Asian J. Pharm. Res. Vol 12, Issue 1, 1-6, 2022.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

DESIGN AND EVALUATION OF SULINDAC INCORPORATED SELF NANO EMULSIFYING DRUG DELIVERY SYSTEMS

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ABSTRACT

Nano-emulsions are a novel type of emulsions that are distinguished by their homogeneous and extremely tiny droplet sizes, often in the range of 20–200 nm. When exposed to aqueous media under conditions of gentle agitation or digestive motility that would be countered in the GIT, self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of lipid/oil, surfactant, co-surfactant, and drug substance that rapidly form a fine oil-in-water micro (SNEDDS) and nano (SNEDDS) emulsions. To increase the oral bioavailability of hydrophobic/lipophilic medicines, SNEDDS is one of the most promising strategies for overcoming formulation challenges associated with dissolution/solubility. The purpose of this study is to create and evaluate the SNEDDS of Sulindac ophthalmic emulsion in vitro. The SK9 formulation demonstrated promise. All of the foregoing data demonstrated a significant increase in Sulindac's bioavailability and solubility when administered in the form of Oral SNEDDS. Finally, it was determined that SNEDDS is a potential method for increasing the solubility, dissolving rate, and bioavailability of medicines when administered via the ocular route.

Key words: Nanoemulsions, Sulindac, Self-Emulsification, Oral Bioavailability.

INTRODUCTION

Nano-emulsions are a new class of emulsion which can be defined as an emulsion with uniform and extremely small droplet sizes, typically in the range of 20–200 nm [1]. The physical appearance of nano-emulsion is transparent or translucent because of their small droplets size. Their small droplets size makes it kinetically stable against sedimentation or creaming for a long period of time [2, 3]. The use of nano-emulsions in oral dosage forms, achieve promising results in increasing the effectiveness of the drug at the target site, as well as can increase drug bioavailability, enhanced permeability and therapeutic functions (Sinko, 2012, Swarbrick, 2007). Self-nanoemulsifying system (SNES) is described as an isotropic mixture of natural or synthetic oil and surfactants or one or more hydrophilic surfactant and co-surfactants that have a unique ability of forming fine oil-in-water (O/W) nano-emulsions when mixed with aqueousmedia under mild agitation. Self emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of lipid/oil, surfactant, co-surfactant and drug substance that rapidly form a fine oil-in-water micro (SNEDDS) and nano (SNEDDS)-emulsions, when exposed to aqueous media under conditions of gentle agitation or digestive motility that would been countered in the GIT [Rawan et al., 2020]. The aim of the present study is to formulate and evaluate sulindac incorporated self emulsifying nano emulsions.

MATERIALS AND METHODS

Solubility studies

The solubility of drug was tested in various oils like Arachis Oil, Castor Oil, Palm Oil, Sunflower Oil, Olive Oil, Corn oil by increasing the concentration of drug. Then it is allowed to dissolve in 10 ml of oil until it gets saturated to equilibrium state. The solubility of drug in oil was calculated in mg/ml [Alia et la., 2009; Santosh et al., 2017].

Phase titration method

Microemulsions are formulated by the Spontaneous Emulsification Method (Phase Titration method) and can be shown with the help of phase diagrams. A mixture of fatty acid and oil is added to a caustic solution to prepare a microemulsion.

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Then after it is titrated with a co-surfactant, an alcohol is added, until the system turned clear depending on the chemical composition and concentration of each component. It is found that as the chain length of the surfactant increased, microemulsions with significant transmittances by visible spectrum can be formed with oils of longer chain lengths. It is also found that different alcohols affect the formation of microemulsions in different ways. The best results in terms of the greatest percent transmittance coupled with the wildest range of oil (dispersed in water) concentration are obtained from short or branched alcohols [Goran et al., 2019].

Screening of excipients based on solubility

The choice of excipients is based on the solubility of drug, oil, surfactant and co-surfactant, the solubility of drug in various oils (Arachis Oil, Castor Oil, Palm Oil, Sunflower Oil, Olive Oil, Corn oil), Surfactants (Tween-20, Tween-80, Sodium lauryl Sulphate (SLS), Span-20, Span-80), co-surfactants (Poloxamer 188, Polysorbate 20, Polysorbate 60, Polysorbate 80) was determined by dissolving an excess amount of drug in each vial containing 1 g of the selected vehicle. The mixtures were shaken for 2 hrs in a bath Sonicator maintained at room temperature. Mixtures were centrifuged at 5000 rpm for 5min. the supernatant was taken and filtered. The filtrate was suitably diluted with methanol and concentration of drug was determined in each oil, surfactant, and co-surfactant by UV-spectrophotometer [Kannissery et al., 2015].

