Acta Poloniae Pharmaceutica – Drug Research, Vol. 66 No. 2 pp. 195–200, 2009 ISSN 0001-6837
Polish Pharmaceutical Society

PHARMACEUTICAL TECHNOLOGY

INFLUENCE OF SURFACTANTS OF ROFAM TYPE ON PROPERTIES OF PIROXICAM TABLETS

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Abstract: Possibilities of application of non-ionic surfactants of Rofam type as solubilizers for piroxicam poorly dissolved in water were assessed. Homologous series of Rofams containing oxyethylene segments from 3 to 18 were used in the study. Tablet formulation was made by wet granulation technique using these surfactants in order to improve drug dissolution properties. Influence of both quantity and type of Rofam on morphological parameters of granules and tablets was investigated. All the examined parameters met the pharmacopeal norms. Paddle method was used to evaluate piroxicam pharmaceutical availability. The presence of non-ionic surfactants in composition of tablet mass improved dissolution rate of piroxicam.

Keywords: piroxicam, Rofams, tablet, dissolution

Piroxicam is one of the representatives of nonsteroidal antiinflammatory drugs of the group of oxicams used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases. It is classified in the Biopharmaceutic Drug Classification (BCS) system as a Class II drug with low solubility and high permeability (1). Despite its high absorption from gastrointestinal tract, its maximum concentration in blood is reached after within 1 to 5 hours after oral administration. The apparent plasma half-life is very long (40-70 h) because of extensive enterohepatic recycling (2). Its slow and gradual absorption via the oral route and long half-life elimination results in prolonged therapeutic action and a delayed onset of analgesic and antiinflammatory effect (3). Low solubility in body fluids influences directly its bioavailability and is also the cause of great individual diversity of this parameter. Thus, increasing of aqueous solubility and dissolution of piroxicam is of therapeutic importance.

The drug in the form of molecular dispersion can be obtained, among other methods used, by application of non-ionic surfactants (4-7).

The new group of non-ionic surfactants are Rofams – the products of oxyethylenating of the rape oil fatty acid methyl esters. (8-10). Basic parameters referring to the structure of Rofam homologous series and their physicochemical properties were presented in the publications (11-13). Rofams were also applied previously to improve solubility of other nonsteroidal antiinflammatory drugs (ibuprofen, naproxen, diclofenac) and albendazole (14-17). Available data from the literature indicate their biodegradability (18-20) and low toxicity (21-23).

The present research work was an attempt to improve dissolution rate of piroxicam using Rofams as solubilizers. Rofams containing (3-18) oxyethylene segments in a particle were used in the studies. The influence of the kind and amount of used surfactant in tablet mass on physical properties and dissolution rate of tablets was investigated.

EXPERIMENTAL

Substances

Piroxicam, Avicel PH-101 and potato starch (Sigma-Aldrich, Germany): magnesium stearate (Merck, Germany), lactose (Galfarm, Poland), hydrochloric acid (POCH, Poland).

Rofam (R-3; R-6; R-8; R-10; R-12; R-15; R-18) – non-ionic surfactant, a product of rape-seed oil fatty acids ethoxylation of the general formula

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$R\text{-}CO(OCH_2CH_2)_nCH_3$, where "R" is a fatty acid hydrocarbon chain and "n" is the number of oxyethylene segments (ICSO Blachownia, Poland) (8, 9),

Preparation of piroxicam tablets

Tablets were made containing 10 mg of piroxicam. In order to improve piroxicam pharmaceutical availability, non-ionic surfactants of Rofam class were used. The research was carried out by making use of 6 Rofams (R-3, R-6, R-10, R-12, R-15 and R-18). The Rofams were used in two concentrations of 0.4 % and 4 % of the total mass of granules. The granules were prepared by wet granulation method.

The drug and inactive ingredients were mixed thoroughly and moistened with aqueous solution containing the appropriate Rofam and then kneaded in a mortar with 1% (w/v) gelatine solution. The wet mass was forced though a no. 20 sieve (850 μm) and dried at 40°C in hot air oven for 10 h. The dried granules were resieved through a no. 20 sieve. 14 granules were made with the following recipe contents in relation to one tablet:

- piroxicam 10 mg
- potato starch 110.4 mg
- lactose 55.2 mg
- Avicel PH-101 18.4 mg
- magnesium stearate 6 mg
- Rofam 0.8 mg (8 mg)

The granule without extra surfactant was made additionally as a reference.

Tablets of about 200 mg were made from these granules after adding 1.2% (w/w) magnesium stearate, using single-punch table machine (KORSCH Erweka, Germany) equipped with 8 mm flat-faced punches.

