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Research Article

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The use of nonionic surfactants and phospholipids to increase the solubility of ibuprofen optimized by experimental design

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ABSTRACT

The solubility of the drug substances in water is one of the major factors taken into account in the formulation of oral solutions and parenteral dosage forms. The present study was conducted to improve the solubility of ibuprofen in water by the use of phospholipids and nonionic surfactants (Tween® 80 and Solutol® 15HS). These excipients are well tolerated by the parenteral route and allow the solubilization through a micellar system. In our study, a design of experiments approach was tested using a mixture design of nonionic surfactants, phospholipids and ibuprofen. The results showed a significant increase in the solubility in all used mixtures. The analysis of the design space showed that the solubility of ibuprofen varies very closely with the concentration of the three surfactants in water and also with their association.

Keywords: Solubility, Ibuprofen, Mixture design, Surfactants, Phospholipids.

INTRODUCTION

It is estimated that about 40% of the newly developed active pharmaceutical ingredients and approximately 60% of the drugs coming directly from synthesis have poor water solubility, which lead to bioavailability problems and compel scientists to reject these drugs in early phase development [1]. Oral delivery of these drugs is always plagued by low bioavailability, erratic absorption, high intra- and inter- subject variation, and lack of dose proportionality [2].

Therefore, delivering drugs via the oral route presents great challenges. The addition of miscible organic solvents (or cosolvents) is the most common and feasible method to increase the solubility of drugs [3].Various approaches to solubilise drugs, such as inclusion complexes with cyclodextrins, microemulsions or liposome formulations [4]have been described in the literature.

However, all these systems are not generally applicable to every active drug substance, e.g. cyclodextrins need special guest molecule structures for complexation, or exhibit other disadvantages, e.g. microemulsion systems are characterized by high surfactant concentrations which are mostly not well tolerable [5]. By against, surfactants are known to play a vital role in many processes of interest in both fundamental and applied science. They form colloidal-sized clusters in solutions, known as micelles, which have particular significance in pharmacy because of their ability to increase the solubility of poorly soluble drugs in water and thus increase their bioavailability [6-7].

With respect to parenteral application, one can deduce from liposome research that phospholipids represent the only class of excipients offering unique benefits for a surface active ingredient as they are non-toxic, parenterally well tolerated, and exhibit a high biocompatibility. However, phospholipids are forming bilayer structures and typically

not micelles which could be used to solubilize a water-insoluble drug. Under specific conditions, phospholipids and phospholipid derivatives do form mixed micelles instead of vesicles when being combined with suitable hydrophilic surfactants [8-9].

Mixed micelles present a convenient drug delivery system as they are thermodynamically stable (in comparison to liposomes), nano-sized vehicles with sizes of usually 5–60 nm [10-11]. Mixed micelles can be produced by combining natural phospholipids with specific surfactants. In a classical mixed micelles system, the phospholipid serves as a water insoluble but swellable amphiphilic component next to a water soluble surfactant [12]. Although it is possible for phospholipids to form mixed micelles, only one mixed micellar system has found its way to the pharmaceutical drug market: In Konakion® MM unsaturated phosphatidylcholine (lecithin) is mixed with glycocholic acid (sodium salt) representing the classical mixed micelle system composed of lecithin/bile salt.As concern the surfactants, Macrogol 15 Hydroxystearate (Solutol® 15HS) and polysorbate (Tween® 80) are two commonly used nonionic surfactants. Each of them has got pharmaceutical and medicinal values. For instance, Solutol® 15HS is widely used as formulation stabilizer and also an excellent solubilizer for parenteral use. The same is true for Tween® 80. It promotes solubilization of water insoluble drugs besides improving formulation stability.

In this work, we tried to increase the solubility of ibuprofen in water using surfactants and phospholipids. Ibuprofen was given preferences as it has gained the utmost popularity as an analgesic and antipyretic agent. According in the European Pharmacopoeia, Ibuprofen is convenient water-insoluble, Ibuprofen is low solubility and high permeability[13].However, in the formulation of liquid dosage forms, its solubility should be increased because of the volume limitations of the formulations. For this purpose, a mixture of nonionic surfactants and phospholipids are combined with ibuprofen using experimental design approach that is effective to identify optimal concentrations of actives and excipients [14-15].

