Scientia Pharmaceutica www.scipharm.at

Research article Open Access

Development and Characterization of New Indomethacin Self-Nanoemulsifying Formulations

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Sci Pharm. 2009; 77: 443–451 doi:10.3797/scipharm.0811-24

Published: March 14th 2009 Received: November 26th 2008
Accepted: March 12th 2009

This article is available from: http://dx.doi.org/10.3797/scipharm.0811-24

Abstract

In the present work a new indomethacin (IND) self-nanoemulsifying drug delivery formulation (SNEDDF) have been prepared to enhance its dissolution which in turn could provide a better chance for IND oral absorption. IND SNEDDF have been prepared using different concentrations of castor oil as a solvent for IND, Cremophor RH 40 (Cr-40) as surfactant and Capmul MCM-C8 (Ca-8) as co-surfactant. Droplets size and turbidity of IND SNEDDFs were measured. Dissolution profile of IND SNEDDFs filled in gelatin capsules was determined by using USP apparatus 2. Ternary phase diagram was constructed to identify the self-nanoemulsifying region after evaluation of IND SNEDDFs by the visual observation. The IND SNEDDFs were thermally characterized using differential scanning calorimetry (DSC) to ensure the compatibility among its ingredients. The present study revealed that the SNEDDFs increased IND dissolution rate and has the potential to enhance its bioavailability without interaction or incompatibility between the ingredients.

Keywords

Indomethacin • Nanoemulsion • DSC • SNEDDF • Dissolution

Introduction

IND is a lipophilic non-steroidal anti-iflammatory drug commonly used to reduce fever, pain, stiffness, and swelling [1]. It is the drug of choice for the closure of a patent ductus

arteriosus in neonates by virtue of its vasoconstrictive action in the tissues of the ductus [2]. Because IND inhibits both COX 1 and COX 2, it inhibits the production of prostaglandins in the stomach and intestine which maintain the mucous lining of the gastrointestinal tract [3], therefore, like other nonselective COX inhibitors, IND may cause peptic ulcers [4]. The ulcers may result in serious bleeding and/or perforation which requiring hospitalization of the patient, some even die from these complications [5]. IND is extensively bound to plasma proteins, and has wide inter-subject variability in the plasma concentrations, half life and therapeutic response in premature neonates [2]. SEDDFs are isotropic mixtures of natural or synthetic oil, surfactant(s) with or without a co-surfactant. Upon mild agitation these systems can form fine oil in water emulsions in aqueous media, such as dissolution media or gastrointestinal fluids, [6]. Self-emulsifying formulations spread readily in such aqueous media providing the drug in nanometer droplets size which in turn enhance the dissolution rate of lipophilic drugs by increasing their aqueous solubility. However, studies have shown that the self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs [7, 8]. The present study is a trial to formulate IND in a SNEDDF to increase its solubility in water and hence improving its dissolution rate which in turn may enhance IND oral bioavailability.

Materials and methods

Chemicals:

IND, and castor oil were purchased from Sigma Chemical Co. (St. Louis, Mo., USA). Macrogol-glycerol hydroxystearate (Cr-40) was obtained from BASF Corp. (Mount Olive. N.J., USA). Glyceryl monocaprylate (Ca-8) was obtained from Abitec Corp. (Jamesville, Wisc., USA). Hard gelatin capsules were supplied by Shionogi Qualicaps (Whitest, N.C., USA). All chemicals were used as received.

Preparation of IND SNEDDFs:

A series of IND SNEDDFs were prepared with fixed concentration of IND (25 mg) and varying concentrations of castor oil, Cr-40 and Ca-8. IND was dissolved in the amount of castor oil and then Cr-40 and Ca-8 were accurately weighed and added to IND oily solution. The mixture was mixed using magnetic stirrer until a clear solution was obtained. An exact amount of each formulation equivalent to 25 mg IND was filled into hard gelatin capsules. The filled capsules were stored in a refrigerator until their use in subsequent studies. Table 1 shows all the formulations composition.

In vitro characterization of IND SNEDDF

1. Visual observations:

From each formulation, 1025 mg was introduced into 50 ml of water in a glass Erlenmeyer flask at 25 °C and the contents were gently agitated manually. The tendency to spontaneously form a transparent emulsion was judged as good and it was judged bad when there was poor or no emulsion formation [9, 10]. Phase diagram was constructed identifying the good self-emulsifying region. All studies were repeated in triplicates and the mean values are shown in Figure 1.

Tab. 1. IND SNEDDFs composition.

