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Preliminary Studies on Two Vegetable Oil Based Self Emulsifying Drug Delivery System (SEDDS) for the Delivery of Metronidazole, A Poorly Water Soluble Drug

N.C. Obitte, H. Ezeiruaku and V.I. Onyishi
Department of Pharmaceutical Technology and Industrial Pharmacy,
Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria

Abstract: A preliminary evaluation was carried out on metronidazole-loaded Self Emulsifying Drug Delivery System (SEDDS) using two vegetable oils-Palm Kernel Oil (PKO) and Palm Oil (PO). Purification of oils, drug solubility in the oils, pre/post formulation isotropicity tests, emulsification times and release studies of metronidazole from the SEDDS were carried out. Results indicated solubility values of 4.441 and 4.654%w/w, respectively for metronidazole in PKO and PO. Preformulation isotropicity test revealed that out of the 24 batches evaluated 10 of the SEDDS formulations containing different oil: surfactant ratios and PKO:PO admixtures were found to be isotropic after 5 h. However when the SEDDS were loaded with metronidazole there was a reduction in the number (to 7) of formulations that maintained isotropicity and stability after 72 h. All the batches had emulsification times of less than two minutes except batch 4D with oil:surfactant concentration of 50:50. The release profile showed that most of the formulations released 50% of drug in less than 8 min and 85% of drug in less than 30 min. We therefore conclude that SEDDS containing the two vegetable oils are potential alternatives when immediate release and delivery of metronidazole is the primary motivation.

Key words: Self-emulsifying drug delivery system, emulsification time, metronidazole, vegetable oil, isotropic

INTRODUCTION

The low aqueous solubility and the resultant bioavailability of poorly water soluble drugs have made their oral delivery a major challenge to drug formulators. This is because when they are administered orally the dissolution rate in the gastrointestinal tract becomes the rate limiting step in the absorption (and hence bioavailability) from the gastrointestine (Hiroshi *et al*., 2005). In addition since their dissolution rate is affected by diet and the flow of bile secretion these drugs are usually subject to widely variable oral bioavailability (Cakaloglu *et al*., 1993). Incidentally several research efforts have been geared towards the improvement of the absorption and bioavailability of these poorly water soluble drugs/insoluble drugs. These include chemical modification, lipid and surfactant dispersions, liposomes, niosomes and self emulsifying oil formulations (SEOF)/ Self Emulsifying Drug Delivery System (SEDDS) (Craig *et al*., 1993). Of all these the most promising technology to improve the rate and extent of these poorly water soluble drugs, which has hitherto drawn significant scientific curiosity and effort is Self Emulsifying Oil Formulations (SEOF). SEOF or SEDDS is a mixture of oil(s), surfactant(s) and if necessary a solubiliser. Self emulsification is initiated under gentle agitation following contact with aqueous phase and forms a thermodynamically stable O/W microemulsion with particle diameter of 100 nm or less (Odeberg *et al*., 2003; Devani *et al*., 2004). They are reputed to improve the oral bioavailability of poorly water soluble drugs (Shah *et al*., 1994) which is accomplished by rapid selfemulsification thus yielding fine O/W emulsions within which the lipophylic or hydro-lipophylic drug is present in solution or solubilised form, in small oil droplets (Constantinides, 1995). Moreover these small oil droplets occupy large interfacial area, thus facilitating drug diffusion into intestinal fluids (Erica *et al*., 2005).

Metronidazole, a poorly water soluble drug was used in our study as the model drug to improve its aqueous solubility, possibly optimise its amount per dose thus creating the opportunity for increase in its bioavailability, by incorporating it into vegetable oil-based SEDDS. These edible oils were chosen because of their inexpensiveness, availability and biocompatibility. Palm Kernel Oil (PKO) and Palm Oil (PO) extracted from the hard seeds and fruits of Elaeas garbonensis are glycerides belonging to the homolipid family of lipids. Oral lipid drug delivery systems are usually designed to increase solubility and bioavailability of drugs that belong to class

Corresponding Author: N.C. Obitte, Department of Pharmaceutical Technology and Industrial Pharmacy,
Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria

ii and iv of the biopharmaceutical drug classification system (O'Driscoll, 2002). Medium chain triacyl glycerols, though useful drug carriers, seem to have no significant pharmacological activity. They are subject to intraluminal hydrolysis and are mainly absorbed as free fatty acids (Bach and Babayan, 1982). Intraluminal digestion uptake by the mucosal cells and transport of medium chain and long chain triacyl glycerols to the systemic circulation are very distinct (Milan and Stanislav, 2001; Yhi-Fu, 1987). Hence triacyl glycerols possess potential usefulness in lipid drug delivery.

