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RESEARCH PAPER

Diclofenac Sodium Microcapsules: In Vitro Testing Considerations

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ABSTRACT

Despite the great proliferation of microcapsules in the pharmaceutical field, there are no official guidelines for "in vitro" testing. This lack of official information means that many devices and processes have to be used to determine accurately the dissolution characteristics of microcapsules. Our objective is to review the "in vitro" dissolution tests performed by researchers and to establish the best conditions to test diclofenac sodium microcapsules obtained by using a polymeric solvent extraction method, with three different in vitro systems. Some mathematical adjustments have been made with the results, in order to establish the most appropriate in vitro dissolution system.

INTRODUCTION

One of the most important goals in the pharmaceutical field is the prediction of "in vivo" behavior with an "in vitro" test, so that "in animal" experimentation can be reduced. For this reason, FDA, USP, BP, and others have accepted the use of dissolution tests to study drug product bioavailability or bioequivalence. However, we have to take into consideration that the dissolution characteristics of a pharmaceutical dosage form can be modified by the formulation and manufacturing process (1). In consequence, these tests are not only used to predict bioavailability but are also useful in the early stages of drug development and formulation.

For whatever reason, dissolution tests have become an interesting and essential assay, and a tool used in the detection of manufacturing variations, as they provide enough information to permit the next step, the "in vivo" assay. Although for many oral dosage forms, these kind of tests have been well defined, there is no official information about the device to be used or the conditions to be established by researchers with the new oral drug delivery systems, such as microcapsules. This lack of information and the absence of a good "in vitro–in vivo" correlation for any one system have caused a great discrepancy among researchers. As a result, different devices, systems, and conditions have been designed and at present are being used all over the world.

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These facts justify our purpose: to look for the best conditions for performance of an easy and reproducible "in vitro" dissolution test, which must be able to detect manufacturing variations. We have structured our work as follows:

1. Review part: comprises a review of the different dissolution devices, systems, and conditions employed in microcapsule testing. The review goes on to refer to different pharmaceutical dosage forms of diclofenac sodium.
2. Experimental part: comprises a description of the microencapsulation process of diclofenac sodium and the results obtained in the dissolution test performed with three different devices.

REVIEW

"In Vitro" Systems Used with Microcapsules

Microencapsulation can be described as a process in which thin coatings of polymeric material are deposited around particles of solids or droplets of liquids (2).

Although the first research in this field was carried out between 1930 and 1940 by Bungerberg de Jong (3), the first microcapsules to be commercialized did not appear until 1968, in the form of pressure-sensitive copying paper (4). Since that time, hundreds of microencapsulation processes have been developed in different fields.

Once microcapsules are obtained, parameters such as size and shape, the payload of the process, encapsulation efficiency, and the "in vitro" dissolution behavior are subjected to study. Thus, if two or more manufacturing processes are performed, easy and reproducible tests become necessary. It is therefore necessary to pay attention to the following parameters for the selection of an in vitro model, because they have a great influence on dissolution (5,6):

- Temperature: Must be similar on physiological conditions.
- Container: The shape is linked to the agitator device. It is should be thermostable and adapted to the volume of the solvent necessary for the study.
- Agitation: Places the substrates in contact, increases fluid diffusion, maintains a constant temperature, and favors a regular transference of material.
- Volume: Depends on the affinity of the active substance to the solvent. Saturation problems must be avoided.
- Media: Distilled water is the easiest medium to choose, but pH variable media are used in order to reproduce digestive phases. Additives such as surfactants, polysorbates, or enzymes (pepsin, pancreatin) can be incorporated.
- pH: The segments of the G.I. tract differ in the specific surface and the protonic activity of their digestive secretions.

In our search for the most appropriate device and conditions to test our diclofenac sodium microcapsules, and in the absence of any official guidelines, we decided to consult the literature on microcapsules, as we thought this would be the best way to find the device most employed by the different researchers. Unfortunately, however, the variety of devices, rates of agitation, dissolution media, and other variables used to not permit us to elucidate which was the most appropriate system, as there was no relationship between these parameters, as can be observed in Table 1.