The purpose of this study is to evaluate the utility of a mixture design to determine the optimum composition for obtaining a significant increase in the solubility of ibuprofen in water[16-28].

EXPERIMENTAL SECTION

Instruments and Reagents

The sample of Ibuprofen ($C_{13}H_{18}O_2$) was obtained as a donation from Pharma 5 Pharmaceutical Company (Morocco). Nonionic surfactants Solutol® HS 15 (mixture of free polyethylene glycol 660 and 12-hydroxystearate of polyethylene glycol 660) was purchased from BASF (Ludwigshafen, Germany) and Tween® 80 (polysorbate 80) from Merck (Germany). Lipoid®S75, a fat free soybean phospholipid for parental application with 70% phosphatidylcholine was a donation from Lipoid GmbH (Ludwigshafen, Germany).Has noted that all solutions are prepared with water freshly distilled and filtered.

In order to determine the maximum amount of ibuprofen which can be solubilized by the mixtures of surfactants and phospholipids, absorbance measurements were carried out using UV/visible spectrophotometer (Shimadzu UV 2450; Japan).For size control in dispersion, a dynamic light scattering (DLS) by Zetasizer 3000HS (Malvern Instruments, France) was used.

Experimental design

To define the formulation space for the ibuprofen mixtures, we tested an experimental design by using software *Design-Expert*® that is a statistical tool that enables calculation for factorial designs and drawing graphs for design evaluation. To make this experimental design, we used a constant concentration of ibuprofen at 1% w/w in all experiences.

In this article, a D-optimal experimental design (mixture design) was selected to evaluate and model the effects of surfactants and phospholipids on enhancing solubility of ibuprofen in water. This provides maximum information from a limited number of experiments. The studied factors were: the amounts of Lipoid® S75(X1 = B), Tween® 80 (X2 = C) and Solutol® HS 15 (X3 = D). Output parameters included drug solubility and size measurements[28].

Table I shows the ranges of these components for the determination of functional design space. The lower and upper limits of others components were determined to allow a solubilizing effect and a suitable concentration for parenteral administration [10-17].

Table I. Lower and upper limits of surfactants and phospholipids used to make the experimental design

Components	Lower limit %	Upper limit %
X1: Lipoid®S75	0	0.5
X2: Tween® 80	0	2
X3: Solutol® HS 15	0	2

With the software Design Expert® we experimented a matrix of 19 formulations at different ratios of all components, summarized in the table II.

Preparation of the samples

Mixed surfactant-phospholipid system was prepared by a direct dispersion method according to methods previously described in the literature [18-19].

Pure surfactant and pure phospholipid stock solutions were prepared by accurately weighting the appropriate quantity of material and diluting with distilled water to the final volume. The stocks solutions of the water-insoluble phospholipid component and the water soluble surfactants were dispersed together in phosphate buffer 0.067M at pH 7.4in conical vials by weighting the appropriate amounts of surfactants and then adding the desired amounts of phospholipids [20-21]. The respective amounts are defined according to the mixture design already realized.

Starting at a higher temperature of 60°C in order to obtain an optimal hydration of the phospholipids above its thermotropic transition temperature, the samples got equilibrated at 25°C for at least 24 h in thermostated water bath (GFL1083, Germany)[22-23]. The final concentration of surfactants (Lipoid® S75 + Tween® 80 + Solutol® HS 15) in each vial is changing according to our mixture design, from 0 to 4% w/w[28].

Drug solubilization study was conducted at normal day temperature following direct dispersion method where the model drug at fixed concentration of 1% w/w, was mixed with the surfactants dispersion previously prepared. The vials were then shaken in a thermostated water bath at 37◦C for at least 24 h. After 24 h storage at room temperature the samples reached equilibrium. Excess amounts of the drug were then separated by 12 min centrifugation at 12.000 rpm in a centrifuge (industria epf12, Argentina)[28].

Solubility determination

Of the clear supernatant solution in all conical vials, a definite quantity was properly removed and diluted with methanol. Absorbance was determined at 249 nm. The amount of drug solubilized was then obtained from the standard curve drawn with absorbance versus concentration.

All data reported are the average of three independent samples. For the calibration curve, five different concentrations in a range from 1.10^{-3} % w/w to 4.10^{-3} % w/w were prepared by dilution from a stock solution of the drug in methanol. The concentration absorption relationship obeyed the Beers–Lambert law ($Y = 9.206X + 0.005$ with Y = absorbance, X = concentration; and $R^2 = 0.992$).

