Evaluation of Olive Oil Ester-Buffer System for the Development of Piroxicam Micro-Emulsion

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Abstract:

The objective of the current study was to assess the prospective of formulating piroxicam micro-emulsion using olive oil ester PEG–buffer system. Surface tension, interfacial tension, spreading coefficient, miscibility were determined for different media containing drug, olive oil, phosphate buffer (pH 4, 6, 7.4), surfactants alone and combination using standard protocols. Micro-emulsion was prepared to assess the feasibility of the selected medium. The results observed indicate that the oil phase has lower surface tension when compared to the olive oil ester buffer system. Further, it was observed that the drug has no effect on the surface tension and interfacial tension of the olive oil ester-phosphate buffer system. This behavior of piroxicam confirms the feasibility of olive oil ester-buffer system as a potential vehicle for the formulation of micro emulsion.

Key Words: Micro-emulsion, olive oil ester, Piroxicam, Phosphate buffer, Surface tension.

Introduction:

Inclusion of highly lipophilic materials in liquid dosage forms is of a great concern for formulation scientists due to the immiscibility of these substances. Different formulation approaches such as emulsions has been proposed and formulated to surmount this issue. The major cause for the low miscibility of liquids is principally because of the formation of interface due to the different characteristics of these substances. Two major reasons for this behavior are the different physiochemical properties the molecules exhibit and the impact of liquid or substance over another. Hans *et al* (2001) have described that the intracellular and extracellular forces between the two phases are likely to be responsible for this behavior, even though, the earlier studies have identified these forces as surface tension and interfacial tension (Sinko, 2006).

Particularly focusing on this issue, it has been observed that the surface activity of some drugs, for instance Non-steroidal anti-inflammatory drugs (NSAIDs), is highly dependent on the pH of the medium in which they are dispersed, (Chakradhara *et al*., 1992; Ridell *et al*., 1999). This category of drugs is widely used as analgesics, and in the treatment of local

inflammation. In most of the cases, it has been observed that their surface activity is highly dependent on the pH of the media. The common example in this regard is Ibuprofen, which is weakly acidic in nature and is available in market in the form of topical and systemic preparations. However, it is often noticed that the surface activity of ibuprofen is highly dependent on pH. The same criterion is also applicable to other NSAIDs as they found to exhibit good surface activity when they are in ionized form (Chakradhara *et al*., 1992). However, piroxicam (another NSAID) exhibit a distinct property when compared to other NSAIDs and possess a limited or no surface activity at aqueous phase and this property can be one of the reasons that may help in reducing the interfacial tension among the ingredient in the formulation (Klang *et al*., 1996).

Piroxicam is widely used as analgesic and antipyretic, especially for the treatment of rheumatoid arthritis, osteoarthritis, and traumatic contusions. However, the drug possesses several limitations such as gastrointestinal side effects. It is generally available as topical formulations targeting local effect (Park *et al*, 2005; Lopes *et al*, 2006). In this context, the micro-emulsions are one of the ideal ways to achieve the maximum drug delivery to the target site. Micro-emulsions are the finest form of emulsion that are clear, translucent and thermodynamically stable than that of a conventional emulsion. Hoar and Schulman (1943) were the first to coin the concept of micro-emulsion when they prepared a clear single-phase solution by mixing a milky emulsion with hexanol. In general, it is seen that micro-emulsions are more stable in terms of thermodynamics and kinetic stability than that of a normal emulsion system (Shinoda and Lindman, 1987). Another most important dissimilarity is that the emulsions are cloudy while micro-emulsions are clear or lustrous. In addition, for the preparation of micro-emulsion a very small amount of energy/ shear force is required to make the two phases miscible. These properties of the micro-emulsion have enhanced its application in the field of pharmaceutical technology.