"In Vitro" Systems Concerned with Diclofenac Sodium Oral Dosage Forms

Due to this lack of any scientific explanation for using one or another device, we decided to take into account the characteristics of our active substance, diclofenac sodium. This substance is a nonsteroidal antiinflammatory agent which undergoes an intramolecular cyclization in an acidic medium (37), so that the presence of gastric juices may result in the inactivation of the compound. Moreover, the solubility of this substance depends on the pH of the medium, so that it does not exceed 2 mg/ml in acidic conditions but is freely soluble above pH 6.5 (38–40).

This insolubility in acidic conditions is perhaps the most important factor to consider, as it is not possible to perform the dissolution at these low pHs, because only a very small percentage will be dissolved. This fact may lead to erroneous conclusions, and this low release in acidic conditions could be interpreted as the result of the favorable characteristics of the gastric resistance of the polymer or the favorable characteristics of the microcapsules that prevent the release of the active substance, instead of being interpretated as the result of the very low solubility of this substance at those pHs.

Our next step in setting up the in vitro conditions was to look for references concerning all kinds of oral diclofenac sodium pharmaceutical forms. The results are shown in Table 2.

Table 1

Active Substance	Coating	Sample Weight (mg)	Device	Agitation Speed	Media	Vol. (ml)	Ref.
Pilocarpine	Gelatin Albumin	10 (7)	Magnetic stirrer	—	Distilled water	100	
Methylglyoxal	Polymethylmeth-acrylate Gelatin	1800	Magnetic stirrer	—	HCL (4.6%)	500	(8)
Mitomycin-C	Albumin	30	Magnetic stirrer	—	Phosphate buffer (pH 7.4)	30	(9)
Griseofulvin	PLA	1.5 (pure drug)	Spin filter dissolution test	600 rpm	HCl–KCl (pH 2.0)	900	(10)
5-Fluorouracil	EC	—	Shaker bath	—	pH 1.2/pH 7.4/pH 9.6/ saline solution	—	(11)
Chlorpheniramine maleate	EC	20	Horizontal shaker	26 str/min	0.1 M phosphate buffer	50	(12)
Salbutamol sulfate	CAP	—	Flask method	—	0.2 M KCl–HCl (pH 1.2)	—	(13)
Antibacterial drugs	Albumin	—	G-25 Brunswic shaker	—	Buffer solution (pH 3/pH 7/pH 9)	200	(14)
Viral antigen concavalin-A	CAP	2500	Clinical rotator	160 rpm	Gastric juice (USP) Simulated intestinal juice (USP)	20 20	(15)
Phenobarbitone sodium	Eudragit-RS	200	Beaker method	100 rpm	Distilled water	500	(16)
Theophylline	Nylon 6, 10	30	Rotating bottle	—	0.1 N HCl Phosphate buffer (pH 7.4)	60	(17)
Sodium salycilate	HEA	1125	Erweka device	40 rpm	Buffer solution (pH 7.4)	500	(18)
Phenazopyridine hydro-chloride	EC	25	Erweka DT-6	100 rpm	0.1 N HCl	900	(19)
Lipoproteins	CAP	200	Dissolution test	—	pH 1.2 pH 5.6 pH 7.5	500 750 1000	(20)
5-Fluorouracil	EC	200	—	—	pH 7	100	(21)
Potassium chloride	CAP/EC/HPMC/CAB	500	—	100 rpm	HCl (pH 2)	2000	(22)
Progesterones	Albumin Gelatin	12	—	—	Buffered solution (pH 7.4)	100	(23)

(*continued*)