The objective of this study was to formulate metronidazole, a poorly water soluble drug into SEDDS using palm kernel oil and palm oil with the hope that its aqueous solubility will be improved.

MATERIALS AND METHODS

This research was carried out in the Drug delivery unit, Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka in 2006.

Metronidazole (Evans Nigeria), Tween 65 (Fision Scientific, England), palm kernel oil, palm oil (locally sourced and further purified in our Laboratory), HCl (BDH). This research work was carried out in our Drug Delivery laboratory, Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka.

Purification of Palm Kernel Oil (PKO) and Palm Oil (PO): A 2%w/w suspension of activated charcoal in oil was heated in a beaker at 80-90°C for an hour. Thereafter the suspension was vacuum-filtered using Burkner's funnel. The purified oil was stored for further use.

Drug solubility in oil: This experiment was carried out to determine the maximum amount of metronidazole that could be dissolved in the oil without precipitation. Exactly 1.75 g of metronidazole was weighed out into a 25 mL beaker. Aliquots of the oil were introduced and each time stirred at 37±1°C. The minimal amount of oil needed to completely solubilise the whole drug was noted.

Preformulation isotropicity test: Twenty four batches of SEDDS consisting of oil:surfactant ratios of 30:70, 40:60 50:50, 60:40, 65:35, 70:30 were prepared as shown in Table 1. The appropriate quantities of the two ingredients were weighed out and melted with stirring at 50°C. The mixture was then stored for 5 h at ambient temperature and later evaluated for isotropicity.

Formulation of SEDDS containing metronidazole: Formulation was limited to only the SEDDS that passed the isotropicity test. Palm oil, palm kernel oil and different ratios of their admixtures were respectively used. Appropriate quantity of metronidazole was weighed and introduced into a beaker containing weighed amount of oil and Tween 65 and stirred for 10 min on a water bath maintained at 50°C (Hiroshi *et al*., 2005). Table 2 shows the various quantities of the materials used in the formulation of drug-loaded SEDDS of target weight 525 mg.

Table 1: Formulation of SEDDS for isotropicity test

	% w/w oil admixture							
Batch	PKO	PO	Oil:surfactant ratio	Amount of PKO (mg)	Amount of PO (mg)	Total amount of oil (mg)	Amount of surfactant (mg)	Total amount SEDDS (mg)
1A	75	25	60:40	4275.0	1425.0	5700	3800	9500
1B	75	25	50:50	3562.5	1187.5	4750	4750	9500
1C	75	25	40:60	2850.0	950.0	3800	5700	9500
1D	75	25	30:70	2137.5	712.5	2850	6650	9500
2A	60	40	60:40	3420.0	2280.0	5700	3800	9500
2B	60	40	50:50	2850.0	1900.0	4750	4750	9500
2C	60	40	40:60	2280.0	1520.0	3800	5700	9500
2D	60	40	30:70	1710.0	1140.0	2850	6650	9500
3A	25	75	60:40	1425.0	4275.0	5700	3800	9500
3B	25	75	50:50	1187.5	3562.5	4750	4750	9500
3C	25	75	40:60	950.0	2850.0	3800	5700	9500
3D	25	75	30:70	712.5	2137.5	2850	6650	9500
4A	50	50	70:30	3325.0	3325.0	6650	2850	9500
4B	50	50	65:35	3087.5	3087.5	6175	3325	9500
4C	50	50	60:40	2850.0	2850.0	5700	3800	9500
4D	50	50	50:50	2375.0	2375.0	4750	4750	9500
5A	100	0	70:30	6650.0	0.0	6650	2850	9500
5B	100	0	65:35	6515.0	0.0	6175	3325	9500
5C	100	0	60:40	5700.0	0.0	5700	3800	9500
5D	100	0	50:50	4750.0	0.0	4750	4750	9500
6A	0	100	70:30	0.0	6650.0	6650	2850	9500
6B	0	100	65:35	0.0	6515.0	6175	3325	9500
6C	0	100	60:40	0.0	5700.0	5700	3800	9500
6D	0	100	50:50	0.0	4750.0	4750	4750	9500