Formulation No.	IND (mg)	Castor oil (mg)	Cr- 40 (mg)	Ca-8 (mg)
1	25	100	800	100
2	25	100	700	200
3	25	100	600	300
4	25	100	500	400
5	25	100	400	500
6	25	100	300	600
7	25	100	200	700
8	25	100	100	800
9	25	200	700	100
10	25	200	600	200
11	25	200	500	300
12	25	200	400	400
13	25	200	300	500
14	25	200	200	600
15	25	200	100	700
16	25	300	600	100
17	25	300	500	200
18	25	300	400	300
19	25	300	300	400
20	25	300	200	500
21	25	300	100	600
22	25	400	500	100
23	25	400	400	200
24	25	400	300	300
25	25	400	200	400
26	25	400	100	500
27	25	500	400	100
28	25	500	300	200
29	25	500	200	300
30	25	500	100	400

2. Turbidity measurements:

From each formulation, 1025 mg was introduced into 50 ml of water at 25 °C and the contents were gently stirred manually. Turbidity of the resultant emulsions given in nephrometric turbidity unit (NTU) was measured using Orbeco-Hellige model 966, Orbico Analytical System Inc., Farming dale, NY, USA. All measurements were done in triplicate.

3. Emulsion droplets size analysis:

From each formulation, 1025 mg was introduced into 50 ml of water at 25 °C and the contents were gently stirred manually. The mean droplets size distribution of the resultant emulsion was determined by laser diffraction analysis (NiComp Particle Size system ZW380 Version 2 Santa Barbara, California, USA). The sizing of the emulsion was determined in a small volume module. Samples were directly placed into the module and

the data were collected for 15 min. Droplets size was calculated from the volume size distribution. All measurements were done in triplicate.

4. Dissolution study:

Dissolution of IND SNEDDFs filled in hard gelatin capsules was determined using USP24 rotating paddle apparatus (VK7000, vankel, USA) at 37 ± 0.5 °C and a rotating speed of 50 rpm in 900 ml of water. Capsules were held to the bottom of the vessel using copper sinkers. A sample (3 ml) withdrawn after 30 minutes was filtered using a 10 µm VanKel filter and assayed for IND using spectrophotometric method at 320 nm [11]. The dissolution experiment was carried out in triplicates.

Tab. 2. Physical parameters for IND SNEDDFs.

Formulation No.	Visual observation	Mean turbidity (NTU)	Mean droplets size (nm)	% Release
1	Bad	–*	–	–
2	Bad	–	–	–
3	Bad	–	–	–
4	Good	34	174 ± 4.51	70
5	Good	14	112 ± 8.33	78
6	Good	5.4	72 ± 3.51	82
7	Good	3.7	54 ± 4.51	87
8	Good	1.2	30 ± 4.04	93
9	Bad	–	–	–
10	Bad	–	–	–
11	Good	103	396 ± 7.51	59
12	Good	77	262 ± 8.31	64
13	Good	31	158 ± 5.86	72
14	Good	24	131 ± 3.06	74
15	Good	16	120 ± 4.04	78
16	Bad	–	–	–
17	Bad	–	–	–
18	Bad	–	–	–
19	Bad	–	–	–
20	Good	102	379 ± 5.03	67
21	Good	84	291 ± 7.00	61
22	Bad	–	–	–
23	Bad	–	–	–
24	Bad	–	–	–
25	Bad	–	–	–
26	Good	109	411 ± 8.08	55
27	Bad	–	–	–
28	Bad	–	–	–
29	Bad	–	–	–
30	Bad	–	–	–

* Values are not determined

5. Differential scanning Calorimetry:

Samples of IND alone and its physical mixture with additives (castor oil, Cr-40, and Ca-8) in a ratio of 1:1 were accurately weighed, encapsulated and hermetically sealed in flat bottomed aluminum pan with crimped on lid. The pans were positioned on sample pan holder of a Perkin-Elmer DSC7. The samples were heated in an atmosphere of nitrogen over a temperature range from 30 to 250 °C with a constant heating rate of 10 °C/min. Thermograms were obtained by the DSC7 thermal analyzer program and recorded at constant chart speed of 1 in./min. The thermogram, transition temperature range, the onset of peak transition and the maximum peak of transition were recorded using Okidata Microline 320 and 9 Pin Printer. Two replicates were made for each DSC thermogram using an empty sealed aluminum pan as reference and indium as instrument calibration standard.