Several aspects need to be considered during the preparation of micro-emulsions such as selection of an ideal oil phase which is compatible with the pH of the solvents and the influence of the material (to be dispersed) on the surface tension and intracellular forces of the two phases. Once dispersed such systems would be expected to behave in vivo much the same way as oil-in-water (o/w) micro-emulsions. Nowadays, micro-emulsion is often prepared for the non-steroidal anti-inflammatory drugs to enhance the stability and penetration to the target site. Moreover, the literature reveals that micro-emulsions system for piroxicam not only will enhance the

thermodynamic stability but will also enhance the penetration of the active material through both lipophilic and hydrophilic membranes (Yuan *et al*, 2006). However, the stability of this formulation is highly dependent on the surface and interfacial activity of the system. Typically, this formulation is stabilized using surfactants, preferably using non-ionic surfactants which are stable at a wide range of pH and enhance the drug permeation through the skin (Lawrence and Rees, 2000; Fang *et al*, 2001).

The objective of the current study was to assess the potential of olive oil ester-buffer system for the development of piroxicam micro-emulsion.

Materials and Methods:

Materials:

Potassium dihydrogen phosphate, sodium hydroxide, orthophosphoric acid, olive oil ester PEG 7, Tween 80, Span 20 and piroxicam were purchased from Sigma-Aldrich, St Louis, MO, USA. All other chemicals used were of analytical grade.

Methods:

Determination of surface and interfacial tension:

Surface tension of different systems containing piroxicam, olive oil ester and phosphate buffers (pH 4, 6 and 7.4), surfactants [1% Tween 80 and Span 20 (4:1)] alone and in combinations were determined using Tensiometer (White Electrical Instrument Co. Ltd., Worcestershire, UK). The dunouy ring technique was preferred for the surface tension determination of all samples. The samples were tested for various concentrations i.e. 20, 10, 5, 2.5, 1.25 µg/ml in phosphate buffer pH 4, 6 and 7.4. Similarly, the interfacial tension was measured for different systems using Tensiometer.

Determination of spreading coefficient:

Spreading coefficient of various systems were determined using the following equation:

Spreading coefficient = $\gamma S - (\gamma L + \gamma SL)$

Where, γS is surface tension of the spreading liquid, γL is surface tension of sublayer liquid and, γSL is the interfacial tension (Sinko, 2006).

Miscibility studies:

A normal equilibrium miscibility determination was carried out by weighing the calculated amount of piroxicam (1 g), olive oil (100 mL), buffer (300 mL) and surfactant (1%) in a glass vial. The system was stirred for 1 h at 250C and kept at rest for 1 h to assist the attainment of

equilibrium. The miscibility of the system was checked by visual inspection for a separate phase and presence of drug particles.

Preparation of micro-emulsion:

Piroxicam (1 g) was dissolved into the pre-weighed oil component (100 mL) of the system at a concentration of 1% (w/w). The olive oil was mixed with surfactants [1% Tween 80 and Span 20 (4:1) - ethanol mixture]; the aqueous buffer phase (300 mL) was prepared and then added to obtain the desired micro-emulsion compositions. All the procedures were carried out in room temperature (~250C).

Statistical analysis:

Statistical analysis on the effect of surface tension and interfacial measurements was performed by one-way analysis of variance (ANOVA) and t-test using Graphpad Prism 5, Graphpad software, Inc., CA, USA, to test the effects of various treatments. P value less than 0.05 was considered statistically significant.

Results:

The surface tension, interfacial tension, spreading coefficient of different media containing piroxicam, olive oil, phosphate buffer (pH 4, 6, 7.4), surfactants alone and combination were depicted in Table 1. Overall, it is seen that oil phase was found to show a lower surface tension in comparison with the buffer solutions (Table 1). In addition, varying the concentration of piroxicam has not influenced the surface tension of olive oil ester and buffer. Similarly the interfacial tension of the different systems was found to be comparable (Table 1). It is also apparent from the table that the spreading coefficient value was not significant ($P>0.05$), irrespective of the pH of the media. The high values obtained here demonstrate the potential of possible miscibility of the oil phase with the phosphate buffers. However, the addition of surfactant to the system have changed the interface activity significantly ($P<0.05$). The miscibility of piroxicam in presence of surfactant was found to be complete (Data not shown). The prepared formulation showed the feasibility of the olive oil buffer system for preparing micro-emulsions.