Evaluation of granules

Tap and bulk densities, as well as a moisture content were determined in the obtained granules. Tap density was estimated using Polfa W2 type volumeter. For each granule series, measurements were made threefold. The results obtained allowed to calculate Carr's index (IC) following the formula:

$$IC = (TD - BD) \times 100/TD$$

where: TD – Tap density (g/cm^3), BD – Bulk density (g/cm^3).

The values of tap density and bulk density also served to calculate BD/TD quotient i.e. the Hausner's coefficient. Angle of response was determined by making use of methodology described in (24). Moisture content was determined using equipment with an infrared unit (Radwag, Poland).

Characterization of tablets

Using official Polish Pharmacopoeia methods (25), physical parameters of tablets were evaluated, including their weight (Sartorius, Germany) and friability (ZDM, Polfa, Poland). Disintegration time for 6 tablets was determined with the disintegration apparatus (F2, ZDM Polfa, Poland) at 37°C ± 0.5°C in water.

***In vitro* dissolution studies**

The paddle-type dissolution rate test apparatus was used for *in vitro* release studies. The dissolution medium used was 0.1 M HCl maintained at 37°C ± 0.5°C. The paddle speed was 60 rpm. Samples (3 mL) were collected periodically and replaced with equal quantity of dissolution medium. After filtration, samples were analyzed using UV spectrophotometer (Cecil, England) at 353 nm. Piroxicam concentration was calculated from the equation describing the calibration curve. The results of piroxicam concentration measurements were presented in the form of percentage of the released dose (Q). The release rate was characterized by determining a release rate constant (k).

Statistical analysis

Results are expressed as the mean ± SEM. A value of $p\ (\alpha) \leq 0.05$ was considered statistically significant. ANOVA followed by Dunnett's "*t*" test was performed as a *post-hoc* test of significance taking formulation without Rofam as control.

RESULTS AND DISCUSSION

The basic factor which enables evaluation of granulate properties is both tap and bulk density.The results of studies carried out for the granules are shown in Table 1. Introduction of Rofams to the granule recipe increases tap and bulk density compared with the granules without either of them. On the basis of the study results it was shown that there is a dependence between the kind of the surfactant used, its concentration in a granule and the discussed parameters. It was found that the higher oxyethylene segment contents was in a Rofam particle the higher were the values of tap and bulk density. An increase of their values made further progress parallel to an increase of Rofam content in a granule.

The determined values of tap density and bulk density served to calculate Carr's index and Hausner's coefficient. Carr's index values obtained for the examined granules containing Rofam of 0.4 % were found within the range between 16.67% and 20.0% – so they were statistically lower ($p < 0.01$) –

Table 1. Characteristic properties of granules.*

Parameters → Batch ↓	Bulk density (g/cm³)	Tap density (g/cm³)	Carr's index (%)	Hausner's coefficient	Angle of response (°)	Moisture content (%)
R0C0	0.40	0.51	21.57 ± 1.69	1.28 ± 0.012	29.12 ± 1.17	5.83 ± 0.051
R3C1	0.40	0.48	16.67 ± 0.52 [a]	1.20 ± 0.033[a]	22.11 ± 1.13[a]	5.83 ± 0.043
R6C1	0.40	0.48	16.67 ± 0.53 [a]	1.20 ± 0.007[a]	25.84 ± 1.16[a]	5.77 ± 0.053
R8C1	0.42	0.52	19.23 ± 0.40[b]	1.24 ± 0.014[a]	26.49 ± 1.15[a]	5.73 ± 0.058
R10C1	0.41	0.5	18.00 ± 2.20 [a]	1.22 ± 0.014[a]	28.35 ± 1.12[a]	5.83 ± 0.058
R12C1	0.42	0.51	17.65 ± 1.01[b]	1.21 ± 0.009[a]	28.31 ± 0.99[a]	5.73 ± 0.061
R15C1	0.44	0.54	18.52 ± 1.73[b]	1.23 ± 0.039[b]	27.96 ± 0.69[b]	5.82 ± 0.048
R18C1	0.48	0.6	20.00 ± 1.50	1.25 ± 0.014 [c]	28.45 ± 0.58 [c]	5.77 ± 0.061
R3C2	0.42	0.51	17.65 ± 0.97[a]	1.21 ± 0.017[a]	25.32 ± 0.67[a]	6.87 ± 0.06[b]
R6C2	0.42	0.52	19.23 ± 1.56[b]	1.24 ± 0.009[a]	27.31 ± 0.87[a]	6.33 ± 0.05[b]
R8C2	0.43	0.53	18.87 ± 0.24[b]	1.23 ± 0.013[a]	28.49 ± 0.55[a]	6.07 ± 0.04[b]
R10C2	0.42	0.52	19.23 ± 1.02	1.24 ± 0.030[b]	29.46 ± 0.77[b]	6.00 ± 0.10
R12C2	0.46	0.57	19.30 ± 1.59	1.24 ± 0.032[b]	28.77 ± 0.91[b]	5.80 ± 0.10
R15C2	0.48	0.61	21.31 ± 0.61	1.27 ± 0.010	29.01 ± 0.62	5.67 ± 0.05
R18C2	0.50	0.64	21.88 ± 1.71	1.28 ± 0.006	29.45 ± 0.54	5.87 ± 0.06