Size determination

Dynamic Light Scattering was used to measure a size in a range between 0.3nm and 10µm[24-25]. It is employed for the point having the maximum of solubility. Measurement was carried out at 25°C after 5min of equilibration. To avoid any loss, like larger vesicles, the produced sample was analyzed without a dilution and filtration step.

RESULTS AND DISCUSSION

Solubility of ibuprofen

All the mixture experiments were conducted in random order and the calculations performed by the Design Expert® software. The solubility results of the 19 mixtures of ibuprofen in various ratios of surfactants and phospholipids are shown in Table II.

Table II. Mixture design of experiments and solubility results of the 19 mixtures of ibuprofen

Run	Ibuprofen % w/w	X1: Lipoid® S75 % w/w	X2:Tween® 80 % w/w	X3: Solutol® HS15 % w/w	X4: Water % w/w	Solubility % w/w
1	1,00	0.50	2.00	2.00	94.50	0,196
2	1,00	0.00	0.00	2.00	97.00	0,348
3	1,00	0.38	1.50	1.50	95.63	0,022
4	1,00	0.25	2.00	0.00	96.75	0,130
5	1,00	0.00	0.00	2.00	97.00	0,348
6	1,00	0.50	0.00	2.00	96.50	0,304
7	1,00	0.00	0.00	0.00	99.00	0,109
8	1,00	0.25	0.00	1.00	97.75	0,304
9	1,00	0.25	1.00	1.00	96.75	0,348
10	1,00	0.13	0.50	0.50	97.88	0,282
11	1,00	0.00	2.00	2.00	95.00	0,804
12	1,00	0.38	1.50	0.50	96.63	0,282
13	1,00	0.50	0.00	2.00	96.50	0,412
14	1,00	0.00	2.00	1.00	96.00	0,369
15	1,00	0.25	1.00	2.00	95.75	0,261
16	1,00	0.50	1.00	0.00	97.50	0,239
17	1,00	0.00	1.00	1.00	97.00	0,282
18	1,00	0.13	1.00	1.50	96.38	0,500
19	1,00	0.50	1.00	0.00	97.50	0,369

These experiments show an improvement of solubility, up until to 80%, compared to the solubility of ibuprofen in water, without additives, examined by the run7.

Experimental design and mathematical modeling

Experiments were carried out to determine the mathematical relationship between the factors influencing the performance and the characteristics of the formulation. A third order polynomial regression model represented by aspecial cubic model equation was as follows:

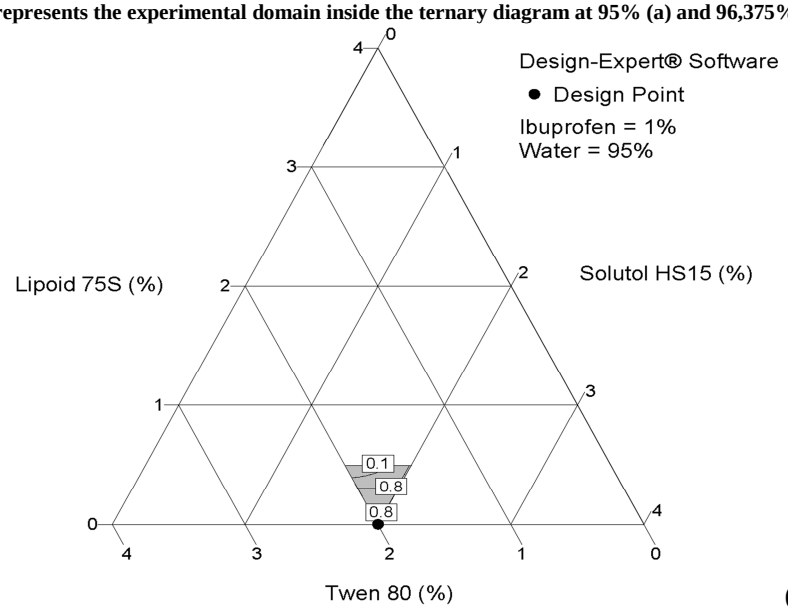
$Y= a_1.X1 + a_2.X2 + a_3.X3 + a_4.X4 + a_1a_2.X1.X2 + a_1a_3.X1.X3 + a_1a_4.X1.X4 + a_2a_3.X2.X3 + a_2a_4.X2.X4 + a_3a_4.X3.X4 + a_1a_2a_3.X1.X2.X3 + a_1a_2a_4.X1.X2.X4 + a_1a_3a_4.X1.X3.X4 + a_2a_3a_4.X2.X3.X4$

