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STUDY OF PHYSICOCHEMICAL PARAMETERS AFFECTING THE RELEASE OF DICLOFENAC SODIUM FROM LIPOPHILIC MATRIX TABLETS

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Abstract

In the present work different parameters, which influence the release of diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid mono sodium salt) from lipophilic matrix prolonged release tablets, were investigated.
Solubility characteristics of diclofenac sodium in aqueous media with various ionic strengths, ionic compositions and pH in the range of 1 to 10 were determined. According to the obtained results different experimental conditions of the dissolution test on the drug release profiles were studied, i.e. different dissolution apparatus, various rotation speeds of the stirring elements, different buffer media with a pH in the range of 5.8 to 10.0 and various ionic strengths. The amount of released diclofenac sodium was determined by ultraviolet spectrophotometry at the wavelength of maximum absorbance at 276 ± 2 nm.
From the obtained results it can be concluded, that solubility of diclofenac sodium depends mainly on composition and pH of the dissolution medium and also on ionic strengths of the dissolution medium. Besides these parameters, on the release of diclofenac sodium from lipophilic matrix tablets influence also type of dissolution apparatus and particularly rotation speeds of the stirring elements.

Key words: drug release, lipophilic matrix tablets, ionic strengths, diclofenac sodium

Introduction

Modified-release dosage forms are preparations that regulate the rate and/or time and/or site of release of the active ingredient, in order to achieve specific therapeutic objectives, which cannot be achieved by conventional immediate release dosage forms, similarly administered.[1]

The most important advantage of modified-release therapy is improved efficiency in treatment. The result of obtaining constant drug blood levels from modified-release systems is to promptly achieve the desired effect and maintain it for an extended period

of time. Reduction or elimination of fluctuations in the drug blood level allows better disease state management. Minimizing the patient compliance problems is also an obvious advantage of modified-release preparations. Because of the nature of their release kinetics, modified-release systems are able to use less total drug over the time course of therapy than conventional preparations. Furthermore, the advantages are decrease or elimination of local and systemic side effects, less potentiation or reduction in drug activity with chronic use, and minimization of drug accumulation in body tissues with chronic use. In addition, the method by which modified release is achieved can improve the bioavailability of some drugs. Potential advantage is also a lower average cost of treatment over an extended time period.[2-4]

There are four main types of modified-release delivery systems:

- Delayed- or repeated-release systems, which use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form.[1-4]
- Prolonged-, sustained- or extended-release systems, which release the active ingredient more slowly than conventional dosage forms similarly administered. Prolonged-release dosage forms generally contain a higher dose of active ingredient compared to conventional dosage forms, and reduce administration frequency.[1-4]
- Site-specific targeting systems, where the target is adjacent to or in the diseased organ or tissue.[2]
- Receptor targeting systems: the target is the particular receptor for a drug within an organ or tissue.[2]

According to the technological aspects prolonged-release dosage forms can be classified into:[1-4]

- Reservoir (membrane) systems,
- Inert-matrix systems (homogenous matrices, heterogeneous matrices),
- Swelling-matrix systems,
- Osmotic systems,
- Ion-exchange systems.

Diclofenac sodium is a non-steroidal anti-inflammatory drug used in the treatment of rheumatic disorders. This drug is very interesting in modified release oral dosage forms, especially due to its relative short biological half-life, the hazards of adverse gastro-intestinal reactions and chronic nature of treatment.

Diclofenac sodium prolonged-release lipophilic matrix tablets produced by Krka are a combination of reservoir (membrane) system and inert-matrix system. The formulation is based on a hydrophobic matrix formed by cetyl alcohol. The drug exhibits a classical diffusion-controlled drug release mechanism. Diffusion in such systems depends on membrane permeability, system geometry, polymer properties and polymer structure. The drug is dispersed in the polymer whose chains are surrounded by a network of channels. Therefore, the drug is released following dissolution and diffusion in the medium, which fills the interconnected pores. The materials used in preparation of these matrices are predominantly inert (insoluble) polymers and hydrophobic-lipophilic compounds.[1,3]

The general guidelines for development of a drug release test should cover the method reliability, the capacity to show formulation changes and batch variations and the possibility to differentiate among batches having different in-vivo performances. The choice of equipment and the test procedures, such as hydrodynamic conditions, should be the result of knowledge of the formulation design and release mechanism, and of the indications drawn from actual performances of the dosage form subjected to the particular in-vitro test.[1,2]

The knowledge of understanding the factors influencing in-vitro dissolution of diclofenac sodium from lipophilic matrix tablets is important to develop optimal conditions for in-vitro studies of drug release in similar formulations.

