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DEVELOPMENT AND CHARACTERIZATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF A POORLY WATER SOLUBLE DRUG USING NATURAL OIL

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Abstract: Objective of present study involves preparation and evaluation of self emulsifying drug delivery system (SEDDS) of ibuprofen using peanut oil. SEDDS were composed of varying concentrations of peanut oil (solvent), Tween 80 (surfactant) and Span 20 (co-surfactant). Influence of concentration of surfactant/co-surfactant and globule size on dissolution rate was investigated. Dissolution rate was studied in phosphate buffer pH 6.8 using Dissolution Apparatus II. The dissolution rate of self emulsifying capsule was found to be significantly faster than that from conventional tablet. The optimized SEDDS released approximately above 85% of ibuprofen within 30 min, while conventional ibuprofen tablet could released only 36% in 30 min. Therefore, these SEDDS could be a better alternative to conventional drug delivery system of ibuprofen.

Keywords: self emulsifying drug delivery system (SEDDS), peanut oil, ibuprofen

The most versatile, convenient and commonly employed route of drug delivery for systemic action is oral route (1). Due to the convenience and improved patient safety, oral administration is a preferred method of drug administration (2). It has been estimated that about 40 to 70% of chemical entities entering drug development programs possess insufficient aqueous solubility to allow consistent gastrointestinal absorption of a magnitude sufficient to ensure therapeutic efficacy (3). In recent years, steps are taken to develop systems for delivery of drugs having low aqueous solubility to improve bioavailability of such lipophilic drugs. Many new drug candidates exhibit low oral bioavailability due to their poor aqueous solubility. To overcome this problem, various formulation strategies are reported, including salt formation, complexation with cyclodextrins, micronization, solid dispersions and lipid-based formulations (4). Lipid-based formulations approaches, particularly the self emulsifying drug delivery system (SEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability (5). SEDDS are described as mixtures of oil, surfactant, co-surfactant and drug. They form fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. Such mixtures are expected to self-emulsify quickly in the aqueous media of stomach, the digestive motility providing the agitation required for emulsification. Several mixtures of oils (long and medium-chain triglycerides), non-ionic surfactants with relatively high hydrophilic–lipophilic balance (HLB) and suitable solubilizing agents have been used to produce self-emulsifying systems (4). Self-emulsifying drug delivery systems are an alternative to traditional formulations of lipophilic drugs (6). A long-chain fatty acid in the SEDDS may also increase the oral bioavailability of highly lipophilic drugs by forming chylomicrons (80–1000 nm) within the enterocytes during the digestion and absorption of lipids, resulting in the stimulation of transport into Payer's patches for systemic circulation directly without experiencing hepatic metabolism (7).

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) which is used in the treatment of pain conditions and rheumatic disorders. It is a lipophilic

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drug and have a low dissolution rate. SEDDS of ibuprofen has been developed to improve dissolution rate (8).

Peanut oil is selected for this study since it is an edible natural oil and consist of long chain fatty acid which enhances the absorption of lipophilic drug, ibuprofen (9). Tween 80 and Span 20 form a good combination of surfactants with high HLB value and favors the formation of stable o/w emulsion (10).

EXPERIMENTAL

Materials and Methods

Ibuprofen was obtained as a gift sample from Vats Pharmaceuticals, Meerut (India), Tween 80 (Batch No-QX03525) was procured from Qualikem Fine Chemicals Pvt. Ltd, New Delhi, India. Span 20 and peanut oil (Batch No-10029) were procured from CDH Laboratory, Mumbai, India. n-Octanol (Batch No-R230G07) was purchased from RFCL Ltd., New Delhi, India

Preparation of self emulsifying drug delivery systems

The formulations were prepared by dissolving the formulation amount of ibuprofen in a mixture of surfactant, co-surfactant and oil at 25°C. The final mixture was vortexed until a clear solution was obtained. The formulations were examined for signs of instability and 550 mg of stable formulation (equivalent to 100 mg) were filled in hard gelatin capsules (size 0) and studied to examine the dissolution profile (11). Ten batches were prepared which varied in concentration of oil, surfactant and co-surfactant but concentration of drug was kept constant for each batch. Composition of batches has been summarized in Table 1.

Solubility studies

Solubility studies were conducted by placing an excess amount of ibuprofen in 10 mL each of water, phosphate buffer 6.8, oil, surfactant and co-surfactant. The mixture was heated at 60°C on water bath to facilitate solubilization and vortexed for 48 h using vortex mixer. After this period, the solutions were filtered. The oil solutions were filtered using vacuum filter. Aliquots of filtered solutions were diluted by methanol (11) and analyzed by double beam UV spectrophotometer at 264 nm.

