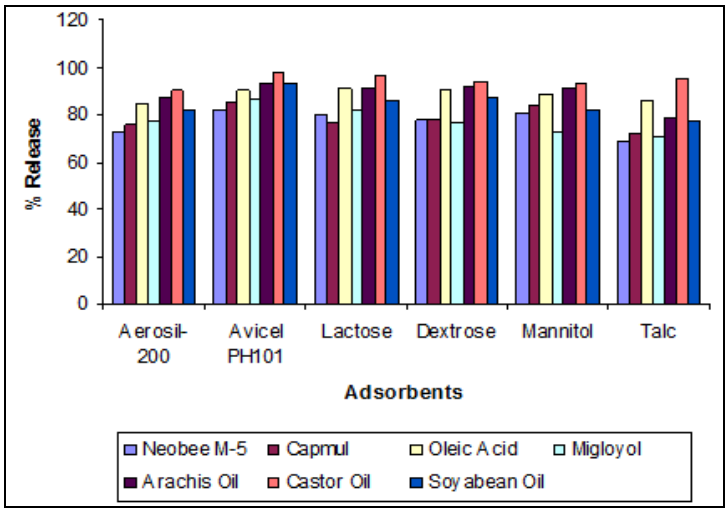

FIGURE 2: EFFECTS OF PERCENT RELEASE OF SPIRONOLACTONE SEDDS FROM DIFFERENT ADSORBENTS (AEROSIL-200, LACTOSE, DEXTROSE, MANNITOL AND TALC)

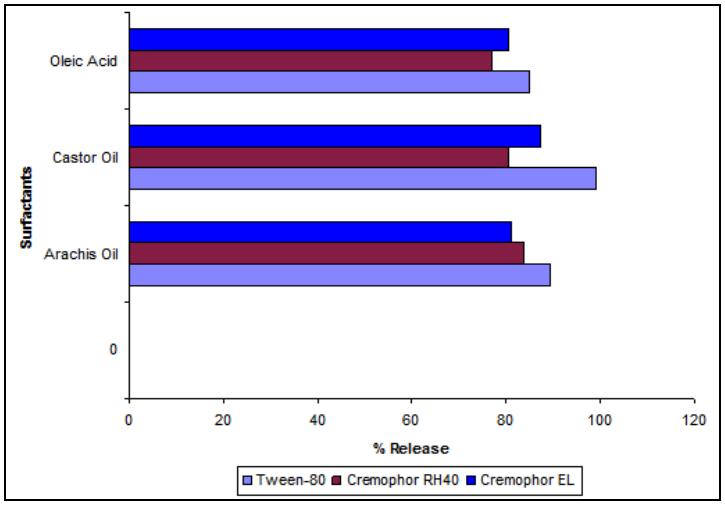

FIGURE 3: PERCENT RELEASE OF SPIRONOLACTONE SEDDS WITH DIFFERENT OILS (CASTOR OIL, SOYA BEAN OIL AND ARACHISE OIL) USING DIFFERENT SURFACTANTS (TWEEN 80, CREMOPHOR RH 40 AND CREMOPHOR EL)

Solubility studies: Solubility studies were aimed to identify a suitable oily phase for the development of Spironolactone SEDDS. The solubility of the drug was tested in different oils phases and maximum solubility was determined in castor oil 120.61±1.13 mg/ml and was selected as oily phase for SEDDS formulation that has shown in **figure 4**. Besides the solubility of the drug was tested in different surfactants and co-surfactants and maximum solubility determined 80.48 ± 2.89mg/ml of tween-80 as a surfactant phase and 160.65 ± 1.78 mg/ml of PEG-600 as a co-surfactant phase that has shown in **figure 5**. It was selected as surfactant for SEDDS formulation.