Experimental

Materials

Concentrated hydrochloric acid (analytical grade) was obtained from Riedel de Haën (Munich, Germany), sodium hydroxide was from J. T. Baker (Phillipsburg, NJ, USA), potassium dihydrogen phosphate, sodium chloride, potassium chloride, boric acid and sodium acetate, all analytical grade and from Fluka (Munich, Germany), acetic acid and methanol were from Merck (Darmstadt, Germany) and purified water for chromatography was from a Milli-Q purification unit (Millipore, Milford, MA, USA). Injection syringes (10 mL and 20 mL) were from Sartorious GmbH (Goettingen, Germany), 10 μm full flow filters and bent cannulas for dissolution sampling were from Van Kel (Cary, NC, USA) and pipettes from Hirshman (Germany). Filter papers blue

ribbon; Φ 90 mm (589[3]; ashless) for solubility experiments were from Schleicher & Schuell (Germany). Glass microfibre filters grade GF/F (for flow through cell analyses) were from Whatman (Maidstone, England), beakers, tall form, with graduation and spout (400 mL, 1000 mL, 2000 mL and 5000 mL), bottles with a narrow neck (5000 mL and 10000 mL), measuring cylinders with graduation (50 mL, 100 mL, 250 mL, 500 mL and 1000 mL), Erlenmayer flasks (100 mL, 250 mL) and volumetric flasks (20 mL, 25 mL, 50 mL, 100 mL, 1000 mL and 2000 mL) were all from Duran (Mainz, Germany). Diclofenac sodium (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monosodium salt) used for solubility experiments was obtained from Dipharma S.p.A. (Milano, Italy). Diclofenac sodium prolonged-release lipophilic matrix tablets containing 100 mg of diclofenac sodium were produced by Krka, d.d., Novo mesto, Slovenia.

Instrumentation

For solubility experiments, Vibromix 402 EVT shaker (Slovenia) and pH meter (Radiometer Analytical S.A.; Copenhagen, Denmark) were used. Van Kel VK 7010 dissolution tester with baskets or paddles (Van Kel, Cary, NC, USA) on-line connected to Cary 50 Bio UV-VIS spectrophotometer (Van Kel, Cary, NC, USA) and apparatus 4/flow through cell Sotax on-line connected to Lambda 25 Perkin Elmer UV-VIS spectrophotometer were used. Furthermore, ultrasonic bath (Donau-lab-sonic, DLS 700-T; Zurich, Switzerland) and analytical balance (Mettler-Toledo AT261 DeltaRange; Greifensee, Switzerland) were used.

Methods

Solubility experiments

The solubility of diclofenac sodium (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monosodium salt) at ambient temperature (23 ± 2 °C) was checked by shaking-flask method. This method is an indispensable test for characterizing solubility characteristics of active ingredients in development of new formulations. It is a conventional solubility test where the drug is added to a standard buffer solution until saturation occurs. The flasks should be shaken for at least 24 h. The amount of dissolved drug is determined by assaying filtrated solution.[5] The drug was added to aqueous media in the flasks until excess of drug occurred and saturation was achieved. Solubility determinations were

performed in triplicate. After 72 h of shaking the sample solutions were filtered through filter papers blue ribbon and the amount of dissolved diclofenac sodium was determined by ultraviolet spectrophotometry at the wavelength of maximum absorbance at 276 ± 2 nm.

All the aqueous media used for solubility experiments, i.e. hydrochloric acid (0.1 M, 0.01 M and 0.001 M), acetate buffer solutions (pH 4.1, 4.5, 5.5), phosphate buffer solutions (pH 5.8, 6.0, 6.8, 7.0, 7.4, 7.8, 8.0) and alkaline borate buffer solutions (pH 8.0, 9.0, 10.0) were prepared according to the prescriptions in the USP 26, p. 2524 - 2525.[6]

The dissolution media with different ionic strengths and pH in the range of 5.8 to 8.0 (phosphate buffer solutions) and pH in the range of 8.0 to 10.0 (alkaline borate buffer solutions) were prepared by diluting stock buffer solutions prepared according to the prescriptions in the USP 26 (phosphate buffer solutions: dilutions 6:10 and 8:10 with purified water; alkaline borate buffer solutions: dilutions 1:10 and 5:10 with purified water) or by adding potassium chloride to the stock buffer solutions, prepared according to USP 26 in order to achieve higher ionic strengths of buffer solutions. The amount of potassium chloride in the dissolution media was defined according to literature data for the media simulating intestinal conditions.[7] Ionic strengths of the phosphate buffer solutions were 0.6- and 0.8-times lower and 3.65- and 6.3-times higher compared to ionic strengths of stock phosphate buffer solutions. Ionic strengths of the alkaline borate buffer solutions were 0.1- and 0.5-times lower and 3.65- and 6.3-times higher than ionic strengths of stock alkaline borate buffer solutions.

Basket and paddle apparatus (apparatus 1 and 2) - drug release conditions

Basket and paddle apparatus (according to Ph.Eur.) or apparatus 1 and 2 (according to USP) are prescribed in different pharmacopoeias as conventional testers for characterizing dissolution or drug release of active ingredients from different types of formulations.

Dissolution media with different ionic strengths and pH in the range of 5.8 to 8.0 (phosphate buffer solutions) and pH in the range of 8.0 to 10.0 (alkaline borate buffer solutions) were prepared in the same way as for solubility experiments).

Technical data for the drug release experiments using basket or paddle apparatus are shown in Table 1.

Table 1. Technical data for the drug release experiments using basket or paddle apparatus.