Evaluation of SEDDS of ibuprofen

The amount of ibuprofen was kept constant, i.e., 100 mg, and was dissolved in varying concentration of oil, surfactant and co-surfactant and stirred to ensure uniformity. The formulated SEDDS were kept for 48 h and visual observation, emulsification time and phase separation studies were conducted after 48 h. *In vitro* dissolution test and droplet size study was carried out for stable emulsions by using Zetasizer.

Visual observation

The efficiency of emulsification was assessed using a standard USP dissolution apparatus II. Five milliliters of each formulation was added dropwise to 100 mL of phosphate buffer pH 6.8 at 37 ± 2°C.

Table 1. Compostion of batches.

Batch code	Ibuprofen (mg)	Oil (mg)	Surfactant (mg)	Cosurfactant (mg)	Total amount of SEDDS (mg)	
					Amount per capsule	× 30
P_1	100	450	50	0	550	16500
P_2	100	445	3	2	550	16500
P_3	100	427	18	5	550	16500
P_4	100	430	15	5	550	16500
P_5	100	415	25	5	550	16500
P_6	100	435	10	5	550	16500
P_7	100	410	30	10	550	16500
P_8	100	380	40	30	550	16500
P_9	100	425	20	5	550	16500
P_{10}	100	390	35	25	550	16500

Gentle agitation was provided by stainless steel dissolution paddle rotating at 50 rpm. 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 (12).

Absolute drug content

The content uniformity test is used to ensure that every capsule contains the amount of drug substance intended with little variation among capsules within a batch. For calculating the percentage of drug content, self emulsifying capsule was added in a conical flask containing 100 mL of methanol, kept overnight and shaked gently using mechanical shaking device. The resulting solution was filtered using Whatman filter paper, diluted suitably and absorbance of resultant solution was measured using PC based double beam UV spectrophotometer at 264 nm using methanol as a blank.

Emulsion droplet size analysis

The emulsion that came out to be good and stable during visual observation study was sent for size analysis by Zetasizer.

Disintegration time

Self emulsifying stable formulation containing ibuprofen equivalent to 100 mg was filled into hard gelatin capsules and put into USP dissolution vessel containing 900 mL of phosphate buffer pH 6.8 and paddle of apparatus was rotated at 100 rpm. Time taken for capsule shell to burst and release its content to dissolution media i.e., disintegration time was noted.

***In vitro* dissolution profile**

Dissolution profiles of the capsules filled with the self nano-emulsified formulations were determined by using USP dissolution apparatus II at 37 ± 2°C and a rotation speed of 100 rpm in 900 mL of phosphate buffer pH 6.8. During the study, 5 mL aliquots were removed at predetermined time intervals from the dissolution medium and 5 mL of fresh phosphate buffer was replaced. The amount of ibuprofen released in the dissolution medium was determined by UV spectrophotometer at λ_{max} 264 nm. The dissolution experiment was carried out in triplicate.

RESULTS AND DISCUSSION

Solubility studies

Solubility of ibuprofen was studied in water, methanol, phosphate buffer pH 6.8 and oil. The drug was found to be poorly water soluble and solubility in organic solvents, phosphate buffer pH 6.8 and oil was found good. The miscibility of selected oil in surfactant and co-surfactant, i.e., Tween 80 and Span 20, respectively, at 2:1 volume ratio, was checked by clarity of oil/surfactant mixture. Tween 80 has HLB value 15 and co surfactant Span 20 has HLB value of 8.6 and their combination gives a system with high HLB, i.e., more than 10, that favors the formation of o/w emulsion easily. Peanut oil was selected as a solvent in which drug is dissolved to form oil phase because it is having long chain fatty acids i.e., oleic acid, linoleic acid, stearic acid, palmitic acid, behenic acid and arachidic acid present as glycerides. These all fatty acids contain carbon chain with more than 12 carbon atoms, because of which the formed emulsion containing ibuprofen can direct the drug towards lymphatic system and can bypass hepatic metabolism of ibuprofen. Mixing of oil, drug, surfactant and co-surfactant yielded oil phase, which upon dilution with phosphate buffer pH 6.8 gave o/w emulsion.

Particle size analysis

The stable formulations (P_3, P_4, P_5, P_6,and P_9) were subjected to size analysis by Zetasizer. It was concluded by size analysis study that initially, as the amount of surfactant increases, globule size decreases due to an increase in adsorption of surfactants around the oil water interphase of a droplets and a decrease in interfacial tension. After reaching a particular amount of surfactant, further increase in surfactant amount results in increased globule size. It could have occurred because excess adsorption of surfactant on the interphase resulted in retardation of efficiency of emulsification and more energy was required to produce an emulsion.