Preparation of SNEEDS systems

A series of SNEEDS were prepared using Olive oil as the oil, Span 80 as the surfactant and Poloxamer as the co-surfactant. In all formulations, the amount of drug was kept constant at 20mg. accurately weighed drug was placed in a beaker and oil, surfactant, and co-surfactant were added. The components were mixed by gentle stirring with magnetic stirrer and the resulting mixture was placed in ultra-sonication about 10-15 min for size reduction. Then the mixture was heated at 40^0C, until the drug was completely dissolved. The homogenous mixture was stored at room temperature until further use [Swathi et al., 2013].

Thermodynamic stability studies

After completion of all formulations thermodynamic stability studies was performed, Studies like, heating cooling cycle, freeze thaw cycle and centrifugation.

Characterization of SNEDDS

Phase separation study

Accurately about 1 ml of drug loaded SNEDDS was added to100 ml of distilled water in a glass beaker at 37^0 C and vortexed for 2 min. The mixture was stored at 37^0C (Room Temperature) a period of 2 hrs and observed visually for any phase separation.

Visual assessment

Approximately about 100 µl drug loaded SNEDDS was diluted with purified water (100 ml) and gently stirred with magnetic stirrer. Temperature should be maintained at 37^0C. Formulation SK1 was less clear emulsion, which has a white bluish appearance. Formulations SK2-SK9 were clear, slightly bluish appearance with good stability [Hessin et al., 2011].

Transmission test

Transmittance of light from selected SNEEDS formulations as well as 50 times, 100 times and 200 times dilution with water was checked by UV-Spectrophotometer at respective nm by using water as a blank.

Scanning electron microscopy

Scanning electron microscopy (SEM) is used to characterize the surface morphology of the selected optimized Microemulsion. The samples were mounted on alumina stubs using double adhesive tape, coated with gold in HUS-5GB vacuum evaporator. Then the sample was observed in Hitachi S-3000N SEM at an acceleration voltage of 10KV and magnification of 5000X.

Particle size determination

The average particle size of SNEEDS was determined by dynamic light scattering (DLS) at scattering angle 173^o and temperature of sample holder is about 25^oC by using (Nanopartica SZ-100 HORIBA Scientific, Japan). The sample of dispersion was diluted to 1:2500 v/v with double distilled water to ensure that the light scattering intensity was within the instruments range.

Determination of % drug content

The oil based dispersed system of Drug were analyzed spectrophotometrically for the drug content at wave length 241nm for Sulindac with proper dilution of formulations taking dichloromethane as a blank.

***In-vitro* drug release study** The percentage (%) in-vitro drug release from formulations was used to measure the consistency of emulsifying property. The Dialysis membrane model was used to determine the dissolution to study the drug release from the oil in aqueous medium. SNEEDS filled dialysis bag was tied to the paddle to prevent floating of bag in dissolution media. 900 ml of phosphate buffer pH (7.4) was used as dissolution media. The bath temperature as well as bowl temperature was maintained about 37 ± 0.5^0C and paddle allowed rotating 50 rpm. 5ml of sample was withdrawn at time intervals 5, 10, 15, 20, 25, 30 min and dilution was made to 10ml. 5ml of fresh medium was replaced to

dissolution jar. The diluted samples are analyzed spectrophotometrically at 241nm for Sulindac and their % drug release was calculated.

RESULTS AND DISCUSSION

Thermodynamic stability studies

After completion of all formulations thermodynamic stability studies was performed, Studies like, heating cooling cycle, freeze thaw cycle and centrifugation. On the basis of heating, cooling and centrifugation six formulations were selected out of nine formulations. On the basis of thermodynamic stability studies, it was found that six formulations were passed and selected for further characterization. The formulations named as SK1, SK2, SK3, SK4, SK5, SK6, SK7, SK8 and SK9 and out of these formulations SK4, SK5 and SK6 passed the thermodynamic studies in Sulindac SNEEDS.

CHARACTERIZATION OF SNEDDS

Phase separation study and Visual assessment

SK1 to SK9 formulation shows No phase separation when compared to other 1 formulation K1 microemulsion. From the studies, it infers that it shows most of the formulation are highly stable under vortex condition.

Transmission test

The results shows the Sulindac SNEDDS formulations SK4 and SK5 were less clear and turbid. Formulations SK2-SK9 was less clear and transparent Table 4.

Determination of % Drug Content

The lipid based dispersed system of Sulindac were analyzed spectrophotometrically for the drug content at wave length 231nm with proper dilution of formulations taking dichloromethane as a blank.