Table 2: Formulation of drug-loaded SEDDS

Batch	% w/w oil admixture		Oil:surfactant ratio	Amount of PKO (mg)	Amount of PO (mg)	Total amount of oil (mg)	Surfactant (mg)	Amount of drug (mg)	Total amount SEDDS (mg)	
	PKO	PO							Per cap	X50 caps
1C	75	25	40:60	150.0	50.0	200	300	25	525	26250
1D	75	25	30:70	112.5	37.5	150	350	25	525	26250
2C	60	40	40:60	120.0	80.0	200	300	25	525	26250
3B	25	75	50:50	187.5	62.5	250	250	25	525	26250
4C	50	50	60:40	150.0	150.0	300	200	25	525	26250
4D	50	50	50:50	125.0	125.0	250	250	25	525	26250
5C	100	0	60:40	300.0	0.0	300	200	25	525	26250
5D	100	0	50: 50	250.0	0.0	250	250	25	525	26250
6C	0	100	60:40	0.0	300.0	300	200	25	525	26250
6D	0	100	50:50	0.0	250.0	250	250	25	525	26250

PO = Palm Kernel Oil, PKO = Palm Kernel Oil

Postformulation isotropicity test: The above prepared SEDDS were stored for 72 h at ambient temperature and observed for phase separation, drug precipitation and isotropicity. The SEDDS that passed this test were used for further tests.

Emulsification time: Five hundred and twenty five milligram of SEDDS was syringed into a 250 mL beaker containing 0.1 N HCl. The beaker was then mounted on a hot plate-magnetic stirrer assembly. The stirrer speed was maintained at approximately 50 rpm. The time for complete emulsification was visually noted.

Encapsulation of SEDDS: Five hundred and twenty five milligram of SEDDS was weighed out and introduced into a 500 mg capsule and stored for further use.

Drug release studies: A magnetic stirrer-beaker-hotplate assembly was used. Each encapsulated SEDDS was introduced into the beaker containing 500 mL of 0.1 N HCl and dissolution run at a rotation speed of 100 rpm at 37±1.0°C. At predetermined time intervals 5 mL samples were withdrawn and assayed spectrophotometrically for metronidazole content at 277 nm.

Absolute drug content: Five hundred and twenty five milligram of SEDDS was withdrawn and emulsified in 1 L of 0.1 N HCl and thereafter assayed spectrophotometrically for metronidazole content.

RESULTS AND DISCUSSION

Drug solubility in oil: Exactly 39.4 and 37.6 g of palm kernel oil and palm oil respectively were observed to effect complete dissolution of 1.75 g of metronidazole powder without precipitation. Thus the solubility of metronidazole in both oils were 4.441 and 4.654% w/w, respectively. The development of microemulsion systems for poorly water soluble drugs is critical and drug loading per formulation is a very critical design factor that depends on drug solubility in various formulation components (Natesan *et al*., 2004). The solvent capacity of the oil is a crucial factor, although the ability of an oil to accommodate large amount of hydrophobic drug in solution can be improved in the presence of cosurfactants and/or cosolvents. The solvent capacity of the drug for the two oils is closely similar. However, further modification of the oils may likely improve drug solubility in them. Such hydrolysed or modified vegetable oils are known to form good emulsification systems with several surfactants approved for oral administration and exhibit better drug solubility properties (Kimura *et al*., 1994; Hauss *et al*., 1998).

Preformulation isotropicity test: It was observed that formulations containing oil:surfactant ratios of 60:40, 50:50 and some of 30:70 and 40:60 were isotropically stable (Table 3), whereas those of 70:30, 65:35 and some of 30:70 and 40:60 experienced varying degrees of phase separation. This test is often used to determine the oil:surfactant ratio that will confer thermodynamic stability to the formulation. Because of the unique physicochemical properties of oils and surfactants this preformulation evaluation is critical and expedient to avoid posformulation drug partitioning consequent upon phase separation. Different oils may likely have varying oil: surfactant ratios that would impart stability to the SEDDS. The oil: surfactant ratio of 60:40 is preferable to 50:50 and the others with higher surfactant concentrations. Such higher surfactant (Tween 65) concentration may predispose to longer emulsification times. In addition low surfactant concentration is preferable because of the possibility of potential toxic effects with high concentrations. Tween 65 our model surfactant is non-ionic and therefore less affected by ionic strength and PH changes (Kawakami and Oshikawa, 2001). It has been reported that the concentration of surfactants that will form stable SEDDS formulation range between 30-60% w/w (17). As shown in Table 3, formulations that maintained isotropicity had surfactant

Table 3: Preformulation isotropicity test result (comprising of those that passed the test)