Number of replicates	6 tablets/experiment. The results are presented as the mean of six units
Dissolution medium	phosphate buffer solutions pH 5.8, 6.8, 7.0, 8.0 and alkaline borate buffer solutions pH 8.0, 9.0, 10.0
Volume of the dissolution medium	900 mL
Temperature of dissolution medium	37 ± 0.5 °C (as prescribed in pharmacopoeias)
Stirring elements	baskets (apparatus 1) and paddles (apparatus 2)
Rotation speeds of the stirring elements	20 rpm, 50 rpm, 100 rpm, 150 rpm and 200 rpm
Sampling times	24 h (the samples were withdrawn every h)
Filtration	10 μm full flow filters for dissolution sampling (Van Kel)
Determination of released diclofenac sodium	UV spectrophotometrically at the wavelength of maximum absorbance at 276 ± 2 nm

Flow through cell (apparatus 4) - drug release conditions

Flow through cell (according to Ph.Eur.) or apparatus 4 (according to USP) is a conventional tester for characterizing dissolution or drug release of active ingredients with low solubility from different types of formulations, especially from modified-release formulations.

Drug release conditions for experiments using flow through cell are presented in Table 2.

Table 2. Technical data for the drug release experiments using flow through cell.

Flow through cell	standard cell of transparent and inert material (d = 22.6 mm) filled with glass beads (d = 1 mm), with one bead of about 5 mm, positioned at the apex to protect the fluid entry tube
Number of replicates	6 tablets/experiment. The results are presented as the mean of six units
Flow rate	10 mL/min
Temperature of dissolution medium	37 ± 0.5 °C (as prescribed in pharmacopoeias)
Position of the tablets	on the holders attached on the top of the cylinder or on the top of a layer of glass beads
Sampling times	12 h (the sample solutions were collected for one h)
Filtration	Whatman glass microfibre filters grade GF/F were used
Dissolution medium	phosphate buffer solution pH 5.8 (prepared according to the prescriptions in the USP 26)
Determination of released diclofenac sodium	UV spectrophotometrically at the wavelength of maximum absorbance at 276 ± 2 nm

Ultraviolet spectrophotometry

The absorbances of filtered sample and standard solutions in solubility studies were measured manually in 1 cm quartz cells using aqueous media as blank solutions. In drug release experiments the sample solutions were automatically withdrawn in specified time intervals from each dissolution vessel respectively and filtered. The absorbances were automatically measured on on-line connected UV spectrophotometer at the wavelength of maximum absorbance at 276 ± 2 nm using 1 mm quartz cells. The standard linear calibration curve was applied and linear relationship in the concentration range of 0.011 mg/mL to 0.133 mg/mL of standard solutions (0.111 mg of diclofenac sodium/mL = 100% working concentration) was established.

Results

Solubility measurements

In the solubility studies purified water for chromatography, hydrochloric acid (0.1 M, 0.01 M, 0.001 M) and different buffer solutions, i.e. acetate buffer solutions (pH 4.1, 4.5, 5.5), phosphate buffer solutions (pH 5.8, 6.0, 6.8, 7.0, 7.4, 7.8, 8.0) and alkaline borate buffer solutions (pH 8.0, 9.0, 10.0) were used. The solubility of diclofenac sodium in mg/mL, depending on the pH of the dissolution medium at ambient temperature (23 ± 2 °C), is shown in Table 3. Solubility determinations were performed in triplicate, therefore, the results presented in Table 3 are presented as the mean of three values.

The influence of different ionic strengths (I) of the dissolution media on the release of diclofenac sodium from lipophilic matrix tablets was also investigated. According to the obtained solubility results of diclofenac sodium in different dissolution media (pH, I) and considering the pK_a of diclofenac sodium ($pK_a = 4$)[8] it was assumed that the drug release of diclofenac sodium occurs at higher pH.

Therefore, the solubility in the dissolution media with different I and pH in the range of 5.8 to 8.0 (phosphate buffer solutions) and pH in the range of 8.0 to 10.0 (alkaline borate buffer solutions) was checked. Dissolution media with different ionic strengths were prepared by diluting stock buffer solutions prepared according to the prescriptions in the USP 26 and by adding potassium chloride to the stock buffer solutions (specified in Experimental/Methods/Solubility characteristics).

Table 3. Solubility of diclofenac sodium (in mg/mL) in stock buffer solutions prepared according to the prescriptions in the USP 26 and ionic strengths in mol/L of the media at ambient temperature.

Medium	Solubility (mg/mL)	Ionic strength,I (mol/L)
Hydrochloric acid 0.1 M	0.0012	0.1
Hydrochloric acid 0.01 M	0.0017	0.01
Hydrochloric acid 0.001 M	0.28	0.001
Acetate buffer solution pH 4.1	0.0033	0.05
Acetate buffer solution pH 4.5	0.0036	0.05
Acetate buffer solution pH 5.5	0.036	0.05
Purified water	14.18	0
Phosphate buffer solution pH 5.8	0.14	0.06
Phosphate buffer solution pH 6.0	0.15	0.06
Phosphate buffer solution pH 6.8	0.67	0.08
Phosphate buffer solution pH 7.0	1.36	0.09
Phosphate buffer solution pH 7.4	5.15	0.12
Phosphate buffer solution pH 7.8	12.00	0.13
Phosphate buffer solution pH 8.0	12.14	0.14
Alkaline borate buffer solution pH 8.0	17.17	0.05
Alkaline borate buffer solution pH 9.0	15.18	0.07
Alkaline borate buffer solution pH 10.0	12.08	0.09

The solubility of diclofenac sodium in phosphate buffer solutions and alkaline borate buffer solutions with different ionic strengths at ambient temperature is shown in Table 4. Moreover, preparations of dissolution media with lower and higher ionic strengths than stock buffer solutions are presented in Table 4. Solubility determinations were performed in triplicate, therefore, the results presented in Table 4 are presented as the mean of three values.

