Preparation of Ibuprofen Emulsions with Rapeseed Phospholipids and Vegetable Oils

Michał Górecki*, Marian Sosada, Beata Pasker, Monika Pająk and Paweł Fraś

Department of Drug Technology, School of Pharmacy with the Division of Laboratory Medicine, Medical University of Silesia, Jedności 8, 41-219 Sosnowiec, POLAND.

ABSTRACT

One of the formulations of the water poorly soluble drugs is the emulsion. The inner oil phase of the oil-in-water (o/w) emulsion is the carrier for the water poorly soluble drugs. In this study the soybean, rapeseed, safflower and olive oil were considered as a potential ibuprofen carriers and were investigated for dissolving of the ibuprofen. The ibuprofen dissolution test showed the different ability of the tested oils to dissolve the ibuprofen and the olive oil was selected as the proper one. Thus the o/w emulsion based on the olive oil and containing the ibuprofen was prepared. In the role of the emulsifier the rapeseed lecithin ethanol soluble fraction (LESF) was used. Also the comparative emulsion was obtained without the ibuprofen. The comparative emulsion had the stability different from the emulsion system with the drug. As the result of the investigation we concluded that the emulsion with the olive oil and LESF could be a potential ibuprofen formulation in accordance to its high ibuprofen dissolution degree in the olive oil. This emulsion was stable during 28 days at 20°C where the dispersion degree changed from 7.33 to 5.15 cm^{-1}.

Key words: Ibuprofen, Emulsions, Emulsion stability, Rapeseed phospholipids, Vegetable oils.

INTRODUCTION

One of the widely used non-steroidal anti-inflammatory drug is the ibuprofen (2-[4-(2-methylpropyl) phenyl] propanoic acid), which is also has analgesic and anti-pyretic properties. Ibuprofen in the BCS System (Biopharmaceutics Classification System) which is a system to differentiate the drugs on the basis of their solubility and permeability, has belonged to class II with low solubility and high permeability. Those compound are well absorbed and their absorption rate is usually higher that excretion.[1,2] Ibuprofen in the acid form is poorly water-soluble with the solubility range of 0.08-0.14 mg/ml.[3,4] This property may significantly affect the pharmacokinetics of oral ibuprofen administration with respect to different formulations and different ibuprofen salts.[5,6] Furthermore a Cochrane review of ibuprofen in acute pain suggested that rapidly absorbed formulations of salts or features to speed absorption, provided better analgesia that standard ibuprofen as the free acid and so formulation chemistry is of potential importance for analgesics.[7] Formulations with cosolvents and tensides addition e.g. emulsions, micro-and nano-emulsions, solid dispersions and self-emulsifying systems, may increase the absorption of ibuprofen and ibuprofen salts in the stomach.[8-18] Biphasic systems, like emulsions are naturally unstable. The extent and rate of the destabilization process depends mainly on the system composition. The stability of such systems upon storage is an important aspect to ensure their abilities to exert the expected effects and consequently render them pharmaceutically acceptable.[19] Among emulsifiers for emulsions with ibuprofen the natural phospholipids deserve attention. The usage of this phospholipids as emulsifiers may not only increase the bioavailability of ibuprofen[20-22] but also may increase the gastrointestinal safety of orally administered ibuprofen[23,24] Rapeseed lecithin ethanol soluble

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Correspondence Address
Michał Górecki
Department of Drug Technology, School of Pharmacy with the Division of Laboratory Medicine Medical University of Silesia Jedności 8, 41-219 Sosnowiec, POLAND.
Phone no: +48 323 641 180; +48 323 641 181
Email: mgorecki@sum.edu.pl

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fraction (LESF) besides emulsifying properties[25-27] can also inhibit the oxidation of emulsion oil phase with polyunsaturated fatty acid chains,[28,29] contributing to emulsion stability. Using natural biocompatible vegetable oils as emulsion oil phase can provide an additional profits like anti-inflammatory activity in case of olive oil.[30] Taking above aspects into consideration in present work the ibuprofen emulsions based on some vegetable oils with different fatty acids profiles as a lipid phase and LESF as the emulsifier were obtained and the stability of the systems were investigated.