Batch	% w/w oil admixture PKO	PO	Oil:surfactant ratio	PKO (mg)	PO (mg)	Total amount of oil	Surfactant (mg)	Total amount SEDDS
1C	75	25	40:60	2850.0	950.0	3800	5700	9500
1D	75	25	30:70	2137.5	712.5	2850	6650	9500
2C	60	40	40:60	2280.0	1520.0	3800	5700	9500
3B	25	75	50:50	1187.5	3562.5	4750	4750	9500
4C	50	50	60:40	2850.0	2850.0	5700	3800	9500
4D	50	50	50:50	2375.0	2375.0	4750	4750	9500
5C	100	0	60:40	5700.0	0.0	5700	3800	9500
5D	100	0	50:50	4750.0	0.0	4750	4750	9500
6C	0	100	60:40	0.0	5700.0	5700	3800	9500
6D	0	100	50:50	0.0	4750.0	4750	4750	9500

Table 4: Post-formulation isotropicity/stability test results

Batch	% w/w oil admixture PKO	PO	Oil:surfactant ratio	PKO (mg)	PO (mg)	Total amount of oil (mg)	Surfactant (mg)	Amount of drug (mg)	Total amount SEDDS (mg) Per cap	X50 caps
1C	75	25	40:60	150.0	50.0	200	300	25	525	26250
2C	60	40	40:60	120.0	80.0	200	300	25	525	26250
3B	25	75	50:50	187.5	62.5	250	250	25	525	26250
4C	50	50	60:40	150.0	150.0	300	200	25	525	26250
4D	50	50	50:50	125.0	125.0	250	250	25	525	26250
6C	0	100	60:40	0.0	300.0	300	200	25	525	26250
6D	0	100	50:50	0.0	250.0	250	250	25	525	26250

ratios that fall within ref (Gursoy and Benita, 2004), in addition to batch 1C having an oil:surfactant ratio of 30:70. This ratio contains 70% w/w of surfactant which is quite high. All batches having this ratio were not isotropic with the exception of the aforementioned 1C. The reason is probably due to the high PKO:PO ratio of 75:25. PKO at temperatures below 25°C assumes a semisolid consistency unlike PO. This therefore in combination with Tween 65 which is also semisolid in nature will impart better stability into the SEDDS mixture than lower PKO: PO ratios. Batches 1C and 2C were the only two batches having oil: surfactant ratios of 40:60 that were stable; this is also probably because of their high PKO:PO ratios of 75:25 and 60:40, respectively.

Post formulation stability test: The drug-loaded SEDDS were further stored for 72 h. The rationale behind this test was to ascertain if the presence of metronidazole would introduce any instability. Results obtained (Table 4) shows that batches containing palm kernel oil showed phase separation. The batches that retained homogeneity i.e., those containing palm oil, palm kernel oil or their admixtures were then stored for further tests. The loss of stability by some of the above SEDDS in the presence of metronidazole could be due to a complex interaction outcome of oil and surfactant in the presence of the drug. The confirmation of SEDDS stability in the presence of drug is needed to ensure formulation thermodynamic stability. The efficiency of addition of drugs into a SEDDS is specific in each case depending on the physicochemical compatibility of the drug/system (Gursoy and Benita, 2004). More often the drug interferes with the self-emulsification process to a certain degree leading to a change in the optimal oil/surfactant ratio (Gursoy and Benita, 2004). Every oil:surfactant ratio often has a certain solvent capacity for drug, beyond which drug precipitation or phase separation may result. Furthermore stability testing of SEDDS is an evaluation strategy that assesses their vulnerability to environmental factors during storage. The SEDDS containing palm oil and palm oil/palmkernel oil admixtures maintained stability without phase separation. Some reporters (Subramanian *et al.*, 2004) have established the formulation advantage of employing mixtures of oils in microemulsions. Incidentally the oils used in this research that imparted stability to the SEDDS are cheap and readily available.

Table 5: Some drug release parameters

Batch	Emulsification time (min or sec)	Absolute drug content (mg)	$T_{50\%}$ (min)	$T_{85\%}$ (min)
1C	13 sec	22.4	0.6	21.0
2C	17 sec	19.6	23.0	-
3B	1 min	24.8	7.2	18.0
4C	7 sec	25.1	4.4	11.5
4D	5 min	25.1	7.2	13.5
6C	10 sec	26.7	7.5	12.5
6D	1 min	25.1	3.9	8.0

Emulsification Time (EMT): Table 5 shows the emulsification time results of metronidazole SEDDS prepared with PO and PKO-PO admixtures at the stated oil:surfactant ratios. The SEDDS containing oil:surfactant ratios of 50:50 recorded longer EMT than the rest. Also those with the ratio of 40:60 emulsified slightly at a longer