Results and Discussion

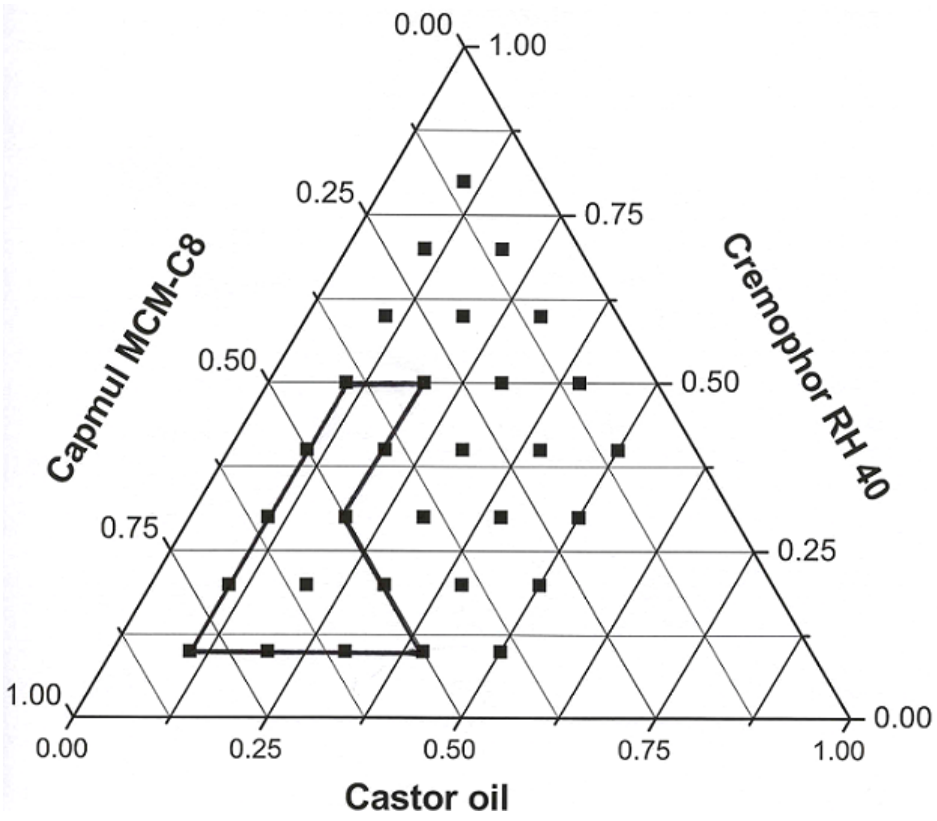

Fig. 1. Ternary phase diagram shows the efficient self-emulsification region.

1. Visual observations:

For the preparing of a SNEDDF, an appropriate mixture of surfactants should be used to produce a stable microemulsion having droplet size in nanometer range [9, 12]. In this study, Cr-40 with an average HLB value of 12 and Ca-8 with an average HLB value of 3.5 were selected. Spontaneity of emulsions formation was evaluated and a ternary phase diagram of the system comprising the Cr-40, Ca-8 and castor oil was constructed

(Figure 1). All the components were converted to percent weight per weight before constructing the ternary phase diagram. The area enclosed within the solid line represents the region of self-emulsification. The area enclosed within the solid line in the ternary phase diagram of IND SNEDDF is different from that obtained with retinol acetate SNEDDF [8] which may be due to the different physicochemical properties of IND. Within this area the prepared formulations form fine oil in water emulsion with gentle agitation. The mechanism of emulsions formation could be explained as follow: Cr-40, due to its water solubility, localized on the surface of the castor oil droplets reducing the interfacial free energy between castor oil and the water so it provides a mechanical barrier to prevent oil droplets from coalescence resulting in a thermomechanically stable emulsion [13]. Cr-8 was used to provide more stabilization for castor oil droplets and solubilization to IND [14]. Furthermore, owing to its crystallization inhibition property, Ca-8 prevent the crystallization of IND in formulation and emulsion which provide stability and efficacy for the formulations as it was indicated from DSC study.

2. Turbidity:

Turbidity values have been reported to be of use in SNEDDS characterization [10], therefore it was performed on IND SNEDDFs which have passed the visual observation test (marked good). In the turbidity measurement, the amount of scattered light (when an incident light is subjected to strike small particles) is measured and used in turbidity calculations as per the Rayleigh's theory [15]. Light scattering by colloids conforms to Raleigh theory, which predicts that light scattering or measured turbidity (r) in a simplified equation can be given by $r = Knv^2$ in which K is a machine constant, v is particle volume and n is the number of particles [15]. The turbidity measurements may be reasonable compromise when dissolution of a drug from SNEDDFs can not be measured because of low solubility of drug. Table 2 shows a good correlation between the visual observation and turbidity of all formulations. Regarding the relation between turbidity of IND SNEDDFs and castor oil, Cr-40 and Ca-8 concentrations, it is obvious that Ca-8 concentration have a great influence on the turbidity of IND SNEDDFs.