MATERIALS AND METHODS

Ibuprofen powder of pharmaceutical grade was obtained from Medana Pharma Terpol Group, Sieradz, Poland. Lecithin ethanol soluble fraction (LESF) was obtained from crude rapeseed lecithin free of erucic acid and glucosinolates (00-type rapeseed), purchased from Oleochemical Plants KRUSZWICA S.A. Brzeg, Poland, with the method described elsewhere.[31] Analytical grade solvents were obtained from POCH, Gliwice, Poland. Vegetable oils of comestible grade like soybean, rapeseed, safflower and olive oils were obtained from commercial sources.

Determination of iodine value

Iodine value (IN) was determined by volumetric pharmacopoeia method[32] as a mean of three measurements for each sample.

Determination of ibuprofen solubility in selected oils

Ibuprofen solubility test was carried out in 100 ml flasks filled 10 ml of selected vegetable oil, and with or without adding 0.5 g of LESF. The 1 g of ibuprofen was added into each flask and the mixtures were shaken for 24 hours at temperature 25^{0}C and next were centrifuged (MPW351 Med. Instr) at 3000 rpm during 5 min. In the supernatant ibuprofen content was determined by UV spectrophotometric method.

Determination of ibuprofen content

Ibuprofen content in oils and emulsions was determined used UV/VIS spectrophotometer (Jasco-V530 Jasco Corp.) at a wavelength λ=264 nm in 1 cm quartz cuvettes. Oil solutions of ibuprofen were diluted 1:1000 with 2-propanol. Absorbance was measured against a blank containing all components in proper concentration except ibuprofen. Ibuprofen content in each sample was calculated from the calibration curve prepared for the ibuprofen concentration 0.1-1.0% in 2-propanol.

Emulsions preparation

Emulsions with compositions showed in (Table 2 and 3) were prepared. LESF and water were added into a 100 ml flask and mixed using a magnetic stirrer (ES21H WIGO) to obtain homogenous dispersion. Next vegetable oil, glycerol and ibuprofen were added into the water dispersion and homogenized during 15 min in 14000 rpm (CAT X 360M Zippener).

Determination of particle size distribution

Particle size distribution was determined using Optiphot-2 microscope (Nikon, Japan) connected with RGB-2252 camera (Cohu Inc., USA) and Lucia G Intrigue Pro 4.51 software. Samples were prepared by smear method and observed at magnification 2500. Particles diameter measurements [μm] were counted in three characteristic fields taking the 100 objects in each. Measured particles diameter were divided to classes and for each class the mean of number and standard deviation were calculated according to formula (1).

FORMULA: 1

$$P = \frac{S}{V} \times 10^{-5} \quad (1)$$

where:

P – dispersion degree [cm^{-1}]

$$v = \frac{\pi}{6} \times \sum_{i=1}^{N} f \times d_i^3$$

V – particles volume [μm^3]

$$S = \pi \times \sum_{i=1}^{N} f \times d_i^2$$

S – particles surface [μm^2]

f_i – particles number in class, d_i – particles diameter in class

Emulsions stability observation:

The emulsion stability was carried out by observing appearance changes as creaming process and phase separation (emulsion breaking) during 28 storage days. The storage was carried out in 30 ml calibrated test-tubes with grinded plug, at temperature 20ºC, without light.

RESULTS AND DISCUSSION

To determine the effect of the kind of oil with different fatty acid profile and LESF addition on the ibuprofen dissolution, the eight samples of ibuprofen in selected vegetable oils with and without LESF were prepared and ibuprofen content was determined by UV spectrophotometry (Table 1).

Table 1: The solubility of 1 g of ibuprofen in selected vegetable oils with and without lesf

Sample number	Vegetable oil [ml]				LESF [g]	Absorbance	Ibuprofen concentration [mg/ml]
	SO	RO	SFO	OO			
1	10	-	-	-	-	0.021	0.017
2	10	-	-	-	0.5	0.125	0.125
3	-	10	-	-	-	0.033	0.027
4	-	10	-	-	0.5	0.087	0.071
5	-	-	10	-	-	0.063	0.051
6	-	-	10	-	0.5	0.256	0.211
7	-	-	-	10	-	0.109	0.090
8	-	-	-	10	0.5	0.705	0.581

Table 2: Vegetable oil content in emulsions with lesf (2.5G), glycerol (1.1G) and water (41.4G)