Table (1)
Surface and interfacial activity measured for various olive oil ester-buffer systems.

Media	Drug (µg/mL)	Surface tension (Nm/m)	Interfacial tension (Nm/m)*		Spreading coefficient (Nm/m)*
			No surfactant	1% surfactant	
Olive oil ester	0	31.5 ± 1.35	--	--	--
Phosphate buffer pH 4	0	49.5 ± 1.22	46.5 ± 2.35	9.8 ± 0.83	-62.1 ± 4.49
	1.25	48.9 ± 1.50	44.8 ± 1.39	9.3± 1.52	-60.1 ± 2.34
	2.5	45.4 ± 1.72	42.5 ± 3.27	9.6 ± 1.36	-61.6 ± 1.92
	5	46.7 ± 2.31	44.6 ± 2.54	9.8 ± 1.55	-65.2 ± 2.26
	10	48.1 ± 0.95	45.8 ± 1.99	9.6 ± 1.40	-60.3 ± 2.62
	20	47.2 ± 1.34	44.3 ± 1.88	9.5 ± 1.22	-63.7 ± 3.46
Phosphate buffer pH 6	0	51.2 ± 2.18	48.1 ± 3.18	9.9 ± 1.21	-64.2 ± 3.95
	1.25	49.6 ± 3.04	49.3 ± 1.52	9.5 ± 1.62	-60.9 ± 2.80
	2.5	53.1 ± 2.64	46.5 ± 3.06	9.2 ± 1.84	-63.1 ± 4.52
	5	50.4 ± 2.32	49.0 ± 2.48	9.5 ± 1.32	-61.6 ± 1.28
	10	50.7 ± 2.38	48.7 ± 1.11	9.7 ± 2.02	-60.5 ± 2.52
	20	50.8 ± 2.46	50.1 ± 2.04	9.1 ± 1.95	-62.3 ± 2.40
Phosphate buffer pH 7.4	0	53.1 ± 2.40	50.3 ± 0.26	9.8 ± 1.38	-70.3 ± 3.12
	1.25	52.4 ± 3.16	49.5 ± 0.26	9.5 ± 0.94	-68.1 ± 1.88
	2.5	54.6 ± 2.82	51.6 ± 3.75	9.2 ± 2.56	-68.8 ± 2.40
	5	52.1 ± 1.42	48.7 ± 2.44	9.3 ± 1.30	-69.3 ± 1.62
	10	50.5 ± 2.62	51.2 ± 1.82	9.4 ± 1.12	-70.6 ± 3.30
	20	51.2 ± 2.64	47.2 ± 2.32	9.5 ± 2.06	-71.0 ± 4.52

*Measured for olive oil ester-buffer system. Each value is the mean $\pm$ SE (n = 3)

Discussion:

Surface tension is the outcome of the intracellular forces that are responsible for the internal construct of a liquid. These forces are generally found to be high in hydrophilic solvents than that of the lipophilic ones. It has been reported that the hydrogen bonding is the major factor for the higher surface tension among the hydrophilic solvent molecules (Sinko, 2006). The data observed in the current study using olive oil esters was found to exhibit low surface tension than that of the various pH phosphate buffers. This observation is in agreement with the findings of Sinko (2006), who address the poor intra-molecular forces, which result in lower surface tension value as compared to buffers (Table 1). In addition, it is also observed that the concentration of piroxicam has little or no effect on the surface tension of the media. These finding also suggests that olive oil esters could be used for the preparation of a piroxicam micro-emulsion. Moreover,

the high miscibility of oil and aqueous phase nullifies the ostwald ripening phenomena that have a major role in destabilizing the micro-emulsion (Capek, 2004). The findings provides adequate information for the future researchers to formulate the piroxicam micro-emulsion dosage form using olive oil ester as the internal phase and phosphate buffer as the external phase.