*All values are expressed as the mean ± SD (n = 3); [a]significantly different from granules without Rofam $p < 0.001$; [b]significantly different from granules without Rofam $p = 0.01$; [c]significantly different from granules without Rofam $p = 0.05$

Table 2. Characteristic properties of tablets.*

Parameters → Batch ↓	Weight variation (%)	Friability (%)	Disintegration time (minutes)
R0C0	6.03	0.59 ± 0.03	3.27 ± 0.15
R3C1	1.56	0.39 ± 0.02 [a]	2.17 ± 0.12 [a]
R6C1	1.21	0.39 ± 0.02 [a]	2.43 ± 0.12 [a]
R8C1	1.72	0.36 ± 0.01 [a]	2.57 ± 0.15 [a]
R10C1	1.83	0.36 ± 0.01 [a]	2.53 ± 0.15 [a]
R12C1	2.44	0.32 ± 0.02 [a]	2.87 ± 0.15 [c]
R15C1	1.91	0.31 ± 0.03 [a]	3.17 ± 0.15
R18C1	2.64	0.29 ± 0.03 [a]	3.03 ± 0.25
R3C2	1.81	0.41 ± 0.10[c]	2.20 ± 0.10 [a]
R6C2	1.21	0.42 ± 0.09 [c]	2.27 ± 0.12[a]
R8C2	2.43	0.37 ± 0.05[b]	2.23 ± 0.12 [a]
R10C2	2.09	0.38 ± 0.04 [b]	2.13 ± 0.06 [a]
R12C2	3.06	0.25 ± 0.06 [a]	2.37 ± 0.15 [a]
R15C2	3.48	0.21 ± 0.03 [a]	2.50 ± 0.10 [a]
R18C2	6.88	0.20 ± 0.02 [a]	2.57 ± 0.06 [a]

*All values are expressed as the mean ± SD (n = 3); [a]significantly different from tablets without Rofam, $p < 0.001$; [b]significantly different from tablets without Rofam, $p = 0.01$; [c]significantly different from tablets without Rofam, $p = 0.05$

Table 3. Dissolution parameters of piroxicam release from tablets.*

Batch → Parameters ↓	R0C0	R3C1	R6C1	R8C1	R10C1	R12C1	R15C1	R18C1
Q5	44.73 ± 5.20	67.12 ± 4.36[a]	63.87 ± 5.62[a]	60.86 ± 5.59[a]	56.98 ± 4.45[a]	55.14 ± 5.12	53.68 ± 7.14[c]	49.89 ± 5.22[c]
Q15	62.50 ± 2.05	84.17 ± 3.08[a]	82.98 ± 3.90[a]	81.90 ± 1.92[a]	77.24 ± 4.08[a]	76.30 ± 5.81[a]	75.80 ± 6.12[a]	71.88 ± 1.93[b]
Q45	77.72 ± 1.69	93.07 ± 2.28[a]	92.36 ± 3.87[a]	91.63 ± 2.15[a]	89.77 ± 3.36[a]	88.39 ± 2.84[a]	89.22 ± 2.69[a]	88.95 ± 3.28[a]
Q60	80.29 ± 0.93	95.50 ± 1.23[a]	94.76 ± 1.45[a]	93.75 ± 1.10[a]	93.11 ± 1.40[a]	92.57 ± 1.42[a]	92.40 ± 1.04[a]	91.41 ± 2.50[a]
k (min^{-1})×10^{-2}	3.09 ± 0.30	1.37 ± 0.12[a]	1.45 ± 0.27[a]	1.57 ± 0.19[a]	1.86 ± 0.21[a]	2.07 ± 0.37[a]	2.18 ± 0.49[a]	2.36 ± 0.28[b]
Batch → Parameters↓	R0C0	R3C2	R6C2	R8C2	R10C2	R12C2	R15C2	R18C2
Q5	44.73 ± 5.20	77.00 ± 5.14[a]	76.56 ± 4.87[a]	75.05 ± 4.97[a]	64.84 ± 3.71[a]	57.76 ± 4.57[a]	53.88 ± 2.39[b]	52.86 ± 2.37[c]
Q15	62.50 ± 2.05	87.22 ± 4.98[a]	87.30 ± 4.60[a]	84.17 ± 3.24[a]	82.28 ± 1.68[a]	76.09 ± 6.09[a]	73.92 ± 4.21[a]	73.28 ± 3.71[a]
Q45	77.72 ± 1.69	94.39 ± 3.17[a]	93.89 ± 3.13[a]	92.51 ± 3.92[a]	92.73 ± 1.65[a]	90.66 ± 2.62[a]	88.50 ± 3.99[a]	87.63 ± 1.81[a]
Q60	80.29 ± 0.93	96.42 ± 2.43[a]	95.66 ± 3.00[a]	94.87 ± 2.90[a]	94.92 ± 1.54[a]	93.71 ± 1.12[a]	92.00 ± 2.90[a]	91.10 ± 2.14[a]
k (min^{-1})×10^{-2}	3.09 ± 0.30	0.94 ± 0.30[a]	0.95 ± 02.5[a]	1.08 ± 0.25[a]	1.56 ± 19[a]	1.89 ± 0.34[a]	2.24 ± 0.22[a]	2.31 ± 0.18[a]