Emulsion number	Vegetable oil [g]			
	SO	RO	SFO	OO
E1	5.0	-	-	-
E2	-	5.0	-	-
E3	-	-	5.0	-
E4	-	-	-	5.0

Table 3: The composition of emulsion with ibuprofen and pure emulsion

Kind of emulsion	IBU [g]	LESF [g]	GLY [g]	OO [g]	WATER [ml]
E-IBU	1.0	2.5	1.1	5.0	40.4
E-0	-	2.5	1.1	5.0	41.4

Table 4: Changes in particle size distribution of pure emulsion e-0 during 28 days of storage at 20°c

Day of storage	Mean number of oil particles (measured in 3 characteristic fields ± SD) in each diameter range [µm]						
	0.21-0.40	0.41-0.60	0.61-0.80	0.81-1.00	1.01-1.20	1.21-1.40	1.40-1.60
0	6.7 ± 3.09	20.7 ± 0.47	28.0 ± 2.94	33.3 ± 5.90	9.0 ± 2.16	1.7 ± 0.47	1.0 ± 0.54
14	5.6 ± 3.3	11.6 ± 2.86	21.3 ± 6.59	28.0 ± 2.16	11.3 ± 1.70	9.0 ± 1.63	6.3 ± 0.94
21	2.3 ± 0.77	8.0 ± 2.82	17.3 ± 2.49	36.7 ± 3.68	19.0 ± 0.81	8.3 ± 2.7	3.7 ± 1.70
28	1.7 ± 0.47	16.3 ± 4.10	25.3 ± 3.02	31.3 ± 1.88	11.0 ± 2.94	5.3 ± 0.94	4.0 ± 0.81

Table 5: Changes in particle size distribution of emulsion with ibuprofen e-ibu during 28 days of storage at 20°c

Day of storage	Mean number of oil particles (measured in 3 characteristic fields ± SD) in each diameter range [µm]						
	0.21-0.40	0.41-0.60	0.61-0.80	0.81-1.00	1.01-1.20	1.21-1.40	1.40-1.60
0	6.0 ± 0.81	28.3 ± 6.54	35.3 ± 2.05	23.3 ± 4.98	6.0 ± 2.82	1.0 ± 1.29	0
14	17.7 ± 6.20	30.0 ± 2.82	24.7 ± 8.17	18.7 ± 1.70	6.0 ± 1.41	0.7 ± 0.94	0
21	1.3 ± 1.24	8.3 ± 1.24	13.0 ± 2.94	41.0 ± 3.31	15.3 ± 3.30	13.0 ± 2.16	3.3 ± 2.05
28	2.7 ± 1.70	7.3 ± 3.09	18.7 ± 3.39	35.6 ± 3.09	16.3 ± 4.49	8.7 ± 1.24	4.3 ± 0.47

Table 6: Changes in particle parameters and dispersioin degree of e-0 and e-ibu during 28 days of storage at 20ºc

Emulsion	Day of storage	Surface of all particles [μm^2]	Volume of all particles [μm^3]	Dispersion degree [cm^{-1}]
E-0	0	196.12	29.16	6.72
	14	306.72	60.88	5.03
	21	293.78	53.93	5.45
	28	278.11	52.01	5.34
E-IBU	0	166.00	22.49	7.33
	14	147.03	20.56	7.15
	21	326.97	62.82	5.20
	28	318.75	61.82	5.15

From all tested oils the highest ibuprofen solubility in olive oil was observed. Furthermore for all testing oils LESF addition significantly increased the ibuprofen dissolution, and thus about sixfold in soybean and olive oils, fourfold and over twice in the case of safflower and rapeseed oils.

In the next step emulsions with different oils and LESF without ibuprofen (composition showed in Table 2) were prepared. To the emulsion systems glycerol as a isotonic component was added.

Among obtained emulsions the E2 emulsion with rapeseed oil immediately after homogenization was separated. Other emulsions after homogenization were stable. Emulsion with soya oil (E1) and safflower oil (E3) have creamed and separated after 3-5 days while emulsion with olive oil (E4) after 28 days was stable and not changes were observed. This recipe of emulsion (E4) was selected for further investigation.

Next two emulsions with ibuprofen (E-IBU) and pure emulsion (E-0) with olive oil and LESF were prepared (Table 3).

