PREPARATION AND EVALUATION OF SELF-EMULSIFIED DELIVERY SYSTEMS FOR CINNARIZINE

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Abstract

Preparation and evaluation of self-emulsified delivery systems for cinnarizine

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Self-emulsifying drug delivery systems (SEDDS) were developed with the objective to overcome problems associated with the delivery of cinnarizine, a poorly water soluble drug having a pH dependent solubility with variable bioavailability. Solubility of cinnarizine in various oils (long and medium chain oils) was determined. Ternary phase diagrams were constructed to identify the efficient self-emulsifying region using different surfactants and co-surfactants. The influence of constituents structure on the phase behavior was assessed. SEDDS were prepared using either oleic acid or Captex 200 as oil phase, Cremophor EL or Tween 80 as a surfactant and Transcutol HP or Capmul MCM C-8 as a co-surfactant. The prepared SEDDS were evaluated for their percent transmittance, particle size, *in vitro* dissolution and FTIR spectroscopy studies. The effect of the chain length of oil phase and the structure of surfactant and co-surfactant on the properties of the resulting emulsion was investigated. Using Cremophor EL and Transcutol HP, as surfactant and co-surfactant respectively, decreased the particle size of the formed emulsion. The percent of cinnarizine dissolved was reduced by increasing either surfactant/co-surfactant ratio or increasing oil concentration. The position of OH band of water of dilution in the FTIR study determined the extent of interaction between formula components and water. The FTIR spectroscopy studies revealed strong interaction between water and formulae

containing high surfactant concentration hence, the possibility of forming gel-like structure at high surfactant concentration. Based on the dissolution studies, there were two optimal formulae. One composed of 10%w/w oleic acid, 45%w/w Cremophor EL and 45%w/w Transcutol HP (LC-SEDDS) and the other composed of 10%w/w Captex 200, 45%w/w Cremophor EL and 45%w/w Transcutol HP (MC-SEDDS) with percent dissolution of 92.44% and 85.46% respectively after 30 minutes. The two formulae were converted into dry non-adherent powder with acceptable flowability by applying the mathematical model of Spireas and Bolton. This was done by loading liquid SEDDS formulation onto carrier and coating materials. Three carriers were used (mannitol, Avicel PH 102 or Avicel PH 200) and CAB-O-SIL M-5® was used as a coating material. The prepared liquisolid systems were filled into hard gelatin capsules and were evaluated for their flow properties using different parameters (Angle of repose, Carr's index and Hausner's ratio). Also, the *in vitro* dissolution and the effect of storage on the prepared systems were studied. Systems prepared with mannitol showed the highest percent of drug dissolution. Furthermore, all systems showed non aggregating powders with acceptable flow properties after three month storage. Following oral administration of LC-SEDDS and MC-SEDDS in rabbits, the relative bioavailability values increased by 1.53 and 1.6 fold respectively compared with cinnarizine suspension. There was no significant difference between LC-SEDDS and MC-SEDDS in the pharmacokinetic parameters.

Our studies illustrated the potential use of SEDDS as an alternative approach for enhancing bioavailability of cinnarizine in aged persons who suffers from achlorhydria.

Keywords: SEDDS, SNEDDS, microemulsion, cinnarizine, achlorhydria, oleic acid, Cremophor EL, phase diagram, liquisolid.

بسم الله الرحمن الرحيم

(و أنزل الله عليك الكتاب و الحكمة و علمك ما لم تكن تعلم و كان فضل الله عليك عظيما)

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Dedication

To my dearest parents, brothers, sisters and my dear husband for their sincere encouragement and support.

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List of Abbreviations

Area under the curve	AUC
Cosurfactant	CoSAA
Cumulative percent dissolved after ten minutes	T_{10}
Cumulative percent dissolved after thirty minutes	T_{30}
Cumulative percent dissolved after two hours	T_{120}
Diglyceride	DG
Equation	Eq.
Fatty acid	FA
Fourier transform infrared spectroscopy	FTIR
Gastrointestinal	GI
Gastrointestinal tract	GIT
Generally regarded as safe	GRAS
Hydrophilic-lipophilic balance	HLB
Internal standard	IS
Liquid crystalline	LC
Liquisolid	LS
Long chain triglyceride	LCT
Medium chain triglyceride	MCT
Oleyl glycerate	OG
Poorly water soluble drugs	PWSD
Porous polystyrene beads	PPB
Relative bioavailability	RB
Self-emulsifying	SE

Self-emulsifying drug delivery systems	SEDDS
Self-emulsifying oil formulation	SEOF
Self-microemulsifying drug delivery systems	SMEDDS
Self-nanoemulsifying drug delivery systems	SNEDDS
Similarity factor	f_2
Solid SEDDS	S-SEDDS
Standard deviation	SD
Surfactant	SAA
Triglyceride	TG

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