Physicochemical parameters affecting the release of diclofenac sodium

In the drug release studies phosphate buffer solutions with pH in the range of 5.8 to 8.0 and alkaline borate buffer solutions with pH in the range of 8.0 to 10.0 were used, because it was presumed (pK_a, solubility results) that the drug release of diclofenac sodium occurs in this pH range.

In the following Figures the results are presented as the mean percentage of released diclofenac sodium from six tablets. By error bars confidence intervals are indicated.

Different dissolution apparatus (apparatus 1/basket apparatus and apparatus 2/paddle apparatus) and different dissolution media (phosphate buffer solutions and

alkaline borate buffer solutions) were applied and results of released diclofenac sodium are shown in Figures 1 and 2.

Table 4. Preparation of phosphate and alkaline borate buffer solutions and solubility of diclofenac sodium in mg/mL in these media with different pH and different ionic strengths in mol/L at ambient temperature.

Medium	pH	g KCl / L or dilution	Ionic strength, I (mol/L)	Solubility (mg/mL)
Phosphate buffer solution	5.8	dilution 6:10	0.04	0.24
		dilution 8:10	0.05	0.19
		5.4	0.22	0.12
		10.8	0.38	0.096
	6.8	dilution 6:10	0.05	1.33
		dilution 8:10	0.06	1.01
		8.2	0.29	0.60
		16.4	0.50	0.39
	7.8	dilution 6:10	0.08	13.23
		dilution 8:10	0.10	12.55
		13.0	0.47	6.77
		26.1	0.82	4.43
	8.0	dilution 6:10	0.08	14.23
		dilution 8:10	0.11	13.25
		13.6	0.51	7.70
		27.2	0.88	4.72
Alkaline borate buffer solution	8.0	dilution 1:10	0.005	18.58
		dilution 5:10	0.03	18.55
		5.3	0.18	14.23
		10.5	0.32	12.33
	9.0	dilution 1:10	0.007	17.83
		dilution 5:10	0.04	16.22
		6.9	0.26	12.14
		13.7	0.44	10.91
	10.0	dilution 1:10	0.009	17.66
		dilution 5:10	0.05	14.71
		9.2	0.33	11.34
		18.4	0.57	8.57

Additionally, apparatus 4 (flow through cell), which is used in the case of low solubility drugs,[2,9,10] was checked. Flow through cell was used for checking the release of diclofenac sodium in phosphate buffer solution pH 5.8, where the solubility of diclofenac sodium is the lowest among dissolution media used in the present study. In

this apparatus the tablets were placed in two different positions: on special holders attached on the top of the flow-through cell and on the top of the layer of glass beads.

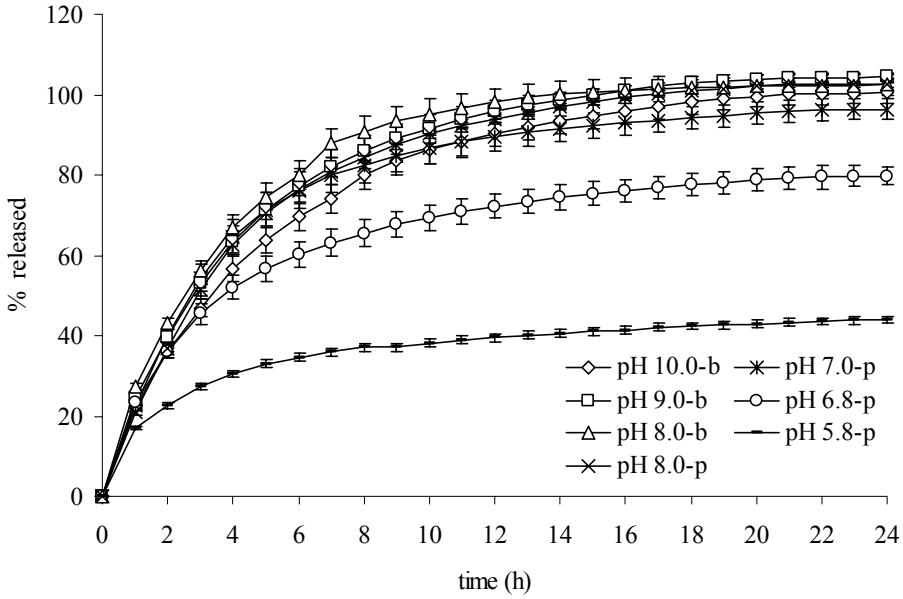

Figure 1. Influence of different dissolution media on the release of diclofenac sodium from lipophilic matrix tablets using ***apparatus 1/basket apparatus*** (***Media: specified in Experimental/Methods***. V: 900 mL. Rotation speed: 100 rpm. Temperature: 37 ± 0.5 °C). -b: Alkaline borate buffer solutions. -p: Phosphate buffer solutions.