Where Y is the solubility prediction of ibuprofen, a_1, a_2, a_3 and a_4 are the estimated coefficients from the observed experimental values of solubility for X1(Lipoid® S75), X2 (Tween® 80), X3 (Solutol® H15S) and X4 (Water). The response of solubility of ibuprofen expressed by a special cubic equation was as follows:

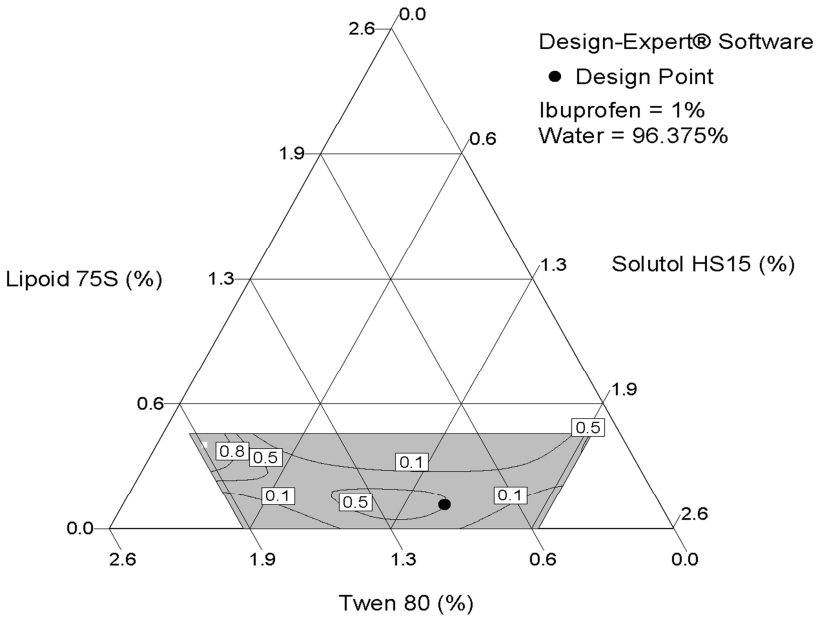
Solubility = -2177.X1+ 150.X2-323.X3 + 0,001.X4 - 479.X1.X2 + 1136.X1.X3 + 22.X1.X4 + 12.X2.X3 – 1,6.X2.X4+3,3.X3.X4-13,1.X1.X2.X3+5,3.X1.X2.X4-11,5.X1.X3.X4-0,09.X2.X3.X4

With solubility measurements, mixtures were designed by Design Expert® to explore the feasibility zone presenting the maximum solubility for ibuprofen.

Figure 1 represents the experimental domain inside the ternary diagram at 95% (a) and 96,375% (b) of water.



(a)



(b)

Figure 1: Contours plots of estimated solubility of ibuprofen (% w/w) with a and b respectively at 95% and 96,375% of water

Statistical analysis

The statistical analysis of variance (ANOVA), the R-Squared and precision was made by Design Expert®. The significance of the model was estimated by applying ANOVA at the 5% significance level. A model was considered significant if the p-value was <0,05. The Model F-value of 5.00 implies the model is significant. At most, there is only a 4.32% chance that this large could occur due to noise. Precision measures the signal to noise ratio should be greater than 4. Our ratio of 10 indicates an adequate signal. Therefore this model can be used to navigate the design space.