Scanning electron microscopy

The study revealed that the most of the SNEDDS was fairly spherical in shape, the surface of the particle showed a characteristic smoothness, and the particle size was in the micrometric range, as depicted by SEM.

Table 1 Composition of Sulindac SNEEDS formulations.

Formulation code	Ingredients %w/w	
	Olive Oil (ml)	Span 80:Poloxamer (S_{mix}) 4:1 (ml)
SK1	10	90
SK2	20	80
SK3	30	70
SK4	40	60
SK5	50	50
SK6	60	40
SK7	70	30
SK8	80	20
SK9	90	10

Table 2: Stability studies of Sulindac SNEEDS formulations SK1-SK9

Formulation	Heating Cooling Cycles (4^0C to 45^0C 72 hrs)	Freeze Thaw Cycle between -21^0C to -25^0C	Centrifugation (3500 rpm 48 hrs)
SK1	Phase separation	Phase separation	Phase separation
SK2	Stable	Phase separation	Phase separation
SK3	Stable	Stable	Phase separation
SK4	Stable	Stable	Stable
SK5	Stable	Stable	Stable
SK6	Stable	Stable	Stable
SK7	Stable	Stable	Phase separation
SK8	Phase separation	Stable	Phase separation
SK9	Phase separation	Phase separation	Phase separation

Table 3: Phase separation of Sulindac SNEEDS formulations

Formulation Code	Phase Separation Observation	Test Result Pass/Fail
SK1	Phase Separation	Fail
SK2	No Phase Separation	Pass
SK3	No Phase Separation	Pass

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SK4	No Phase Separation	Pass
SK5	No Phase Separation	Pass
SK6	No Phase Separation	Pass
SK7	No Phase Separation	Pass
SK8	No Phase Separation	Pass
SK9	No Phase Separation	Pass

Table 4: %Transmission test result for Sulindac SNEDDS

Formulation	**% transmittance**						
	SK2	**SK3**	**SK4**	**SK5**	**SK6**	**SK8**	**SK9**
50 x dilution	24.91	16.34	20.56	22.42	28.66	26.30	28.06
100 x dilution	39.24	40.06	36.48	48.42	56.40	42.60	40.94
200 x dilution	74.42	82.42	84.24	86.76	89.88	84.42	80.06

Table 5: Percentage drug content of the formulations

Formulations	**% of drug content**
SK2	97.21±2.17
SK3	97.54±1.91
SK4	97.43±1.58
SK5	98.17±1.99
SK6	97.55±2.07
SK9	99.69±1.53

Table 6: Invitro drug release from Sulindac SNEEDS

Formulation code	% drug release					
	5 min	10 min	15 min	20 min	25 min	30 min
K1	30.71±2.904	41.00±2.832	45.01±3.384	53.18±3.072	79.35±3.216	83.05±3.288
K2	30.44±3.216	52.24±3.336	60.91±2.856	72.22±2.832	84.48±2.688	90.32±2.544
K3	34.98±3.336	45.40±3.192	50.62±3.288	60.19±3.408	73.73±3.12	86.93±3.456
K4	46.37±2.976	54.24±2.904	67.51±2.928	72.53±2.832	83.89±2.808	93.95±3.216
K 5	42.52±2.76	56.07±3	66.14±2.88	77.98±2.928	84.43±2.808	88.23±2.856
K 6	41.40±3.36	50.82±2.544	68.74±2.832	76.87±2.952	88.34±3.336	91.06±3.048
K 7	55.41±3.456	66.63±3.12	73.73±3.264	79.92±3.024	91.06±2.904	99.01±2.856
K8	35.00±2.664	51.34±2.808	63.23±2.952	69.04±3.192	79.87±3.312	85.36±3.432
K9	62.18±2.928	72.76±2.808	81.71±3.528	88.54±3.408	96.37±3.288	99.82±3.168

Figure 1: SEM image of Sulindac SNEDDS (SK9)