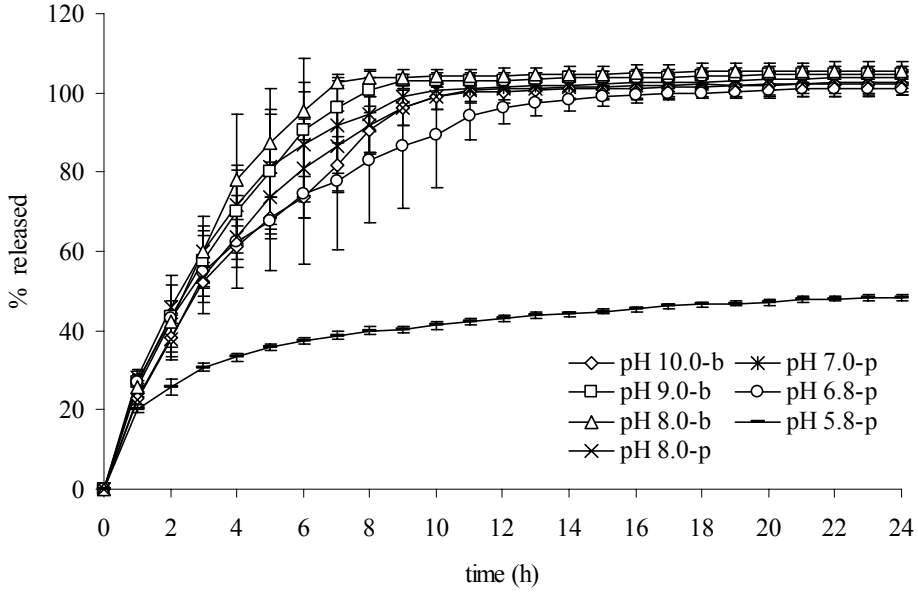

Figure 2. Influence of different dissolution media on the release of diclofenac sodium from lipophilic matrix tablets using ***apparatus 2/paddle apparatus*** (***Medium: specified in Experimental/Methods***. V: 900 mL. Rotation speed: 100 rpm. Temperature: 37 ± 0.5 °C). -b: Alkaline borate buffer solutions. -p: Phosphate buffer solutions.

Comparison of released diclofenac sodium in phosphate buffer solution pH 5.8, using three different dissolution apparatus, is shown in Figure 3.

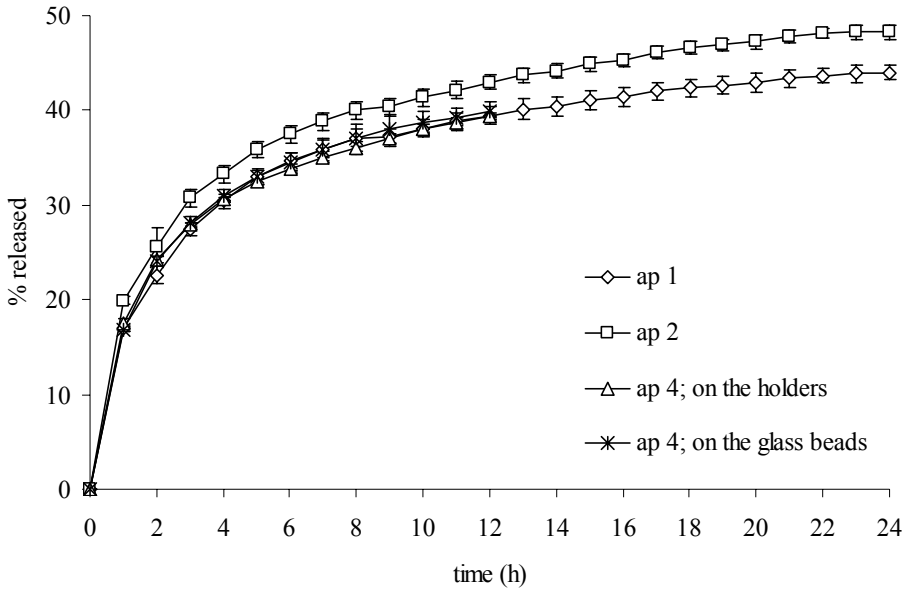

Figure 3. Influence of different dissolution apparatus on release of diclofenac sodium from lipophilic matrix tablets in ***phosphate buffer solution pH 5.8*** (***Apparatus 1 (baskets) and 2 (paddles)***. V: 900 mL. Rotation speed: 100 rpm. Temperature: 37 ± 0.5 °C. ***Apparatus 3 (flow through cell)***. Flow rate: 10 L/min. Tablets were placed on the holders and on top of a layer of glass beads).

Since phosphate buffer solutions prepared according to the prescriptions in the USP 26 better simulate intestinal conditions than alkaline borate buffer solutions,[6,11,12] additional tests were performed in these media.

Influences of the different rotation speeds of the stirring elements (20, 50, 100, 150 and 200 rpm) on the drug release in phosphate buffer solutions pH 5.8 and 8.0 are shown in Figure 4 and Figure 5.

In the drug release studies different ionic strengths of the dissolution medium were also applied and the results (in phosphate buffer solutions pH 5.8 and 8.0) are presented in Figure 6 and Figure 7.