In the present study, batch P_6 had the least amount of surfactant and particle size for this batch was 618.4 nm. Initially, as the amount of surfactant was increased in batches P_4 and P_3, the particle size started decreasing to 600.5 nm and 537.1 nm, respectively. However, on further increasing the

Table 2. Results for particle size study.

No.	Batch	Particle size (nm)
1	P_3	537.1
2	P_4	600.5
3	P_5	699.6
4	P_6	618.4
5	P_9	632.7

Table 3. Some study parameters

Batch code	Visual observation %	Drug content %	Disintegration time (min)
P_1	unstable	98.12 ± 0.25	3.6
P_2	unstable	98.95 ± 0.09	3.8
P_3	stable	99.26 ± 0.01	3.6
P_4	stable	98.54 ± 0.26	3.5
P_5	stable	98.95 ± 0.09	3.7
P_6	stable	99.79 ± 0.15	3.4
P_7	unstable	98.54 ± 0.26	3.8
P_8	unstable	98.10 ± 0.02	3.3
P_9	stable	99.16 ± 0.04	3.7
P_{10}	unstable	99.79 ± 0.15	3.6

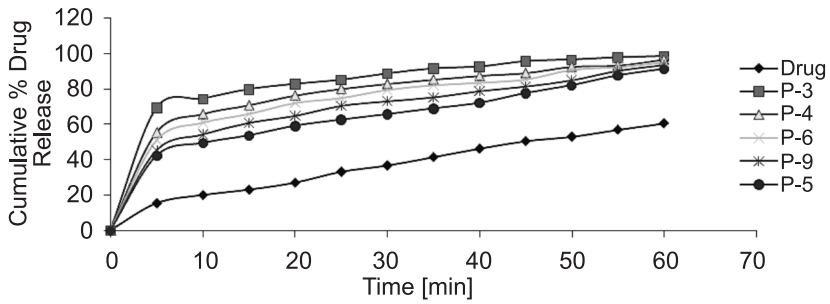

Figure 1. Comparisons of % cumulative release profile of batches of SEDDS with conventional tablet of ibuprofen in phosphate buffer pH 6.8

amount of surfactant or co-surfactant, the particle size also started to increase as in batches P_9 and P_5 to 632.7 nm and 699.6 nm, respectively (Table 2).

Visual observation

Out of ten batches of SEDDS of ibuprofen 5 came out to be stable. From this study it was concluded that on increasing the amount of surfactant beyond 30 mg, the formulation became unstable due to precipitation of excess of surfactant and settling at the base of emulsion. The formulation in which co-surfactant was not added was found to be unstable (Table 3).

Absolute drug content

The drug contents of each of the SEDDS batches are shown in Table 3. They were within compendia limits (95–105%) for ibuprofen.

Disintegration time

All the capsules disintegrated completely within 3 to 4 minutes as shown in Table 3.

***In vitro* dissolution profile**

The test was performed in triplicate. The comparison of release profiles of drug was done with that of stable batches of each group. It was found that the release profile of drug using self emulsifying capsules was much better as compared to pure ibuprofen. As the particle size decreases, the release of drug from self emulsifying capsules increases. The dissolution profile was studied for a period of 60 min. Over the period of 60 min, the cumulative % release from pure drug was about 61% only, while all stable formulations of self emulsifying capsules released above 90% of drug in that time. Over a period of 30 min, the cumulative % release from pure drug was only 36%, while self emulsifying capsules released approximately above 80% of drug within 30 min.

In the present study, P_3 was having minimum size and so maximum cumulative % release i.e., 98.434 ± 0.81%. The particle size of P_4 was lower as compared to P_6 and so the release profile of P_4, i.e., 96.557 ± 1.72%, was higher than that of P_6, i.e.,

94.869 ± 0.54%. The particle size of P_9 was greater as compared to P_6 and so the release profile of P_9 was 93.649 ± 1.40 and was lower than that of P_6. P_5 was having maximum particle size and minimum release among formulations of groups P, i.e., 91.128 ± 1.12%.

The release of ibuprofen from conventional tablet of ibuprofen was 60.645 ± 2.56%. It was found that as the droplet size decreased, the surface area increased. This increased surface area resulted in increased dissolution rate and hence enhanced drug release (Fig. 1).

CONCLUSION

It was concluded that the ibuprofen release rate depends upon droplet size of emulsion and release rate of ibuprofen from SEDDS was found to be higher than that from conventional ibuprofen tablet. By use of SEDDS, the release and bioavailability of poorly water soluble drugs can be increased.

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