Studies on Improving Solubility in Different Media for Said Formulations with Topical Application

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Abstract

The studied compounds are gels with meloxicam, piroxicam and tenoxicam in different solvents. The problem of solubilization of these compounds is generated by their poor solubility in hydrophilic media. Also, when applying local non-steroidal anti-inflammatory drugs (NSAIDs) in the form of ointments, the local concentration of the active substance is much higher than in the untreated tissue. The amount of NSAIDs required to produce a therapeutic effect by topical administration is much lower than in oral administration. Side effects may, however, occur as a local irritation from the time a topical formulation is applied. This paper presents the solubilization tests performed for pharmaceutical compounds of the NSAID class in different hydrophilic media. The test conclusions are useful because their solubility can be increased by using solvents (polar or non-polar) and surfactants. The conclusions of the solubility tests help in choosing solvents in the formulation and technologicalization of semi-solid preparations with topical application.

Keywords: topical application, oxicams, piroxicam, meloxicam, tenoxicam.

Introduction

Oxicams represent the newest NSAID agents introduced in therapy after the 1980s. Their appearance is related to the processes recorded in the field of biopharmacy, respectively pharmacokinetics [1], [2].

The study of these derivatives was initiated by Lombardino and Wiseman, as early as 1970, starting with the predecessors of oxicams, followed by 1st generation oxicams and 2nd generation oxicams, in which the benzene nucleus of the heterocyclic system was replaced with other heterocyclic, in general sulfur (ex. tenoxicam), or the introduction of a hepta-atomic heterocycle in the case of meloxicam, [2], [3]. Although hundreds of derivatives with oxicam structure have been synthesized and experimented with, in therapy, following strict screenings, a few rigorously studied representatives, with a high therapeutic security remain. In addition to the anti-inflammatory activity, they possess a good analgesic, platelet antiaggregant, anti-arrhythmic activity. Oxicams are acid reactive substances, quite strong acids. Possible explanations for the high acidity refers to the involvement of hydrogen bonds that lead to the stabilization of the enolate anion. The molecules are ionized and therefore are distributed in the plasma, in the extracellular water, and at the same time are lipophilic due to the heteroaromatic nucleuses, as well as to the sulfonic group, so that the biological membranes are permeable to them [4]. These physicochemical properties are determined by the chemical, electronic and spatial structure (molecules have a flat shape), which foreshadows a possible adaptation for fixing on the active center of some enzymes (cyclooxygenase, phospholipase).

Material and Methods

Materials

Piroxicam (P), meloxicam (M), tenoxicam (T) (LaborMed Pharma, Romania), ethanol 96% (v/v) (Chimopar, Bucharest), propylene glycol (BASF Chem Trade GmbH, Germany), polyethylene glycol (PEG 400, BASF Chem Trade GmbH, Germany), tween 80, tween 85 (polysorbate 80, 85, Eigenmann & Veronelli, Italy), 1% sodium lauryl sulphate (Fluka Chemie AG, Sweden), paraffin oil solutol (Ra.M. Oil, Italy), oleic acid (Merck, Germany), cetyl stearyl alcohol (Cognis GmbH, Germany), lanolin (Lanolines De La Tossee, France), cetomacrogol self-emulsifying wax (B.P. 2009), distilled water (F.R. X), solutol H 15 (BASF Chem Trade GmbH, Germany), isopropyl miristat (Merck, Germany), [5].

Methods

Determining the solubility of piroxicam, meloxicam and tenoxicam in different solvents and adjuvants, using the saturation method by shaking the vial. For the purpose of determining the solubility of piroxicam, meloxicam and tenoxicam in different solvents, saturated solutions have been obtained by shaking for 96 h at 25°C, 50°C respectively [4], [5], due to the fact that the mixture is solid at normal

temperature. The composition and conditions used for obtaining their saturated solutions are shown in Table 1.

Apparatus

spectrophotometer, model CINTRA 10 E;

1 cm quartz cuvette (Hellma, Germany);

Analytical balance Sartorius BP 210 S, model FW 4798 (Germany).

Table 1. Composition and conditions for obtaining saturated solutions of Piroxicam, Meloxicam and Tenoxicam

No.	Carrier code	Carrier used	Temperature (ºC)
1	Aq	Distilled water	25
2	Et	Ethanol 96% (v/v)	25
3	Pg	Propylene glycol	25
4	PEG 400	Polyethylene glycol 400	25
5	T80	Tween 80	25
6	T85	Tween 85	25
7	LSS	1% sodium lauryl sulphate watery solution	25
8	UP	Paraffin oil	25
9	AO	Oleic acid	25
10	AC-UP	Cetyl stearyl alcohol/paraffin oil 1:17	50
11	AC-L-UP	Cetyl stearyl alcohol /lanolin/paraffin oil 1:1:17	50
12	CA-UP	Self-emulsifying wax /paraffin oil 3:7	50

Results and Discussions

Determining the solubility of piroxicam, meloxicam and tenoxicam in different solvents and adjuvants, [6].