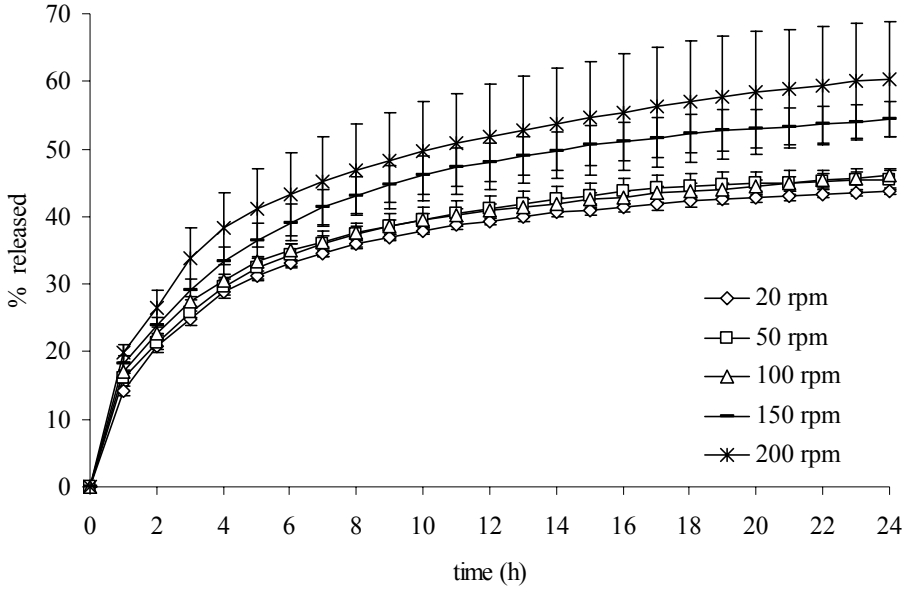

Figure 4. Influence of different rotation speeds of the stirring elements on the release of diclofenac sodium from lipophilic matrix tablets in ***phosphate buffer solution pH 5.8***. (Apparatus: 1/basket apparatus. V: 900 mL. ***Rotation speeds: 20 rpm, 50 rpm, 100 rpm, 150 rpm and 200 rpm***. Temperature: 37 ± 0.5 °C).

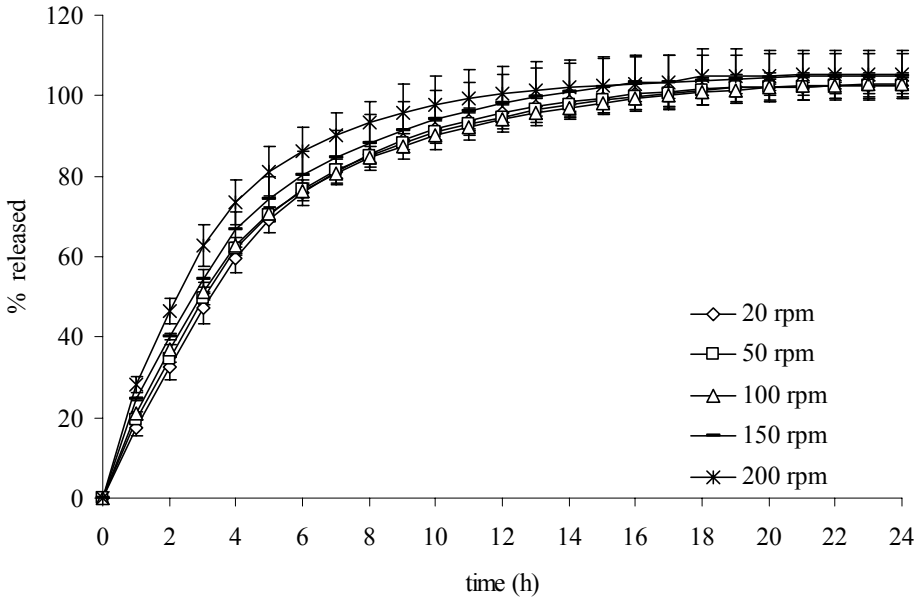

Figure 5. Influence of different rotation speeds of the stirring elements on the release of diclofenac sodium from lipophilic matrix tablets in ***phosphate buffer solution pH 8.0***. (Apparatus: 1/basket apparatus. V: 900 mL. ***Rotation speeds: 20, rpm, 50 rpm, 100 rpm, 150 rpm and 200 rpm***. Temperature: 37 ± 0.5 °C).