Table 1 Continued

Active substance	Coating	Sample Weight (mg)	Device	Agitation Speed	Media	Vol. (ml)	Ref.
Oxprenolol	Gelatin	—	—	60 rpm	0.1 N HCl	—	(24)
Bacampicillin hydrochloride	EC	500	USP—paddle	100 rpm	Water	500	(25)
Vitamin C, B_6, isoniazid, Theophylline	EC	200	Paddle	200 rpm	1st fluid disintegration (JPX)	900	(26)
Sodium salicylate	Milk proteins	—	Paddle	40	Distilled water	1000	(27)
Theophylline	EC	200	Paddle	50	Intestinal fluid	900	(28)
Theophylline	Cellulose propionate	2030	Paddle	100	Intestinal fluid Gastric fluid	1000	(29)
Naproxen	Cetyl alcohol Stearyl alcohol	50 pure subst.	Paddle	50 rpm	Intestinal fluid Gastric fluid	900	(30)
Aspirin	CMEC/HPMCAS-L/ HP-55/CAP/EUD-L/ EUD-/MPM-05/shellac	100	Paddle	100 rpm	1st disintegration test fluids (JPXI)	900	(31)
Cartrazine	HPMCP	500	USP—paddle	100 rpm	0.1 M HCl 0.2 M Na_3PO_4	750	(32)
Aspirin	CAP	100	USP—basket	100 rpm	Distilled water Simulated gastric fluid Intestinal fluid (pH 7.2)	900	(33)
Phenacetin	CAP	65	Flow cell column	50 ml/min	0.1 M HCl/0.2 M NaCl	500	(34)
Doxyphylline Theophylline	PVA	—	Flow-through cell	20 ml/min	Phosphate buffer (pH 6.8)	—	(35)
Nifedipine	PLGA	10	Flow-through cell	8 ml/min	0.1 M phosphate buffer (pH 7.0)	2500	(36)

Nevertheless, we again observed a great discrepancy between the systems and rate of agitation. For this reason, Bain et al. (41) conclude that SGMA (simulator of gastric motility) has the best "in vitro versus in vivo" correlation.

Regarding rate of agitation Bain et al. (41) and Chetty et al. (38) do not observe a great difference between the results obtained with 25, 50, and 100 rpm. On the other hand, they observed differences with 150, 200, and 250 rpm.

We should mention the work of Chetty et al. (38) concerning the influence of ionic concentration of the medium. The results indicate that this factor depends on the polymer of the pharmaceutical dosage form. The same results are obtained in regard to the presence of NaCl in the dissolution medium.

Finally, concerning the dissolution volume, we can appreciate a discrepancy between researchers, where fluctuations of 500–1000 ml can be observed. Therefore, the USP recommends a volume of 900 ml with delayed delivery systems (6).

Once we have chosen the dissolution medium (basic conditions), the volume (900 ml) and the temperature of the assay (37°C), we have to choose the device. Hanson (1) indicates the use of basket system with 80-mesh and higher screening for microcapsules. This mesh size must retain the particles in the basket but must allow solvent penetration without clogging.

However, many researchers use the paddle (USP—II) instead of the basket (USP—I), and some of them use the flow-through cell (USP—IV) with microcapsules, as can be seen in Tables 1 and 2. This is possibly because the use of this latter device is mainly indicated for substances with a very low solubility.

MATERIALS AND MICROCAPSULE PREPARATION

Materials were: diclofenac sodium (Impex Química), cellulose acetate phthalate (Eastman Kodak), Vaseline oil, acetone, ethanol 96%, chloroform, synperonic 61, HLB 3 (PPG/PEG, 9/1, Serva).

The polymeric solvent extraction method was used in microcapsule preparation (50), as described in Fig. 1.

One gram of drug was dispersed in 200 ml of Vaseline oil; 0.75 ml of Synperonic L61 was added to the dispersion; 20 ml of cellulose acetate phthalate (CAP) previously dissolved in a mixture of acetone/ethanol (9/1, v/v) was incorporated in the dispersion to form a W/O emulsion. A constant stirring of 300 rpm (four steel blade Heidolph stirrer) was applied for 20 min. After this time the polymeric solvents (acetone:ethanol) had diffused to the Vaseline oil causing the precipitation of the polymer surrounding the crystals of diclofenac sodium. After the diffusion took place, the solvents evaporated. The microcapsules were washed with chloroform to eliminate Vaseline oil residues.

RESULTS

Microcapsule Appearance and Granulometric Distribution

The appearance observed with a magnifying glass is shown in Fig. 2.

The hand sieving technique was used to separate the different granulometric fractions, graphically represented in Fig. 3.