During 28 days of storage at 20^0C of prepared emulsions (E-IBU and E-0) the creaming process and phase separation were not observed. The particle size distribution directly after homogenization and after 14, 21 and 28 days of storage at 20^0C was determined (Table 4 and 5).

The study shows that the emulsion particles diameter after homogenization are below 1.00 μm in 88.3% and 92.9% of all particles observed, respectively for E-0 and E-IBU. During storage in 20^0C for the pure emulsion (E-0) the 2.8 fold increase in particles diameter range 1.01-1.60 μm after 21 days was observed, while in emulsion with ibuprofen (E-IBU) the about 4.5 fold increase in particles diameter in this same range 1.01-1.60 μm after 21 and 28 days was showed. So ibuprofen only slightly lowers the emulsion stability compared to the pure emulsion. Based on particle size distribution the dispersion degrees of prepared emulsions were determined (Table 6).

In both emulsions E-0 and E-IBU the dispersion degree during 28 days of storage were slight lower than in the initial time. The decreasing was from 6.72 to 5.34 and 7.33 to 5.15 for E-0 and E-IBU respectively.

Emulsions are often used as the carriers of poorly water soluble drugs and also for ibuprofen. In present work emulsions with ibuprofen and selected vegetable oils as well as LESF as a emulsifier were investigated. Also Monzurul and Reza-ul[33] confirmed the high ability of olive oil to ibuprofen dissolving in comparison to other vegetable oils. The vegetable oil dissolving capacity of ibuprofen depends on fatty acids profile of the oil used and in particular on the ratio of the amount of unsaturated, monosaturated and saturated fatty acids in the molecules. Among oils used in our study the olive oil has the lowest content of polyunsaturated fatty acids in the oil. Also rapeseed lecithin ethanol soluble fraction (LESF) used by us as the emulsifier has the lower content of polyunsaturated fatty acids in phospholipid compounds compared to soya one.[25] Our study shows also that the adding of LESF into examined oils significantly increased ibuprofen solubility in tested oils. This may be caused by the better ratio of polyunsaturated fatty acids to monounsaturated and saturated fatty acids in olive oil and rapeseed lecithin. Emulsions obtained for selected oils without ibuprofen have different stability and only emulsion with olive oil was stable during 28 days of storage at 20^0C. Similar, the emulsion based on the olive oil and LESF with ibuprofen was stable during the same time. Only slightly, not important changes in physicochemical properties, particle size distribution and dispersion degree were observed during 28 storage days of study. As a conclusion of our study we found that

obtained results can be the basis for further research on emulsions with olive oil and LESF as the ibuprofen carrier. Ibuprofen is a BCS class II drug and even when administered in high doses has no relevant bioavailability issues. So the approach with using LESF and different vegetable oils might be more relevant to BCS III class drugs that have a poor solubility and bioavailability.

CONCLUSION

The olive oil used for preparing the oil phase of ibuprofen emulsion, seems to be the most appropriate among the investigated oils.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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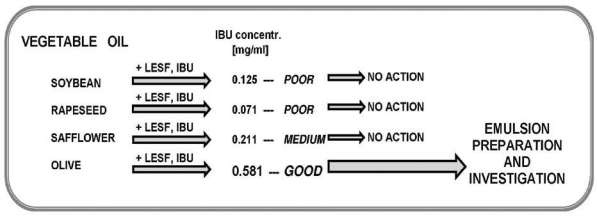
PICTORIAL ABSTRACT



SUMMARY

- Emulsions with soybean, rapeseed, safflower and olive oils with LESF as emulsifier were investigated in aspect of ibuprofen carrying.
- Emulsions obtained without ibuprofen had different stability from the emulsion systems with the drug added.
- Emulsion containing olive oil and LESF could be a potential ibuprofen carrier.

ABBREVIATIONS USED

LESF: Lecithin Ethanol Soluble Fraction; **IBU:** Ibuprofen; **SO:** Soybean Oil; **RO:** Rapeseed Oil; **SFO:** Safflower Oil; **OO:** Olive Oil.

About Author

Michal Górecki: Is an Assistant at the Department of Drug Technology in the Medical University of Silesia, where he obtained his Ph. D. degree in 2009. His doctoral and present research focused on the chemical modification of rapeseed phospholipids in aspects of their use as a drug carriers.