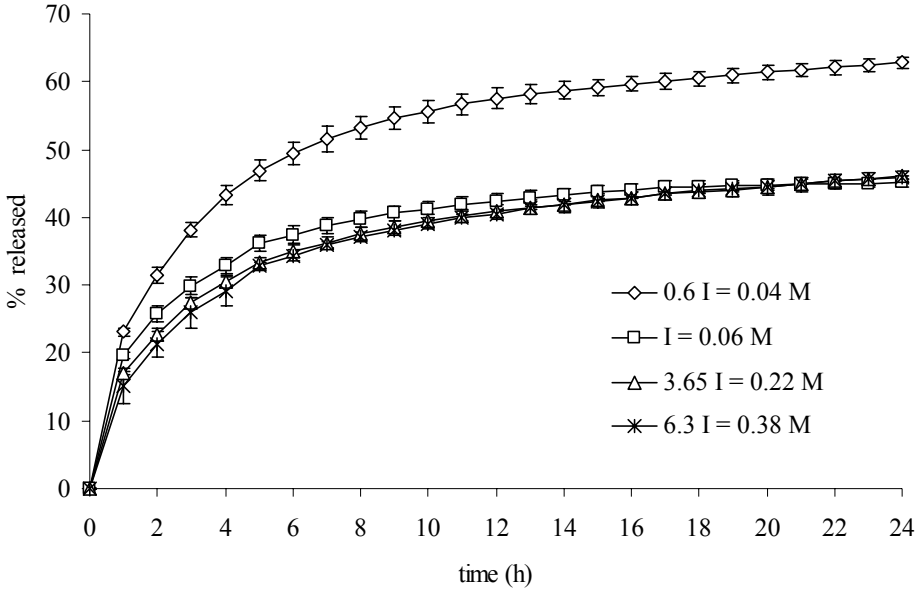

Figure 6. Influence of different ionic strengths of dissolution medium on the release of diclofenac sodium from lipophilic matrix tablets (Apparatus: 1/basket apparatus. ***Medium: phosphate buffer solution pH 5.8. Ionic strengths: 0.04 M, 0.06 M, 0.22 M, 0.38 M***). V: 900 mL. Rotation speeds: 100 rpm. Temperature: 37 ± 0.5 °C). I = ionic strength of the stock buffer solution.

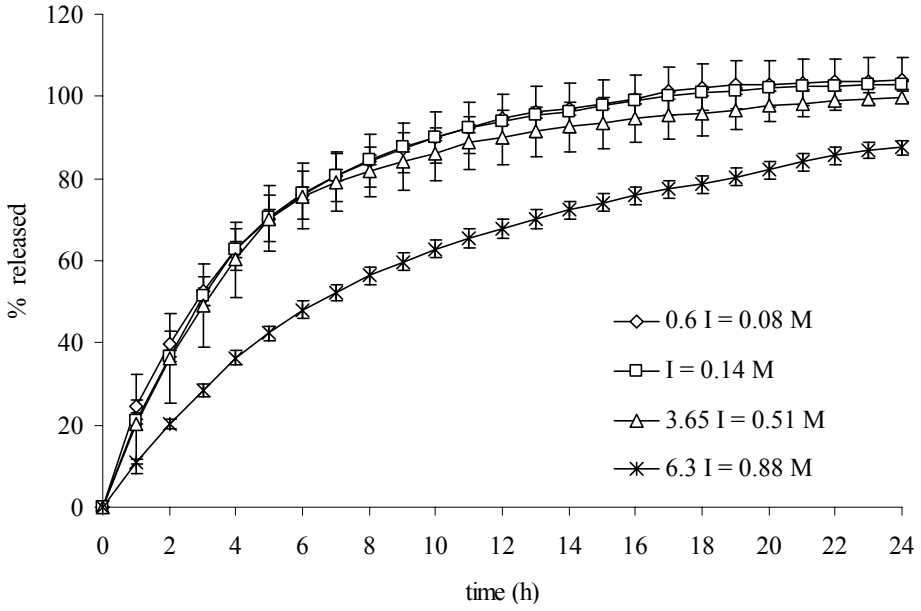

Figure 7. Influence of different ionic strengths of dissolution medium on the release of diclofenac sodium from lipophilic matrix tablets (Apparatus: 1/basket apparatus. ***Medium: phosphate buffer solution pH 8.0. Ionic strengths: 0.08 M, 0.14 M, 0.51 M, 0.88 M***). V: 900 mL. Rotation speeds: 100 rpm. Temperature: 37 ± 0.5 °C). I = ionic strength of the stock buffer solution.

Discussion

In accordance with guidelines for the development of drug release methods, solubility experiments were the first to be performed.[11,12] Referring to the results in Tables 3 and 4 it is evident that the solubility of diclofenac sodium depends on pH, ionic strength and composition of the aqueous medium. Diclofenac sodium is a salt of a weak acid (2-[(2,6-dichlorophenyl)amino]benzene-acetic acid). Therefore, the solubility strongly depends on the ionization constant, K_a, and on the pH of the dissolution medium. The experiments confirmed that the solubility of diclofenac sodium is higher in the media with pH between 7.0 and 10.0. On the contrary, the active ingredient is only slightly soluble or practically insoluble in acidic media. In the dissolution media with pH values more than 1 unit bellow pK_a, the active ingredient is presented mostly in its free acid form, which is even less soluble than the salt.[13] Consequently, the solubility of the active ingredient in the dissolution medium with pH less than 3 is very low. As the pH value increases, the solubility of the active ingredient increases due to the contribution from the ionized form until the highest solubility of the ionized form is reached in phosphate buffer solution pH 8.0.

Chadha et al reported that enthalpy of solution of active ingredients is an important thermodynamic property and can be utilized for solubility characterization. They also found that enthalpy of the solutions of diclofenac sodium is highly pH dependent. They determined that the enthalpy of solution of diclofenac sodium remained constant at pH higher than 6 when only one of the species of the drug predominated. At pH lower than 6 both ionized and unionized forms contribute towards enthalpy of solution of diclofenac sodium. Therefore, the enthalpy decreased with lower pH. Between pH 7 to 9 enthalpy of the solution varied very little.[14]

Thus, solubility results in our study well correlate with results of Chadha's investigations of enthalpy of solutions of diclofenac sodium and can be explained with enthalpies.