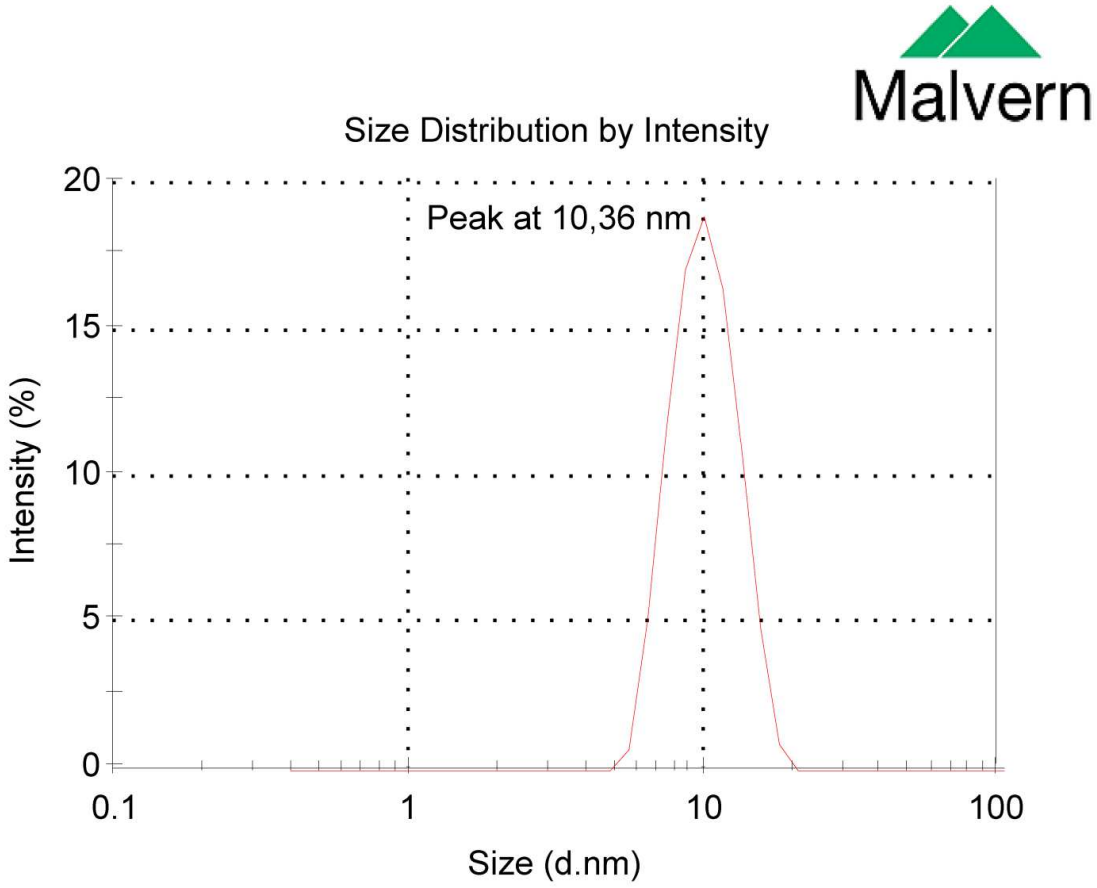


Figure 2: Average size distribution of run 11

Model and results analysis

With this model, the use of high phospholipid concentration tends to significantly decrease the solubility considering the equivalence of the coefficients a_1(Lipoid® S75), a_2 (Tween® 80) and a_3 (Solutol® H15S).The run which solubilizes the maximum of ibuprofen contains no phospholipids. These results can be caused by a probable precipitation of phospholipids and an aggregation in the form of double-layered which does not support the solubilization of the ibuprofen [28]. The run 11 shows an improvement of the solubility, near80%compared to run 3of our matrix probably by forming micelles. The measurement of the size, by DLS, of the run 11, shows an average size of 10 nm(figure 2).

Also, it has already been reported that polysorbate 80 forms mixed micelles as well as vesicles when mixed with phosphatidylcholine[26-27]. Additionally, surfactants like Solutol® HS15 were more able to form mixed micelles with phosphatidylcholine when there hydrophilicity is only located at the polar head region and presents a short chain of fatty acids as there hydrophobic part [10].

In our results, knowing that the run which solubilizes the maximum of ibuprofen contains no phospholipids, this indicates that dissolution is probably made through a conventional micellar dispersion of ibuprofen. The presence of Tween® 80 and Solutol® HS15 may allow the formation of micelles of ibuprofen.

The prediction by the model of a better solubility did not give additional points. This shows that the proportions of the various components bringing the maximum of solubility are already included in our experiment matrix.

Optimization by mixture design of the solubility of a hydrophobic molecule like Ibuprofen associating a phospholipid and nonionic surfactants seems to improve significantly the solubility and defines the effects and the proportions of each component.

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