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Research Article

FORMULATION AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF IBUPROFEN USING CASTOR OIL

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) have been developed as a method to deliver lipophilic drugs.In this investigation self emulsifying drug delivery system of poorly water soluble drug, ibuprofen was prepared using edible, natural castor oil and nonionic harmless surfactants. Tween 80 acted as surfactant and span 20 served as 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 U.S.P 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 80 % of ibuprofen within 30 minutes while conventional ibuprofen tablet could release only 36% in 30 minutes.

Keywords: Self emulsifying drug delivery system (SEDDS), Castor oil, Ibuprofen

INTRODUCTION

The oral drug delivery is one of the preferred routes for chronic drug administration. Approximately 40% of new drug candidates have poor water solubility. The oral delivery of such lipophiilic drugs is frequently associated with low oral bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy[1]. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrins, solid dispersation (suspension), -precipitation, micronisation, salt formation, emulsion, use of micelles [2].

SEDDS are described as isotropic mixtures of oil, surfactant, co-surfactant and lipophilic drug. They form fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation1. These are able to self-emulsify rapidly in the gastro-intestinal fluids, forming O/W under the gentle agitation given by gastro-intestinal motion. In such a system, the lipophilic drug is present in solution, in small droplets of oil that leads to increase surface area and hence increased absorption[3].

The lipophilic drugs that undergo extensive hepatic metabolism have very low bioavailability because most of the amount of drug gets metabolised by the hepatic enzymes. Now a days various steps are taken to improve bioavailability of such lipophilic drugs. The self emulsifying drug delivery system (SEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drug, which are associated with poor water solubility and low oral bioavailability[4]. Main ingredients of SEDDS are lipophilic drug, oils containing long chain triglycerides, surfactants and cosurfactants. Chylomicrons and lipoproteins (associated drug) produced within the enterocytes as an end product of lipid digestion and absorption are having an average diameter (200-800nm). Following secretion by the enterocytes these colloidal particles are too large for blood capillaries and are consequently selectively taken up into the lymphatic capillaries [5]. Hence first pass metabolism of drug is prevented.

Ibuprofen is a nonsteroidal anti-inflammatory lipophilic drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. Ibuprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhoea, and to alleviate moderate pain[6]. The drug undergoes substantial first pass effect and only small amount of drug is available systemically. SEDDS of ibuprofen offers the potential advantage of by passing hepato gastrointestinal first pass metabolism associated with ibuprofen.

MATERIALS AND METHODS

Materials

Ibuprofen was obtained as a gift sample from Vats Pharmaceuticals, Meerut. Tween 80 (Batch No-QX03525) was procured from Qualikem Fine Chemicals Pvt. Ltd, New Delhi, India. Span 20 was procured from CDH Laboratory, Mumbai. Castor oil (Batch No-10029) was procured from CDH Laboratory, Mumbai. n-octanol (Batch No-R230G07) was procured from RFCL Limited New Delhi. Methanol (Batch No- 36946411V) was procured from GlaxoSmithKline pharmaceuticals Limited, Mumbai.

Method of preparation of SEDDS

The formulation amount of Ibuprofen (100mg) was dissolved in the mixture of surfactant, co-surfactant and oil at 25°C..The final mixture was vortexed until a clear solution (liquid SEDDS) was obtained and the resulting oil phase was later used for evaluation study. Oil phase was filled manually in capsules (size 0). 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 [7]. 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. Mixture was heated at 60° C on water bath to facilitate solubilization and vortexed for 48 hours 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 [7] and analyzed by Double Beam U.V 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 hours and visual observation, emulsification time and phase separation studies were conducted after 48 hours. *In-vitro* dissolution test and droplet size study was carried out for stable emulsions by using Zeta sizer.

Visual observation

The efficiency of emulsification was assessed using a standard USP dissolution apparatus II. 5ml of each formulation was added drop

wise to 100 ml phosphate buffer pH 6.8 at 37±2°C. 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 [8].

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.

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 % drug content, self emulsifying capsule was added in a conical flask containing 100 ml methanol, kept overnight and shaked gently using mechanical shaking device [9]. The resulting solution was filtered using whatmann filter paper, diluted suitably and absorbance of resultant solution was measured using PC based Double Beam UV Spectrophotometer at 264 nm using methanol as blank.