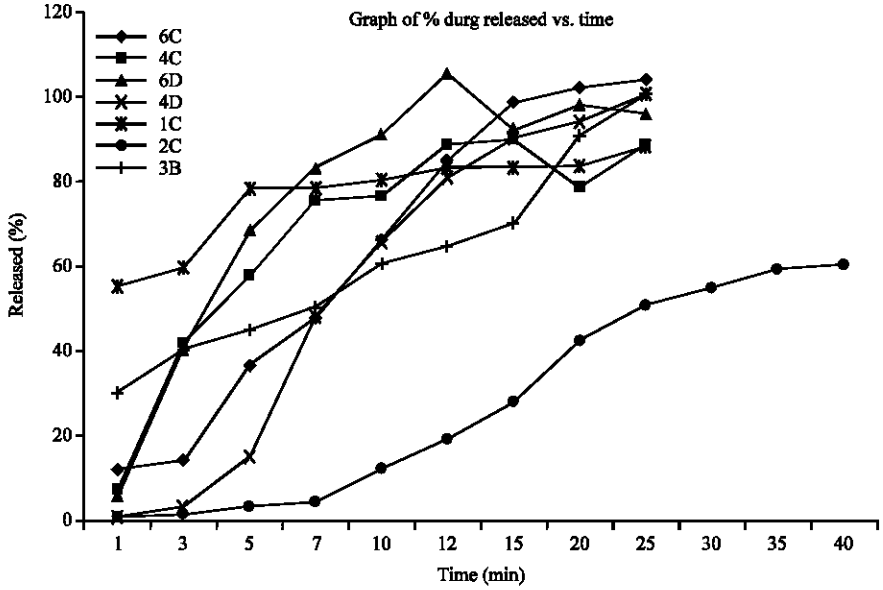

Fig. 1: Dissolution studies result: Graph of % metronidazole released vs. time in 0.1 N HCl

time than those of 60:40, thus still emphasizing that higher surfactant (tween 65) concentration would lead to higher emulsification time. At a PKO:PO admixture ratio of 75:25 fastest EMT of 7 sec was recorded followed by that of 0:100 ratio at the same oil:surfactant ratio of 60:40. It seemed as if admixing the oils at this oil:surfactant ratio promoted faster emulsification time than using PO alone. The EMT of batches 3B, 4D and 6D were not affected by oil admixtures as much as surfactant concentration. The high surfactant concentration of tween 65 whose semi solid nature at room temperature must have imbued a higher viscosity. SEDDS with higher viscosities are likely to experience lower emulsification rates. Carvedilol SEDDS (Lanlan *et al*., 2005) showed a decrease in EMT as the tween 80 content increased from 30-40% and then increased as the tween 80 content increased from 40-60%. Emulsification rate is known to be an important index for emulsification efficiency assessment (Pouton, 1985). Infact 2 min (Khoo *et al*., 1998) has been reported as an evaluation index in the emulsification process. With the exception of 4D the rest of the batches emulsified in less than 2 min. Apart from viscosity, admixing of oils, the free energy of the system has been implicated as one of the factors that affect the EMTs of SEOFS and SMEOFS (Lanlan *et al*., 2005).

Drug release studies: Figure 1 shows the release profile of metronidazole from the four batches, namely, 1C, 2C, 3B, 4C, 4D, 6C and 6D. The onset of drug release was fast in most of the formulations but faster in batches 1C, 4C and 6D, with t_{50} of 0.6, 4.4 and 3.9 min, respectively and t_{85} of 21, 11.5 and 8 min, respectively (Table 5). 4C with least emulsification time of 7 sec released 50% of drug in less than 5 min. Batch 2C with oil:surfactant ratio of 40:60 had the longest t_{50} of 23 min probably because of its high surfactant concentration. However this was not consistent in batch 1C with the same oil: surfactant ratio. According to US-FDA guidance for immediate release product 85% ($t_{85\%}$) of labelled amount of drug should be released within 30 min of study. Based on this almost all the batches conformed to this as their t_{85} were less than 30 min. Therefore it is perfect for them to be adjudged as having had optimum drug release thus justifying SEDDS as a formulation option for improving the release and anticipated bioavailability of metronidazole.

Absolute drug content: The drug contents of each of the SEDDS batches are as shown in the table below. They were within compendial limits (95-105%) for metronidazole, with the exception of 1C and 2C.

CONCLUSION

In conclusion it is safe to say that, from our studies palm oil and palm kernel oil and their admixtures are potential adjuvants in the formulation of metronidazole SEDDS for improved drug dissolution and bioavailability.

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