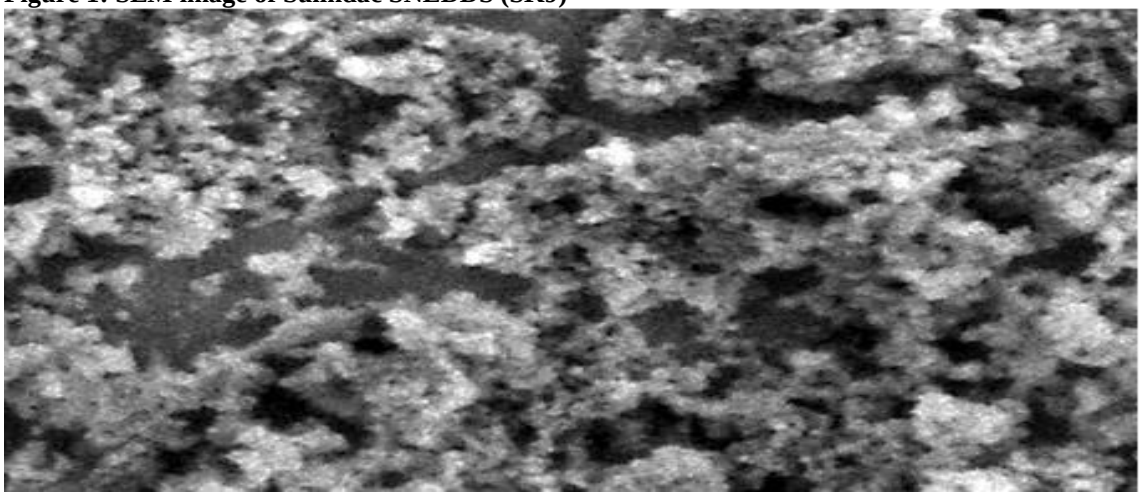

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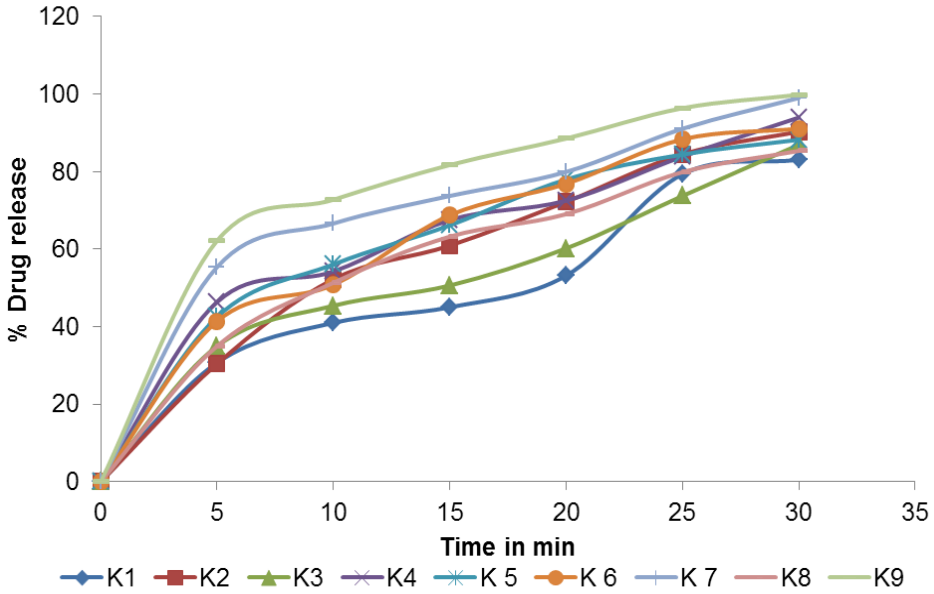
Figure 2: Sulindac SNEDDS-Cumulative Invitro drug release profile



***In vitro* drug release study**

The drug release profile for Lyophilized Sulindac SNEDDS particles was investigated in phosphate buffer (pH7.4) by packing in dialysis membrane. It shows that droplet size decreased, surface area increased allowing more dissolution of drug from SNEDDS. The release of drug from formulation mainly depends on Smix: Oil ratio. When the concentration Smix increased in formulation result in smaller micro droplet was formed this result in increase in the dissolution profile of drug. Thus, the drug release from formulation Sulindac SNEDDS (SK9) was found to be highest (99.96±2.80%) at 30 min. The drug release increases with increase in S_{mix} ratio in SK9, and the effective drug delivery is primarily by micro particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase. The solubilized drug may not precipitate in the lumen, and undergo rapid absorption which is independent of the lipid digestion process.

CONCLUSION

To improve the oral bioavailability of hydrophobic/lipophilic drugs SNEDDS is one of most promising approach to overcome formulation difficulties towards dissolution/solubility. In this study SNEDDS of Sulindac ophthalmic emulsion are effectively developed and measured for its *in vitro* performance. SK9 formulation showed promising result. All the above results in turn showed commendable enhancement of bioavailability and solubility of Sulindac in the form of Oral SNEDDS. Finally concluded that SNEDDS is a promising approach to improve the solubility, dissolution rate and bioavailability of drugs like through ophthalmic route.

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