The solubility of diclofenac sodium also depends on the composition of buffer solutions, which is indicated in the comparison of results of dissolved diclofenac sodium in phosphate buffer solution and alkaline borate buffer solutions with the same pH (pH 8.0). Furthermore, the solubility depends also on ionic strengths of the dissolution media. In phosphate and alkaline borate buffer solutions a similar process occurs. In

buffer solutions with higher ionic strengths and with the same pH, the solubility of diclofenac sodium is lower than in buffer solutions with lower ionic strengths. It is also evident that the influence of ionic strengths on the solubility of diclofenac sodium in alkaline borate buffer solutions is smaller with respect to phosphate buffer solutions with the same pH.

The release of diclofenac sodium from lipophilic matrix tablets was studied considering different experimental conditions: pH of the dissolution medium (5.8, 6.8, 7.0, 8.0, 9.0, 10.0), composition of the dissolution medium (phosphate buffer solutions and alkaline borate buffer solutions), ionic strength of the dissolution medium, type of apparatus (basket and paddle apparatus, flow through cell) and rotation speeds of the stirring elements (20 rpm, 50 rpm, 100 rpm, 150 rpm and 200 rpm).

From the results presented in Figure 1 and Figure 2 it can be concluded that drug release conditions when apparatus 2 (paddle apparatus) was used were too extreme and aggressive, and after a few hours the tablets were mechanically damaged by the stirring paddles. For this reason, the controlled and prolonged release of diclofenac sodium is disabled. This is also indicated in lower reproducibility of the results between second and tenth h of duration of the drug release test, when using apparatus 2 (paddle apparatus). It is evident that apparatus 1 (basket apparatus) is more appropriate for the drug release studies of diclofenac sodium from lipophilic matrix prolonged-release tablets compared to apparatus 2 (paddle apparatus).

Referring to the solubility data of diclofenac sodium in Table 3 in the dissolution media with pH higher than 6.0, the sink conditions are obtained.

When the sink conditions cannot be achieved in a conventional dissolution tester with 1000 mL dissolution vessels (apparatus 1 or 2), apparatus 4/flow through cell should be applied.[2,9,10] The sink conditions for the drug release of diclofenac sodium from lipophilic matrix tablets are not achieved when applying apparatus 1 or 2 with 900 mL of the dissolution medium (phosphate buffer solutions pH 5.8). Hence, this medium was used for checking the effect of apparatus 4/flow through cell on the drug release of diclofenac sodium.

From the results presented in Figure 3 it can be deduced that there are no significant differences between the drug release test performed by apparatus 1 (basket apparatus), apparatus 2 (paddle apparatus) or apparatus 4 (flow through cell) in

phosphate buffer solution pH 5.8. For this reason, it can be concluded that a low percentage of released diclofenac sodium is the consequence of low solubility of the active ingredient in this medium and not the result of unattained sink conditions.

Different rotation speeds of the stirring elements (rotating baskets) were also checked. In Figure 4 it is shown that the release of diclofenac sodium from lipophilic matrix tablets in phosphate buffer solution pH 5.8 increases with higher rotation speeds. However, repeatability of the drug release results is lower at the rotation speeds 150 rpm and 200 rpm. In phosphate buffer solution pH 8.0 the differences between release rates obtained at different rotation speeds are smaller; however at higher rotation speeds the reproducibility is worse as it is shown in Figure 5.

Finally, different ionic strengths of the dissolution media were verified. In phosphate buffer solution pH 5.8 with the lowest ionic strengths the highest profile of released diclofenac sodium is obtained. But there are no significant differences between drug release profiles in phosphate buffer solution pH 5.8 with higher ionic strengths. In phosphate buffer solution pH 8.0 with the highest ionic strength, the release profile is considerably lower than in media with the same pH and lower ionic strengths.

These results correspond to the results obtained in solubility experiments of diclofenac sodium.

Conclusions

In conclusion, solubility of diclofenac sodium is higher in dissolution media with lower ionic strengths and higher pH. Composition of the dissolution medium also has influence on the solubility of diclofenac sodium. Release of the active ingredient depends mainly on the rotation speeds of the stirring elements, especially in media with lower pH and on the type of the dissolution apparatus. Higher release rates are achieved in media with lower ionic strengths and higher pH.

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Povzetek

V sklopu raziskav smo študirali vplive različnih fizikalno kemijskih parametrov na sproščanje diklofenak natrijeve soli (natrijeve soli 2-[(2,6-diklorofenil)amino] benzen ocetne kisline) iz tablet s podaljšanim sproščanjem z lipofilnim ogrodnim sistemom. Najprej smo določili topnost dikofenak natrijeve soli v odvisnosti od sestave, ionskih jakosti in pH vodnih medijev. Na osnovi dobljenih rezultatov smo preučevali različne parametre, ki lahko vplivajo na sproščanje zdravilne učinkovine iz tablet. Spremljali smo vplive različnih tipov aparatur za določevanje sproščanja, spreminjajoče hitrosti mešalnih elementov, pufrske raztopine v območju pH 5,8 do 10,0 in različne ionske jakosti vodnih medijev. Količino sproščene diklofenak natrijeve soli smo določili UV spektrofotometrično pri absorpcijskem maksimumu pri valovni dolžini 276 ± 2 nm. Ugotovili smo, da je topnost diklofenak natrijeve soli precej odvisna od sestave in pH vodnega medija, nekoliko manj pa od ionskih jakosti uporabljenega medija. Poleg navedenih parametrov pa na sproščanje zdravilne učinkovine iz tablet vpliva uporaba različnih tipov aparatur, predvsem pa hitrost vrtenja mešalnih elementov.