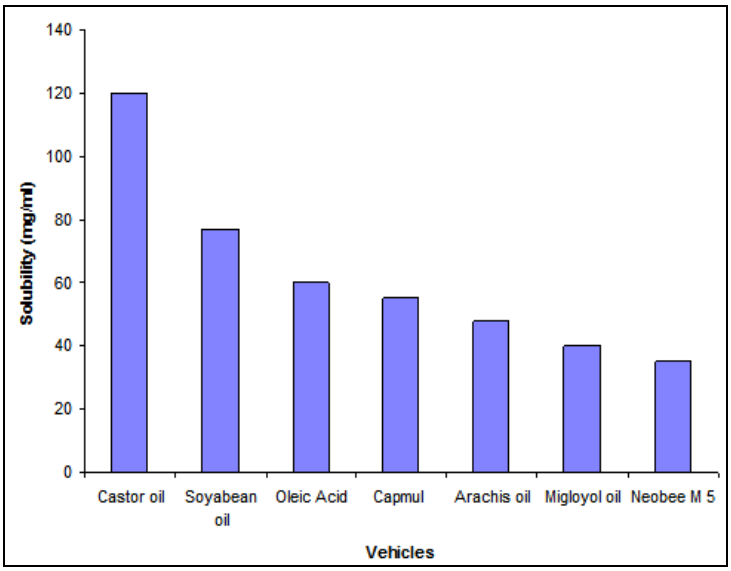

FIGURE 4: SOLUBILITY OF SPIRONOLACTONE IN DIFFERENT OILS (CASTOR OIL, SOYA BEAN OIL, ARACHISE OIL, CAPMUL OIL, MICLOYOL OIL, OLEIC ACID AND NEOBEE M 5)

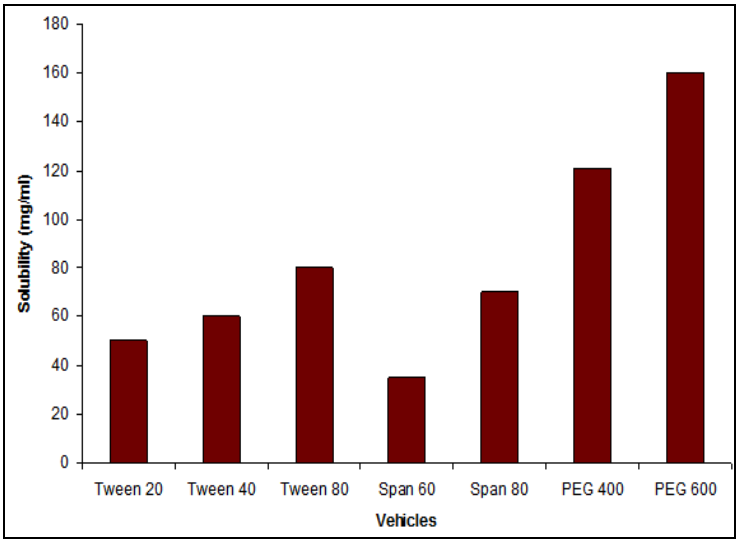

FIGURE 3: SOLUBILITY OF SPIRONOLACTONE IN DIFFERENT SURFACTANTS AND CO-SURFACTANTS (TWEEN-20, TWEEN-40, TWEEN-80, SPAN-60, SPAN-80, PEG-400 AND PEG-600)

CONCLUSION: Spironolactone is a potassium-sparing diuretic, acts as a competitive antagonist to aldosterone. Spironolactone was formulated as a SEDDS in an attempt to increase its solubility. An optimized formulation of SEDDS containing Spironolactone was developed through the construction of in-*vitro* dissolution study, and solubility study. SEDDS provided significant increase in the solubility compared to pure drug formulation. SEDDS appeared to be an interesting approach to improve problems associated with oral delivery of Spironolactone. Spironolactone SEDDS formulation was superior to pure drug formulation with respect to *in-vitro* dissolution profiles activity. Thus, SEDDS can be regarded as novel and commercially feasible alternative in future.

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