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RESEARCH ARTICLE

Formulation and Development of Non-Aqueous Emulsion

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ABSTRACT

The delivery of poorly water-soluble drugs has been the subject of much research, as approximately 40% of new chemical entities are hydrophobic in nature. One area in which published literature is lacking is the field of non-aqueous emulsions and some researchers have used polyethylene glycol (PEG) as a continuous phase for such emulsions (1-6). The nature of this emulsion will allow capsule filling at a later stage. In the present study, an attempt has been made to develop non-aqueous emulsions of the type oil-in-PEG suitable for drug loading.

KEYWORDS

Emulsion, cotton seed oil, polyethylene glycol.

INTRODUCTION

Emulsions have been defined as heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 µm in diameter. The two liquids are immiscible, chemically unreactive, and form systems characterized by a minimal thermodynamic stability. One of the important components for making an emulsion is the emulsifier, and a systematic selection of emulsifier type for a particular emulsion is frequently based on the hydrophilic-lipophilic balance (HLB) concept. It is known that mixtures of emulsifiers can have synergistic effects in enhancing stability of emulsions. A suitable combination of emulsifiers leads to a greatly enhanced stability as compared to individual emulsifiers. Various reasons have been given for this, such as formation of intermolecular complexes at the oil/water (O/W) interface (3) and development of strong interfacial films that prevent coalescence by virtue of their high dilational elasticity.

Water-in-oil (O/W) and oil-in-water (O/W) emulsions have been widely studied since emulsion was recognized. In contrast, oil-in-polar solvent (O/W) emulsion has not been fully explored and therefore remains rather limited. In the present study, an attempt has been made to develop non-aqueous emulsions of the oil-in-PG suitable for drug loading.

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MATERIALS AND METHODS

Excipient Properties

The surfactants, Span®60 and Tween®60, were selected based upon previous work by other researchers in non-aqueous emulsions. Cotton seed oil was selected as the disperse phase. All excipients used were assessed using differential scanning calorimetry (DSC) to analyse phase changes (Mettler Toledo).

Formulation Development

Surfactants (Span®60 and Tween®60) were heated in Propylene Glycol (PG) for 60 minutes in a 55˚C water bath. The mixture was homogenised (Silverson sealed unit with a 5/8" tubular work head) and the oil phase added slowly (batch size 6.25g).

Processing was continued and the emulsion was progressively cooled to room temperature. The emulsions were visually observed over time to assess short term stability.

Preliminary Studies

Initial studies were carried out to assess the impact of varying various formulation and manufacturing variables on the short term stability of these non-aqueous emulsion systems. Parameters assessed were the total surfactant concentration; the weight ratio of surfactants; duration of homogenisation and the speed of homogenisation.

Design of Experiments

Following these initial studies, statistical experimental design was used to further assess factors influencing the short term stability of systems using Cotton seed oil as the lipid phase. A 27-2 experimental design was used (¼ fractional factorial design, Table 6).

The height of separation of the emulsions at 24 hours was used as a response factor for the experimental design and this was calculated to take into account differences in the concentrations of PG and Cotton seed oil in each formulation.

RESULTS AND DISCUSSION

Excipient Properties

The DSC profile in Figure 1 shows the melting point phase changes for Tween® 60 and Span® 60, occurring at 15-27ºC and 45-60ºC respectively.