3. Emulsion droplet size analysis:

Nanoemulsions are characterized by the droplets size of nanometer range. Therefore droplets size analysis was performed on IND SNEDDFs which have passed the visual observation test (marked good) to see whether the resultant emulsions are indeed nanoemulsions. As seen in Table 2, all the droplets size of the prepared SNEDDFs which marked good in visual observation test are in nanometer size range. A careful observation in Table 2 shows that the amount of IND dissolved in 30 min (t_{30} values) increases when the droplets size decreases. It is clear that increasing the concentration of Ca-8 lead to decreasing droplets size.

4. Dissolution study:

The release of IND from selected SNEDDFs (marked good) was markedly different from one formulation to another depending on the ratio of castor oil, Cr-40 and Ca-8 in each formulation. It is obvious that any change in the droplets size and/or the turbidity of the prepared formulations is reflecting dramatically on the dissolution rate of IND. In another words there is an inversely relationship between droplets size of the formulations and its drug release percent. Both castor oil and Ca-8 concentrations have a great impact on IND

release from SNEDDFs. From the data of the dissolution study it is clear that the optimum ratio for Cr-40 to Ca-8 is 1:8 that is obvious in formulation number 8, which gave the lowest droplet size (30 nm) and in turn has the highest amount of drug release (93 %) in 30 minutes. Also, from Table 1 and 2 it is clear that changing the 1:8 Cr-40 to Ca-8 ratio to higher amount of Cr-40 and low amount of Ca-8 led to increasing the droplets size of the formulations and hence decreasing the dissolution of IND from the formulations.

5. Differential scanning calorimerty:

The DSC thermogram of IND (Fig. 2, A) shows a characteristic endothermic peak at 154 °C due to its melting. From Figure 2 it is clear that the physical mixture of IND and the components of SNEDDF ingredients at a ratio of 1 : 1 indicates the presence of small endothermic peak of IND with reduction of intensity and shifting to lower temperature. Moreover, (Fig. 2, E) IND SNEDDF thermogram shows more reduction in size and intensity of the endothermic peak of the drug which may be due to its solubility in the nanoemulsuion ingredients. These data agree with data of mean droplets size (Table 2) where decreasing size of the drug particles led to decrease in crystallinity and shifting of melting peak to lower temperature degree.

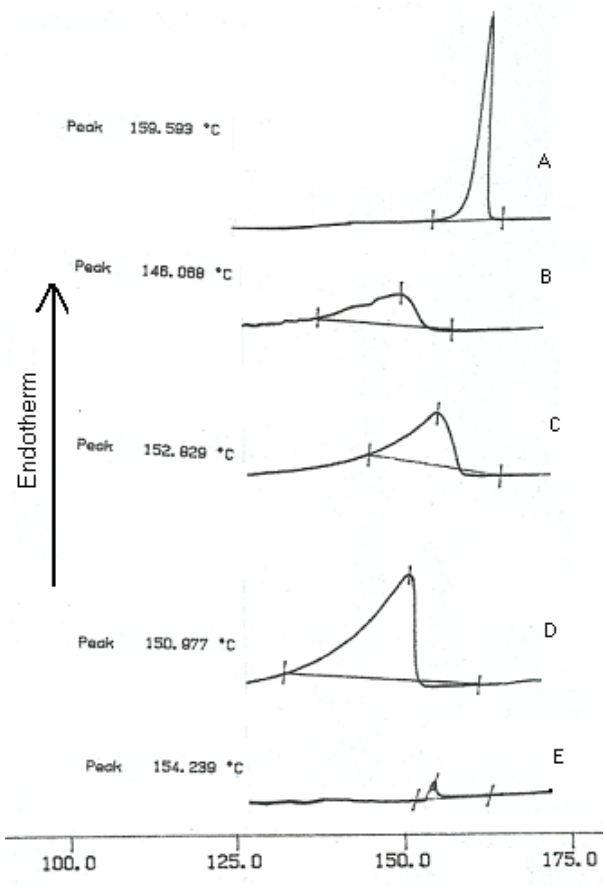

Fig. 2. DSC thermograms of IND (A), IND and castor oil mixture (B), IND and Cr-40 mixture (C), IND and Ca-8 mixture (D) and IND SNEDDF (E).

Conclusion

The results obtained from this study revealed that by using the proper ratio and kind of oil, surfactant and co-surfactant, IND can be easily formulated into a SNEDDF with desired particle size range, turbidity and the amount of drug released. Formulation 8 which contains castor oil, Cr-40 and Ca-8 in a ratio of 1:1:8 characterized by having the lowest turbidity and droplets size values (1.2 NTU and 30 nm, respectively) and the highest amount of drug release after 30 minutes (93%).

Author's Statement(s)

Competing Interests

The author declares no conflict of interest.

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