The statistical diameters (arithmetic: D_a and volume/surface: $D_{v/s}$ were calculated by Hatch–Choate equations (51). The results are shown in Table 3. The granulometric fraction corresponding to 710–840 μm was separated for use in the drug content determination and dissolution test.

Drug Content Determination

This assay was performed to determine the yield of the drug and the efficiency of the microencapsulation process.

Known amounts of microcapsules were dissolved in 0.1 N NaOH solution with the aid of an ultrasonic bath. Diclofenac sodium was spectrophotometrically assayed (Beckman DU-6) using a calibration curve at a wavelength of 275 nm, previously validated. The results are shown in Table 3.

"In Vitro" Dissolution Test

We performed an "in vitro" assay, in triplicate, with three apparatus (I, II, and IV proposed by USP) in order to elucidate which is the most appropriate to test our microcapsules. The conditions of our assays are expressed below:

- Paddle apparatus: 50 rpm, which corresponds to 100 rpm in basket (1,48).
- Basket apparatus: 100 rpm, mesh size = 160 μm.
- Flow-through cell apparatus: 4 ml/min. This low flow was selected to avoid fast dissolution of the

Table 2

Form	Polymer	Sample Weight (mg)	Device	Agitation Speed	Media	Vol. (ml)	Ref.
Microcapsules	EC	100	USP Erweka, DT-6	100 rpm	0.1 N HCl/phosphate buffer (pH 7.4)	500	(42)
Microcapsules	Ca-alginate	—	USP XXII—basket	—	Gradual pH change	500	(43)
Microcapsules	Chitosan-H	—	USP—paddle	100 rpm	Phosphate buffer (pH 6.8)	500	(44)
Microcapsules	HPMCP	0.1	Continuous flow	2 ml/min	0.2 M Na_2HPO_4–NaH_2PO_4 (pH 6.8)	—	(45)
Microcapsules	Nylon-6, 10	100	Continuous flow	7 osc./min	0.2 M Na_2HPO_4–NaH_2PO_4 (pH 6.8)	—	(46)
Microcapsules Tablets	Acrylic latex	—	USP—paddle	50 rpm	0.1 N HCl/phosphate buffer (pH 6.8)	—	(47)
Tablets	Avicel/EC/EUD-RS-100PM	—	USP—paddle	50 rpm	pH 1.2	500	(48)
				130 rpm	pH 6.8	650	
Tablets	Cetoestearyl alcohol/ HPMC	100 pure subst.	IDA	25–250	Phosphate buffer (pH 6.8)	1000	(41)
			SGMA	30		300	
			USP—basket	25–250		1000	
			USP—paddle	25–250		1000	
Matrix Tablets	Cetyl-alcohol HPMC	100 pure subst.	USP—paddle	60/100/200 rpm	Phosphate buffer Na_2HPO_4–H_2PO_4 (pH 6.8)	—	(38)
Tablets	EC/EUD/polytetra flucroethylene	—	Continuous flow	10 ml/min	pH 2.0/pH 4.0/pH 6.5/pH 8.0	80	(49)
Tablets/ capsules	—	100 pure subst.	Flow-through	40 ml/min	pH 1.5/pH 5.3/pH 6.5/pH 7.2	1000	(40)
			Paddle	100 rpm		500	
Pellets/ tablets	EUD-RS-12, 5	100 pure subst.	USP—basket	100 rpm	pH 3.0/pH 7.4/pH 6.8/ distilled water	900	(39)
			USP—paddle	50 rpm			