In order to determine the calibration line for piroxicam, meloxicam and tenoxicam, standard solutions were obtained in ethanol 96% (v/v), "PStd_00", "MStd_00", "TStd_00" with the concentration 100 µg/mL. From the standard solutions were obtained the calibration solutions (in EtOH 96%) in increasing concentrations between 5-45 µg/mL. After thermostat control at 25ºC the spectre UV-VIS on the field 200-900 nm was registered, [7], [8]. The maximum absorption for piroxicam (in EtOH 96%) was obtained at the wavelength of 325 nm, for which the determinations for the unknown solutions were performed [8], [9].

In the case of Meloxicam, the main absorption maxima (in EtOH 96%) were obtained at the wavelengths of 205 nm, 270 nm and 355 nm, but the determination of the concentrations of the unknown solutions was only performed for the representative wavelength of 355 nm [9]. The main absorption maxima for Tenoxicam (in EtOH

96%) was obtained at the wavelengths of 267 nm and 358 nm, but the determination of the concentrations of the unknown solutions was only performed for the representative wavelength of 358 nm. For other solvents we generally observed a bathochromic shift of the absorption maximum, but due to the lack of appropriate quantities of the other solvents, the calibration curves could not be obtained for piroxicam, meloxicam and tenoxicam in such solvents [9]. Therefore, only the calibration curves of piroxicam, meloxicam and tenoxicam in ethanol 96% were used. In Figures 1, 2 and 3 are presented the calibration lines obtained for *piroxicam, meloxicam and tenoxicam*, at the wavelengths of 325 nm, 355 nm and 358 nm, respectively, corresponding to the absorption maximum in ethanol 96%, [10].

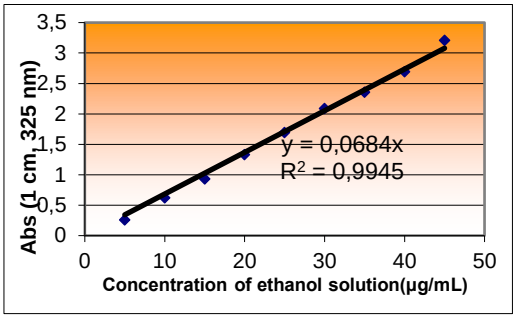

Figure 1. The calibration line of piroxicam for the absorption maximum at 325 nm

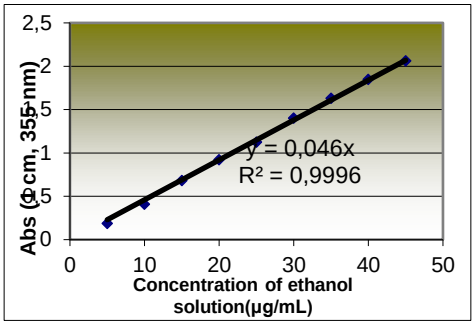

Figure 2. The calibration line of meloxicam for the absorption maximum at 355 nm

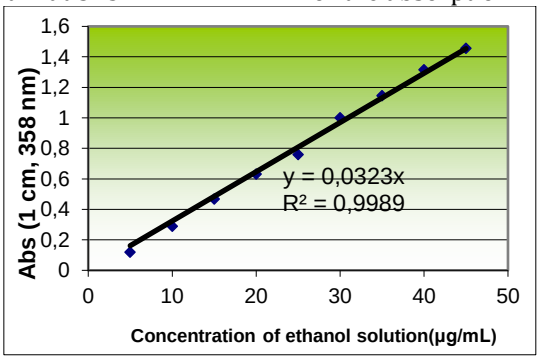

Figure 3. The calibration line of tenoxicam for the absorption maximum at 358 nm

The UV-VIS spectres for the calibration solutions of piroxicam on the relevant field of 230-400 nm, of meloxicam on the absorption field of 200-450 nm and of tenoxicam on the absorption field of 250-450 nm are presented in Figures 4, 5 and 6.

In Table 2 are presented the values of the solubility of piroxicam, meloxicam and tenoxicam, as well as the growth factor of the solubility of these substances in different solvents and adjuvants, ranging between 1 and 1884. The solubility of the three oxicams in the studied *polar* solvents increased with the decrease of the polarity

of the solvent; for the respective solvents, the growth factor ranged between 1 and 486 in the case of piroxicam, between 1 and 503 in the case of meloxicam and, respectively, between 1 and169 in the case of tenoxicam. From the hydrophilic (polar) solvents used, polyethylene glycol 400 showed the highest capacity to dissolve the tree oxicams; the solubility of Meloxicam and tenoxicam in this solvent (5.03 respectively 12.82 mg/mL) was equal to, even higher than, the concentration in which they are include in topical preparations (5 respectively 10 mg/mL). Unlike meloxicam and tenoxicam, the solubility of piroxicam in this solvent (7.78 mg/mL) was lower than the concentration in which the active substance is used in topical preparations (10 mg/mL). In the studied *nonpolar* carriers, the solubility growth factor ranged between 2 and 253 for piroxicam, between 4 and 145 for meloxicam and between 3 and 8 for tenoxicam.