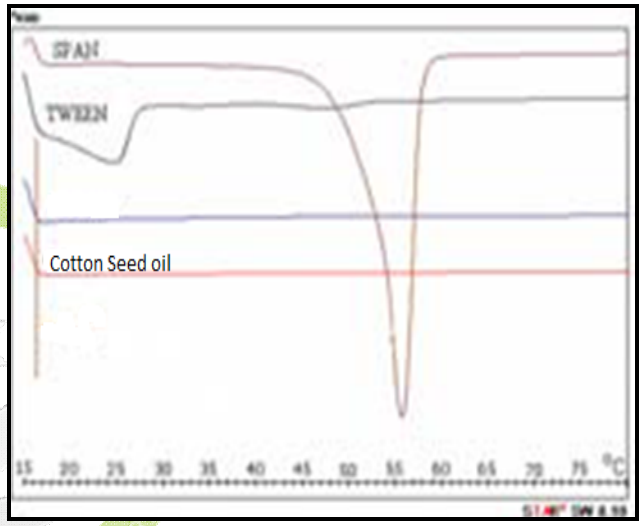

Figure 2: DSC profiles for excipients

Table 1: Design of experiment factors and their levels

	FACTOR	+	0	-
A	Cotton seed oil to PG weight ratio	50 : 50	40 : 60	30 : 70
B	Total surfactant concentration	5%w/w	4%w/w	3%w/w
C	Tween® 60 to Span® 60 weight ratio	25 : 75	50 : 50	75 : 25
D	Homogenisation speed	5500 rpm	4000 rpm	2500 rpm
E	Homogenisation time	25 min	20 min	15 min
F	Rate of oil addition	0.5 mL every 15s	0.25 mL every 15s	0.1 mL every 15s
G	Cooling rate of emulsion	10˚ C per min	5˚C per min	1.5˚C per min

Formulation Development

Preliminary Studies

It was found initially for the formulation parameters that surfactant weight ratios of 50:50 and 25:75 (Tween® 60:Span® 60) and a total surfactant concentration of greater than 4%w/w formed the most stable and elegant emulsions. With regard manufacturing parameters, it was found that a homogenisation speed and time of 4500rpm and 20 minutes respectively was optimal.

Design of Experiments

The statistical experimental design mirrored these initial results. The most important parameter that was found to influence the short-term stability of the systems was the ratio of surfactants (p-value<0.05), with the ratio producing the most stable emulsions being a Tween® 60 to Span® 60 weight ratio of 25:75.

Table 2: Design of experiment results: p-values for each factor assessed

Factor	p-value
A	0.177
B	0.066
C	0.001
D	0.469
E	0.781
F	0.647
G	0.498

Problems were encountered due to poor reproducibility of the emulsions prepared. This was subsequently attributed to the processing temperature. DSC revealed that the initial processing temperature used (55ºC) was in the phase transition temperature range for Span® 60 (Figure 1).

A full factorial experimental design was then performed, with only two of the factors: B, total surfactant concentration and C, Tween® 60 to Span® 60 weight ratio. Increasing the processing temperature to 70ºC enhanced reproducibility and permitted semi-stable emulsions to be formulated. It was found that both factors significantly impacted upon emulsion stability (p-values of 0.012 and 0.000 respectively).

The lead formulation comprises Tween® 60 (1.25%w/w); Span® 60 (3.75%w/w); Cotton seed oil (37.6%w/w) and PG (57.4%w/w). Lead emulsions prepared were found to be semi-stable: there were signs of separation after 24 hours, but complete separation into distinct layers of Cotton seed oil and PG has yet to occur in these systems. Figure 3 shows a polarized microscope image of this emulsion.

Table 3: Optimum values for each factor

	FACTOR	OPTIMUM VALUE
A	Cotton seed oil to PG weight ratio	40 : 60
B	Total surfactant concentration	5%w/w
C	Tween® 60 to Span® 60 weight ratio	25 : 75
D	Homogenisation speed	4000 rpm
E	Homogenisation time	20 min
F	Rate of oil addition	0.25 mL every 15s
G	Cooling rate of emulsion	5˚C per min

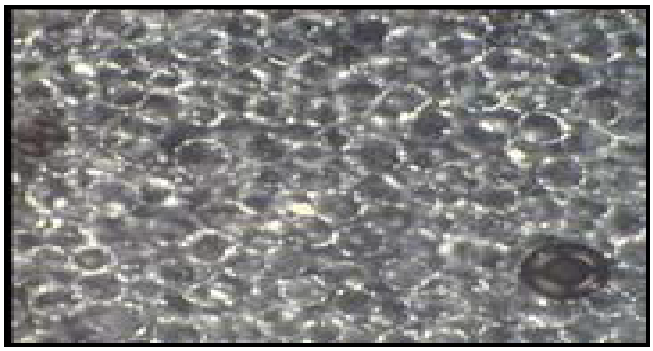

Figure 3: Polarized microscope image of lead emulsion

CONCLUSION

A non-aqueous oil-in-PG emulsion was successfully prepared and experimental design was used to optimize the formulation and manufacturing variables.

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