*All values are expressed as the mean ± SD, (n = 6); [a] significantly different from tablets without Rofam, $p < 0.001$; [b] significantly different from tablets without Rofam, $p = 0.01$; [c] significantly different from tablets without Rofam, $p = 0.05$

except for R18C1, compared with R0C0 batch for which IC equaled 21.57%.

For formulation with addtional surfactant of 4% amount this parameter was found within the range between 17.65% and 21.88% and significantly lower values ($p < 0.01$) were determined for R3C2, R6C2 and R8C2 batches, respectively, This parameter denoted granule compressibility and is advantageous when it does not exceed 20% (adequate flow). The results of compressibility index indicated a decrease in flowability with increasing Rofam concentrations (Table 1).

The angle of response was less than 30^{o} for all the batches of granules indicating satisfactory flow behavior. The obtained results confirmed observations made for Carr's index. The influence of both Rofam's kind and concentration, as a granule component, on its flow was evident.

The flow properties of granules are favorable for the possibly lowest values of Hausner's coefficient. In the studied granules containing a surfactant, significantly lower values of this parameter were found than in the granule without added Rofam (R15C2 and R18C2 series being exceptions).

Summing up the results of granulometric studies, it was found that an increase of oxyethylene content in a surfactant particle, as well as an increase of its content in a granule recipe made granule friability worse. Moisture content of less than 6% indicated optimum drying of granules.

The results of experiments carried out for the tablets are shown in Table 2. The results of physical evaluation of the tablets obtained from the ones with non-ionic surfactants of Rofam type met the FP VI requirements (25).

The changes in tablet mass, i.e. accuracy of dose administration could be predicted from Hausner's coefficient – so the greatest deviations were found in R0C0 and R18C2 tablet series. Table 2 showed that standard deviation indicated good uniformity of weight for all the prepared tablets containing non-ionic surfactant, yet the variation of weight increased in the case of batches with greater Rofam content (4%).

The friability of all the tablets was calculated below 0.6%, which was well within