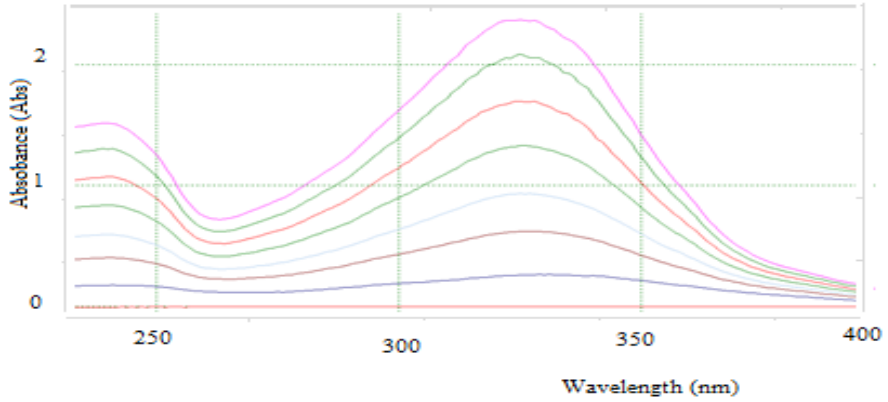

Figure 4. Overlapped absorption spectres for the calibration solutions of piroxicam (230-400 nm)

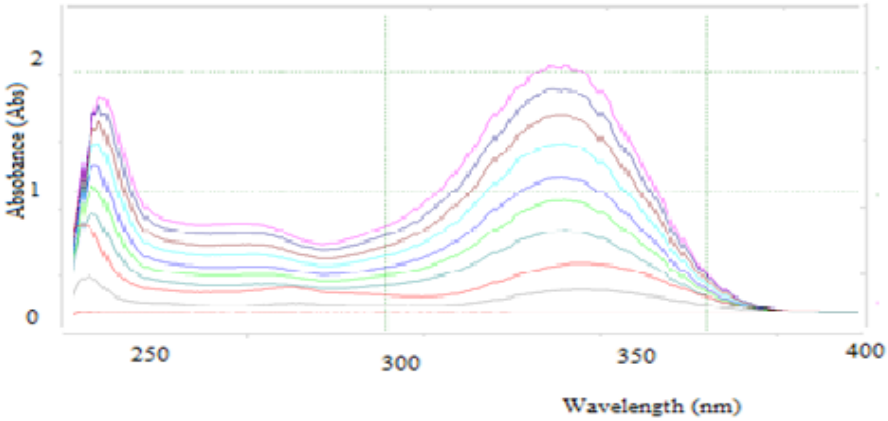

Figure 5. Overlapped absorption spectres for the calibration solutions of meloxicam (200-450 nm)

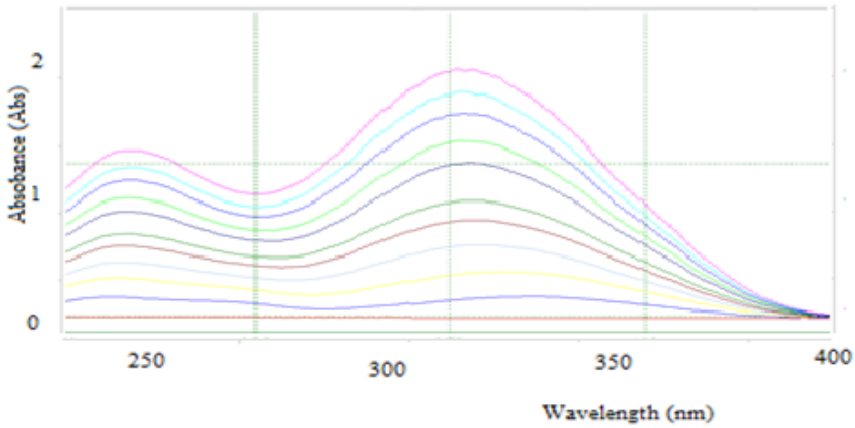

Figure 6. Overlapped absorption spectres for the calibration solutions of tenoxicam (field 250-450 nm)

The solubility of the three oxicams in most of the selected nonpolar carriers (liquid paraffin, cetyl stearyl alcohol/paraffin oil 1:17, cetyl stearyl alcohol /lanolin/paraffin oil 1:1:17, self-emulsifying wax /paraffin oil 3:7) was low, having values close to, generally lower than, those obtained in water and ethanol (for example, the solubility of tenoxicam in these nonpolar carriers, except for the Self-emulsifying wax /paraffin oil 3:7, presented lower values than its solubility in water).