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 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 [10].

In-vitro drug dissolution studies

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 phosphate buffer pH 6.8. During the study, 5ml aliquots were removed at predetermined time intervals from the dissolution medium and 5 ml of fresh phosphate buffer was replaced[5]. The amount of ibuprofen released in the dissolution medium was determined by U.V Spectrophotometer at λ_{max} 264nm.The dissolution experiment was carried out in triplicate [11].

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, 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. Castor oil was selected as 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, arachidic acid present as glycerides. These all fatty acids contain carbon chain >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 (C_2, C_4, C_8) were subjected to size analysis by Zeta sizer as in Table 3. It was concluded by size analysis study that initially as the amount of surfactant increases globule size decreases due to increase in adsorption of surfactants around the oil water interphase of a droplets and 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 emulsion.

In the present study, for Batch C_4 containing 15 mg surfactant and 5 mg co surfactant, particle size was 1208.3 nm. In C_8, when amount of surfactant was increased by 5mg, particle size decreased and came out to be 807.6 nm. But after 25 mg if amount of surfactant or cosurfactant was further enhanced then particle size started to increase as in C_2 where particle size was found to be 1643.3 nm.

Table 1: Shows composition of different batches of self emulsifying delivery system of ibuprofen

Excipients used in various batches					Total drug in SEDDS	
Batchcode	**Ibuprofen(mg)**	**Oil(mg)**	**Surfactant(mg)**	**Cosurfactant(mg)**	**Amount per capsule**	**×30**
C_1	100	450	50	0	550	16500
C_2	100	470	25	5	550	16500
C_3	100	455	40	5	550	16500
C_4	100	480	15	5	550	16500
C_5	100	490	5	5	550	16500
C_6	100	485	10	5	550	16500
C_7	100	460	30	10	550	16500
C_8	100	475	20	5	550	16500
C_9	100	400	50	50	550	16500
C_{10}	100	440	34	26	550	16500

Isual observation

Out of ten batches of SEDDS of ibuprofen 3 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 as shown in Table 2.

Absolute drug content

Drug content the drug content of each of the SEDDS batches are shown in the Table 4. They were within compendia limits (95-105%) for ibuprofen.

Disintegration time

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

In-Vitro dissolution profile

The test was performed in triplicate. The comparison of release profile of conventional ibuprofen tablet was done with that of stable batches. It was found that release profile of drug by using self emulsifying capsules was much better as compared to conventonal ibuprofen tablet. As the particle size decreases, release of drug from self emulsifying capsules increases. The dissolution profile was studied for a period of 60 minutes. Over the period of 60 minutes, the cumulative % release from conventional ibuprofen tablet was about 61 % only while all stable formulations of self emulsifying capsules released above 90% of drug in 60 minutes. Over a period of thirty minutes, the cumulative % release from conventional tablet was only 36% while self emulsifying capsules released approximately above 80% of drug within 30 minutes. C_8 was having minimum size i.e. 807.6 nm among stable formulations and its release (98.075±0.56) was more as compared to C_4 (96.514±1.73)

and C_2 (93.765±1.73) which were having less size as compare to C_8 as shown in Table 5. The release of ibuprofen from conventional tablet of ibuprofen was 60.645±2.56%. It was found that as the droplet size decreased, surface area increased. This increased surface area resulted in increased dissolution rate and hence enhanced drug release (Fig.1).

Table 2: Shows emulsification efficiency and emulsion stability of different batches

S. No	Batch	Visual grading	Emulsification time	Stability after 24 hours
1	C_1	Grade D	>2 min	Unstable
2	C_2	Grade B	<1 min	Stable
3	C_3	Grade C	1 to 2 min	Unstable
4	C_4	Grade A	<1 min	Stable
5	C_5	Grade D	>2 min	Unstable
6	C_6	Grade D	>2 min	Unstable
7	C_7	Grade B	<1min	Unstable
8	C_8	Grade A	<1 min	Stable
9	C_9	Grade C	1 to 2 min	Unstable
10	C_{10}	Grade C	1 to 2 min	Unstable

Table 3: Shows droplet size determination of stable emulsion

S. No	Batches	Particle size(nm)
1	C_2	1643.3
2	C_4	1208.3
3	C_8	807.6

Table 4: Shows weight uniformity, content uniformity, disintegration time study of different batches