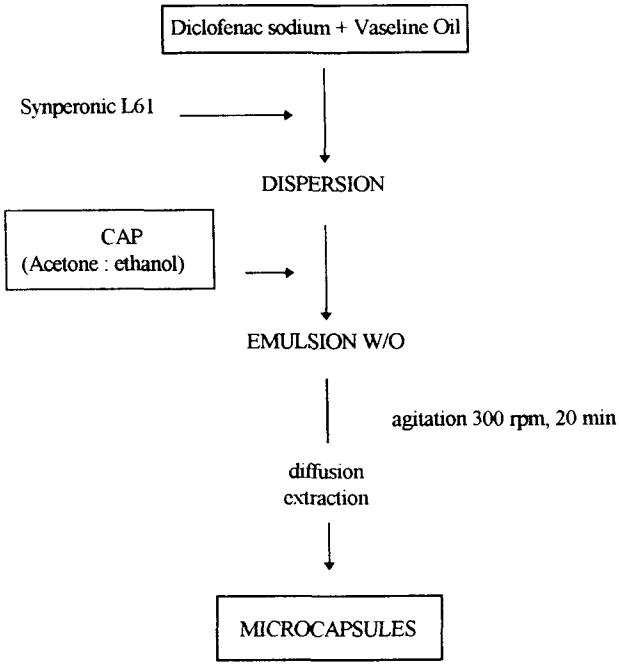

Figure 1. Schematic representation of microencapsulation process.

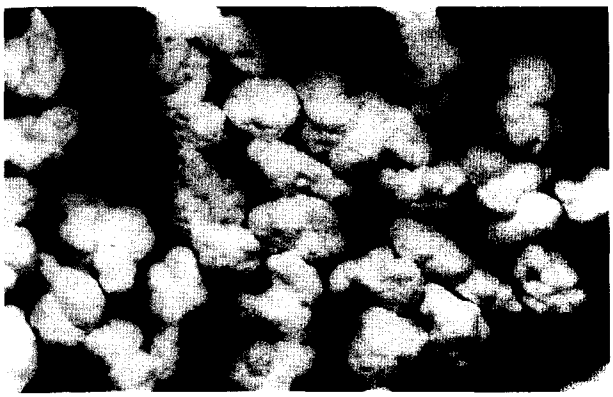

Figure 2. Photograph of microcapsules obtained, taken with a magnifying glass.

coat and because of the high solubility of diclofenac sodium.

- In all experiments the phosphate buffer (pH 6.8) was used throughout the assay.
- Samples of microcapsules: 100 mg.
- Temperature: 37° ± 0.1°C.

All samples were withdrawn from the test device and filtered through a 0.45-μm millipore filter. Diclofenac sodium was determined spectrophotometrically at 275 nm using a Beckman DU-6 spectrophotometer. Figure 4 shows the dissolution profiles obtained with the three systems. The results of the percentages of diclofenac sodium released into the media are shown in Table 4. These percentages have been calculated from the real content of active substance.

DISCUSSION

We can appreciate obtaining similar results when the systems USP—I (100 rpm) and USP—II (50 rpm) as was expected, but these values were lower when we used the system USP—IV (4 ml/min).

It is important to note that when we used the paddle apparatus microcapsules remained floating in the medium because of the low density. We therefore considered it possible to minimize floatability using the baskets, but once the assays had been performed we realized that microcapsules were floating inside the baskets, and that some of them were leaving the baskets due to size decrease as the enteric coat dissolved.

On the other hand, when we used the flow-through cell, we observed an agglomeration process in the first stage. This fact and the low flow explain the slower dissolution.

Table 5 shows the in vitro parameters t_{50}, t_{75}, t_{90}, t_{100}, and their coefficients of variation (CV). These dissolution parameters have been calculated by graphic interpolation. Regarding the *CV* we can appreciate that the lower values correspond to paddles (USP—II) and baskets (USP—I), while the higher values correspond to the flow-through cell (USP—IV).

Different mathematical approaches were used on the data of the dissolution assay: zero-order, first-order, Higuchi, Hixon–Crowell, and Wagner (6). The results of these approaches and the dissolution efficiency (DE) are shown in Table 6. The USP—IV gives the best lin-