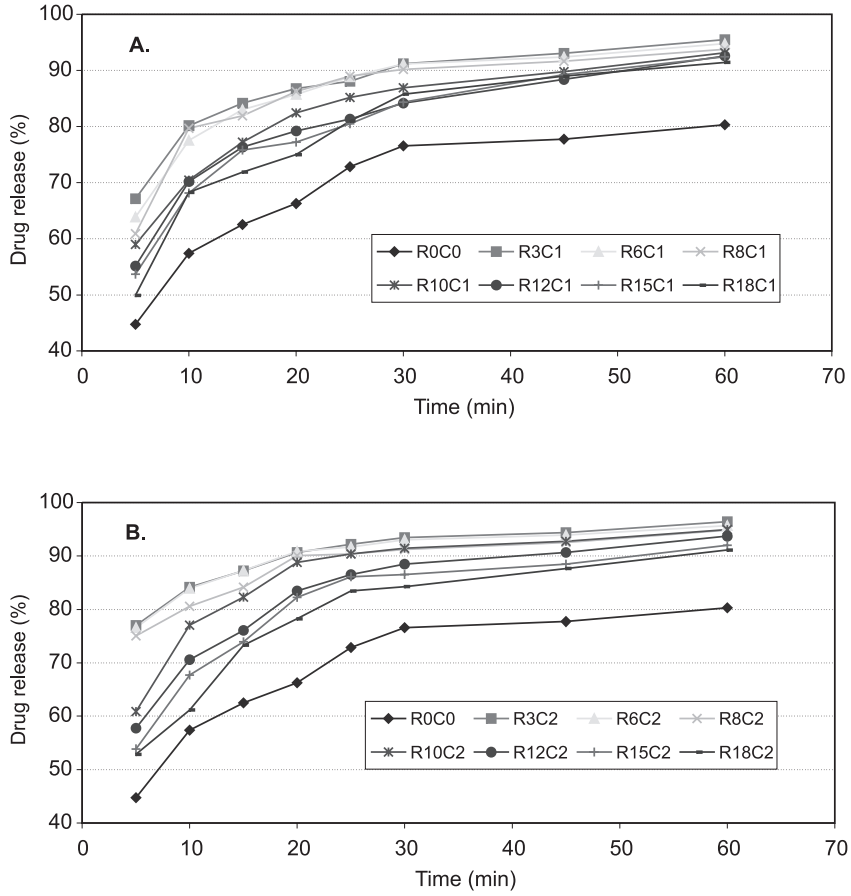

Figure 1. Effect of a kind of Rofam and its content in a tablet on *in vitro* piroxicam release profile. A – 0.4 % Rofam tablet mass content; B – 4% Rofam tablet mass content.

the acceptable range of 1% and indicated that tablet surfaces were strong enough to withstand mechanical shock or attrition during storage and transportation until they will be consumed. The surfactant's presence in a tablet caused a significant increase of mechanical resistance in relation to tablets deprived of it. The larger amount of surfactant in tablet mass the lower was its friability– for the R18C2, R15C2 and R12C2 batches it was lower by 31, 32 and 21% ($p < 0.05$) – in comparison with R18C1, R15C1 and R12C1 (Table 2).

So, an increase of ethylene oxide content in a Rofam particle improved mechanical properties of the tablets and at the same time made their disintegration time shorter.

The longest disintegration time in water was found for R0C0 tablet series that equaled 3.27 minutes; the shortest for R3C1 batches was 2.17 min and for R3C2 – 2.20 min, respectively. The tablets formulated with Rofams disintegrated significantly faster than the ones without Rofams with exception of R15C1 and R18C1. However, disintegration time for the tablets prepared with 0.4% surfactants showed longer disintegration time.

In vitro drug release

The final phase of experiment was the evaluation of piroxicam pharmaceutical availability from the formulated tablets. The release rates of piroxicam from the tablets are given in Figure 1. It was observed that the release rate of piroxicam significantly increased from the batches with formulative participation of micellar solubilizer in comparison with the batch prepared without it (Table 3).

Regardless of the kind of surfactant used in the process of tablet preparation, after their complete decay, a percentage of the released drug was over 90% and without surfactant – 80%, respectively. Values of the release coefficient Q for all the measurement points showed statistically significant dif-

ferences (level of significance within the range of p = 0.0215 – 0.0001) compared with the tablets without Rofam (Table 3). The curves of release rate drawn for all the tablet batches showed the best availability of therapeutic substance from R3C3 tablets. Already in the fifth minute of measurement about 77% of the declared dose of piroxicam was released from the tablet. For R0C0 series the process of piroxicam release was the shortest.

The paired Student's t-test was also used to compare the influence of Rofam content in a tablet on piroxicam release in the prepared tablets. Significant difference was found between R3C1 – R3C2 ($p < 0.01$), R6C1 – R6C2 ($p < 0.01$), R8C1-R8C2 ($p < 0.01$) and R10C1-R10C2 ($p < 0.05$) in the fifth minute of the release process and R3C1-R3C2 ($p < 0.05$) after 15 min.

CONCLUSION

The present study determined the utility of surfactants of Rofam type to enhance dissolution rate of insoluble drugs. It was established that their solubility properties increased with lowering of number of the oxyethylene segments in a particle of surfactants. However, maximum effectiveness of an increase of piroxicam dissolution rate was found to be Rofam R-3 used in the examined tablets. The best biopharmaceutical parameters were found in the tablets containing Rofams in the amount of 4% formulation mass. The results confirmed that the Rofams could be used as potential pharmaceutical excipients.

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Received: 30. 06. 2008