S.No	Batch	Weight uniformity (mean weight±S.D.)	Content uniformity (mg±S.D.)	Disintegration time(mins)
1	C_1	674.3±0.004	99.79±0.15	3.2
2	C_2	676.3±0.003	98.83±0.11	3.5
3	C_3	677.0±0.005	98.95±0.09	3.9
4	C_4	676.2±0.004	98.10±0.02	3.7
5	C_5	677.3±0.005	99.26±0.01	3.4
6	C_6	676.3±0.003	99.79±0.15	3.3
7	C_7	676.4±0.003	98.12±0.25	3.9
8	C_8	676.6±0.003	98.54±0.26	3.8
9	C_9	677.2±0.002	98.75±0.04	3.4
10	C_{10}	675.3±0.004	99.16±0.04	2.9

Table 5: Shows comparisons of % cumulative release profile of batches (c_2, c_4, c_8) with conventional ibuprofen tablet

S. No	Time (mins)	Cumulative % released ± SD			
		C_2	C_4	C_8	Conventional Tablet
1	5	49.466±1.93	55.331±3.03	63.579±1.38	15.374±1.14
2	10	54.322±3.31	65.719±1.94	68.880±1.67	20.042±1.65
3	15	58.472±2.42	69.931±0.86	72.194±1.38	23.085±0.84
4	20	64.475±1.65	72.882±0.82	81.938±0.84	27.062±0.83
5	25	71.243±1.65	76.947±1.12	83.670±0.55	33.259±1.15
6	30	77.131±1.97	82.681±1.14	86.692±0.84	36.740±1.16
7	35	81.033±0.87	84.780±0.86	88.079±1.15	41.522±2.50
8	40	84.037±1.11	86.704±.87	91.304±1.39	46.331±2.43
9	45	85.773±1.67	88.820±2.61	93.444±1.16	50.614±1.41
10	50	85.500±3.62	92.411±0.51	95.410±0.53	53.087±1.10
11	55	89.806±2.44	93.087±1.80	95.735±1.12	57.039±1.11
12	60	93.765±1.73	96.514±1.73	98.075±0.56	60.645±2.56

Results are shown in Mean ± SD. n=3, C=Castor Oil

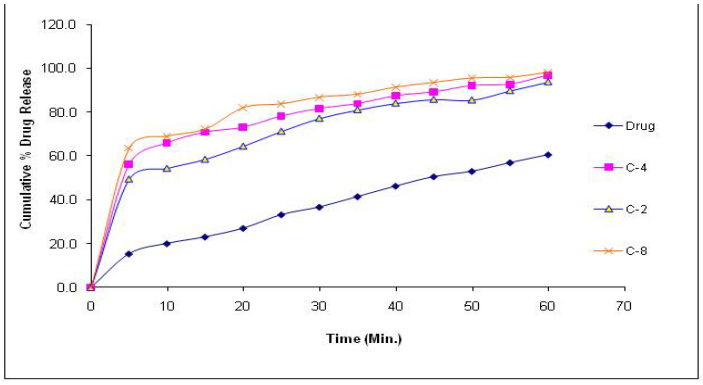

Fig. 1: It shows the comparision of *in vitro* release profile of conventional ibuprofen tablet with the self emulsifying ibuprofen capsule

CONCLUSION

The aim of the present study was to develop and characterize self emulsifying drug delivery system of Ibuprofen using edible and natural castor oil and nonionic surfactant Tween 80 and Span 20 in varying concentrations. Span 20 was used as co surfactant in the self emulsifying capsules. Effect of surfactant concentration on particle size of emulsion and release profile of drug was studied. The self emulsifying capsules were prepared by manual filling of oil phase in capsules. Oil phase was prepared by mixing a proper amount of oil, surfactant, and co surfactant. The oil phase was diluted to form emulsion Use of Self Emulsifying System can by pass hepatic metabolism and hence low and variable oral bioavailability can be improved. *In- vitro* dissolution test showed that the release rate of the self emulsifying capsules of ibuprofen was higher than conventional tablet. As the globule size decreased, the release rate increased.

We can say that self emulsifying capsules may provide a useful oral dosage form for poorly water soluble drugs with low and variable oral bioavailability. This system can be a useful for drugs that are poorly water soluble and highly metabolized by liver. 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 more 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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