In contrast, form the other two nonpolar solvents used, oleic acid presented an increased dissolution capacity for piroxicam and meloxicam, and isopropyl myristate acted similarly only in the case of piroxicam. Comparing the maximum values of the growth factor of the solubility of piroxicam, meloxicam and tenoxicam, calculated in the series of the polar solvents (PEG 400 corresponding values) with the high value of the same factor, calculated calculate din the series of nonpolar vehicles (the values corresponding to oleic acid and to isopropyl myristate), was observes that the former are significantly higher than the latter. The growth factor of solubility in the studied surfactants ranged between 8 and 1348 for piroxicam, between 9 and 1884 for meloxicam and between 8 and 529 for tenoxicam. The dissolution capacity of surfactants for the three studied oxicams varied in the following order: T85 > SH15 > T80 > LSS

Table 2. Values of the solubility of piroxicam, meloxicam and tenoxicam, as well as the growth factor in different solvents and adjuvants.

Carrier	Piroxicam		Meloxicam		Tenoxicam	
	Solubility (mg/mL)	Growth factor*	Solubility (mg/mL)	Growth factor*	Solubility (mg/mL)	Growth factor*

1	Water	0.016	1	0.010	1	0,076	1
2	Ethanol	0.620	40	0.325	33	1.196	16
3	Propylene glycol	1.668	104	0.462	46	0.611	8
4	Polyethylene glycol 400	7.777	486	5.029	503	12.816	169
5	Tween 80	12.701	794	5.430	543	6.154	81
6	Tween 85	21.577	1348	18.843	1884	40.178	529
7	1% sodium lauryl sulphate solution	0.135	8	0.087	9	0.618	8
8	Solutol H 15	19.622	1226	8.592	859	15.792	208
9	Liquid paraffin	0.037	2	0.003	-	0.014	-
10	Oleic acid	4.058	253	1.446	145	0.631	8
11	Isopropyl myristate	2.394	150	0.333	33	0.208	3
12	Cetyl stearyl alcohol/paraffin oil 1:17	0.303	19	0.040	4	0.029	-
13	Cetyl stearyl alcohol /lanolin/paraffin oil 1:1:17	0.302	19	0.046	5	0.012	-
14	Self-emulsifying wax /paraffin oil3:7	0.607	38	0.247	25	0.245	3

*The growth factor: represents the ratio between the solubility of the substance in 1 ml of solvent/ the solubility of the substance in 1 ml of water, at 25ºC

Nevertheless, differences were observed between the solubility of piroxicam, meloxicam and tenoxicam in each of these surfactants. It should be noted that the solubility of the three oxicams in the surfactants T85 and SH15 were a lot higher than the values of this parameter in the polar solvent PEG 400.

Conclusion

The results of this study have shown that although the three analysed oxicams (piroxicam, meloxicam and tenoxicam) are medicinal substances poorly soluble in water, their solubility can be increased significantly through the use of solvents (polar and nonpolar) and surfactants [9], [10]. Also, this study on solubility has helped to rationalize the selection of the carrier for formulation of skin hydrogels containing piroxicam, meloxicam or tenoxicam.

Thus, form the analysis of the obtained results, the following conclusions may be drawn:

From among the selected polar solvents, Piroxicam, meloxicam and tenoxicam presented the highest solubility in PEG 400 and the lowest in ethanol;

In the case of lipophilic carriers, the solubility of piroxicam, meloxicam and tenoxicam presented the highest values for oleic acid; moreover, Piroxicam had a relatively high solubility in isopropyl myristate;

Tween 85 and Solutol H15 were carriers in which piroxicam, meloxicam and tenoxicam presented the highest solubility.

Consequently, in formulating piroxicam, meloxicam or tenoxicam based hydrogels, PEG 400 is the most adequate co-solvent, due to the high solubilisation capacity, and ethanol will mainly act as absorption promoter, because it influences less the solubility of the three oxicams. In formulations containing a lipophilic phase, (creams, emulsions or micro emulsions-gels), oleic acid may be used mainly as promoter al of the skin penetration of the three oxicams, having a lower solubilisation capacity. Based on similar considerations, isopropyl myristate may be included in the same type of formulations, containing piroxicam. Tween 85 and Solutol H15 may be included as elective auxiliary substances both in the formulation of hydrogels and in that of emulsion systems, simultaneously fulfilling three roles: solubilizer, emulsifying and penetration promoter agents.

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