Moreover, it was also seen that the addition of 1% surfactant mixture of Tween 80 and Span 20 (4:1) has significantly ($P<0.05$) reduced the intracellular forces by reducing the intracellular tension among the oil and water phase. These findings confirm the results of previous studies that have used Tween 80 and Span 20 (4:1) mixture to produce a stable cream (Gullapalli and Sheth, 1999; Song *et al*., 2000; Abdulkarim *et al*., 2010). Additionally, the effect of piroxicam on the surface tension of olive oil ester and phosphate buffer using 1% surfactants mixture [Tween 80 and Span 20 (4:1) mixture] was assessed. The results observed suggest that the piroxicam has not influenced the interfacial tension between the two phases. A similar observation was also reported with piroxicam when palm oil esters have been used (Abdulkarim *et al*., 2010). Further, it has been suggested that high solubility of piroxicam might be due to the high physiochemical compatibility with the surfactant solution or the capability of the piroxicam to be adsorbed at the interface of the two phases that were used in the micro-emulsion system (Klang *et al*., 1996; Rosoff, 1998; Yuan *et al*., 2006). On the other hand, it can be presumed that the presence of piroxicam did not alter the interfacial tension, hence increasing the stability of the micro-emulsion system (Akoh, 1992).

Conclusion:

The current study concludes that the surface or interfacial activity of media was not influenced by addition of piroxicam to the olive oil esters and phosphate buffers pH 4, 6, and 7.4. This behavior of piroxicam confirms the compatibility of olive oil esters as a potential vehicle for the preparation of micro emulsion.

Recommendations:

The objective of the current study was to assess the prospective of formulating piroxicam micro-emulsion using olive oil ester PEG–buffer system. Future research should focus to study the stability of the piroxicam micro-emulsion using olive oil esters. Initiative in this regards will further substantiate the potential of this research finding in developing a stable micro-emulsion of piroxicam for the drug delivery to the target site.

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تقييم استخدام إسترات زيت الزيتون متعادل الحموضة في تطوير مستحضر المستحلب الدقيق لمادة بيروكسيكام

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الملخص:

المستحلبات الدقيقة هي أفضل شكل من أشكال المستحلبات وهذا بسبب أنها واضحة وشفافة ومستقرة حراريا مقارنة بالمستحلبات التقليدية. في هذه الأيام كثر استخدام المستحلب الدقيق لتحضير العقاقير المضادة للالتهاب غير الاستيرودية وذلك لتعزيز الثباتية والوصول إلى أهدافها العلاجية. وثباتية هذا المستحلب تعتمد بشكل كبير على نشاط وبيئية النظام. وتهدف الدراسة الحالية إلى تقييم احتمالية تحضير المستحلب الدقيق للبيروكسيكام باستخدام إسترات زيت الزيتون في وسط متعادل الحموضة وقد تم تعيين التوتر السطحي والتوتر البيني، معامل الانتشار في المستحضر المكون من البايروكسيكام وإسترات زيت الزيتون وفوسفات المتعادلة الحموضة (درجة الحموضة 4 و 6 و 7.4) والمادة المقللة للتوتر السطحي كل على حدة وفى مخاليطهم باستخدام الطرق القياسية. حضرت كميات من المستحلب الدقيق لقياس جدوى استخدامها. أظهرت النتائج أن الطور الزيتى له توتر سطحي أقل من إستر زيت الزيتون. كما أظهرت أن البايروكسيكام ليس له تأثير على التوتر السطحى أو التوتر بين السطوح فى إستر فوسفات الزيت. وقد أثبتت هذه الدراسة جدوى استخدام إسترات زيت الزيتون في تحضير المستحلب الدقيق للبيروكسيكام.

الكلمات المفتاحية: المستحلبات الدقيقة، إسترات زيت الزيتون، بيروكسيكام، فوسفات متحاولة الحموضة، التوتر السطحي.