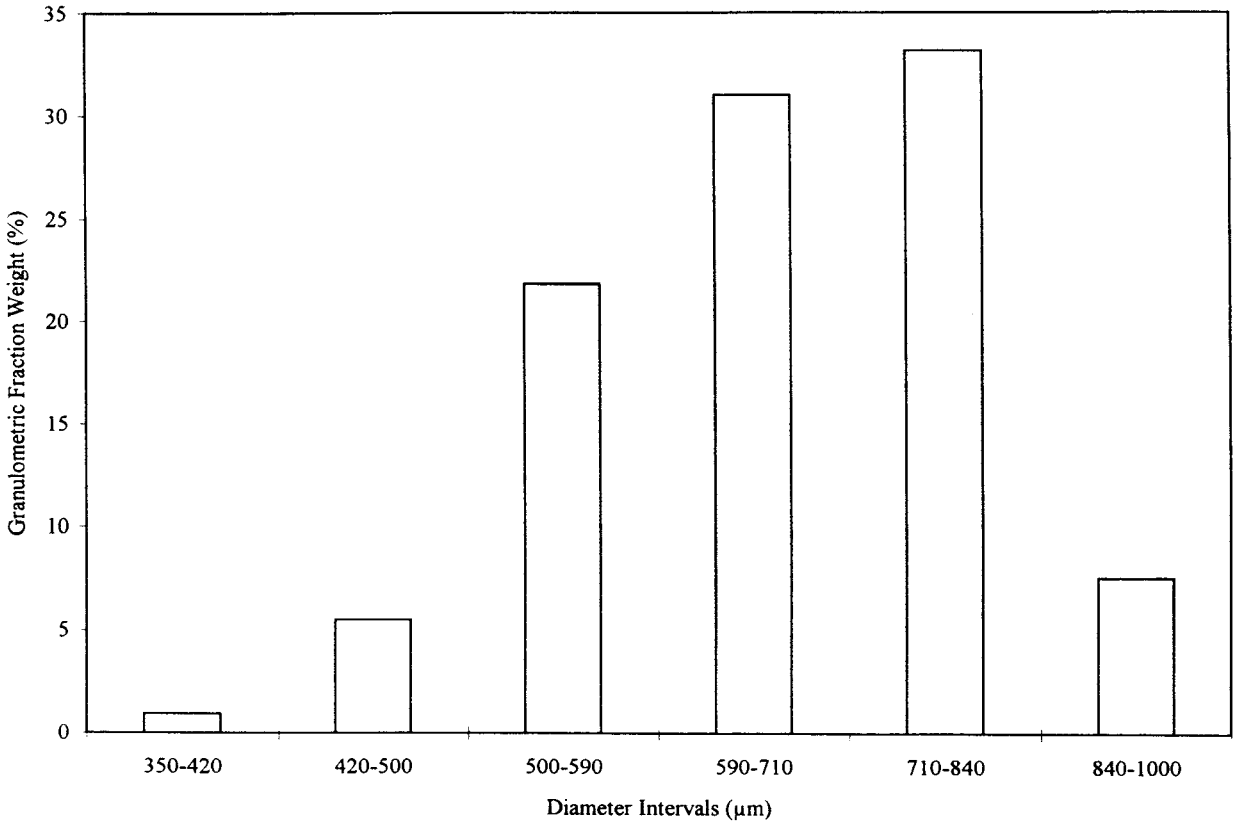

Figure 3. Granulometric distribution of microcapsules, expressed in percentages.

Table 3

Statistical diameters (μm)	
D_a	790.14
$D_{v/s}$	899.78
Drug content (%)	
Payload	7.00
Encapsulation efficiency	35.00

ear regression coefficients in all approaches, with the best approach corresponding to the Higuchi model. The dissolution efficiency is higher in USP—II, suggesting that the lower results are due to the kind of values obtained with the flow-through cell. In this device the results correspond to distributive values so that the end of the assay depends primarily on the limit of detection of the analytical method employed, in our case an ultraviolet-visible (UV-VIS) spectrophotometer.

The lower values of the dissolution efficiency found using the basket are probably due to the effect of floatability mentioned before. This phenomenon avoids the total wetting of microcapsules which are inside the basket at the top.

Table 4

Time (min)	% Released		
	USP—I	USP—II	USP—IV
15	70.11	74.63	51.58
30	90.82	93.40	60.97
45	96.86	99.16	66.34
60	98.15	100.30	70.84
75	99.61	100.08	74.76
90	98.68	100.31	78.07
105	99.52	99.07	80.85
120	99.81	97.90	83.32
150	98.56	100.08	86.81
245	—	—	94.02

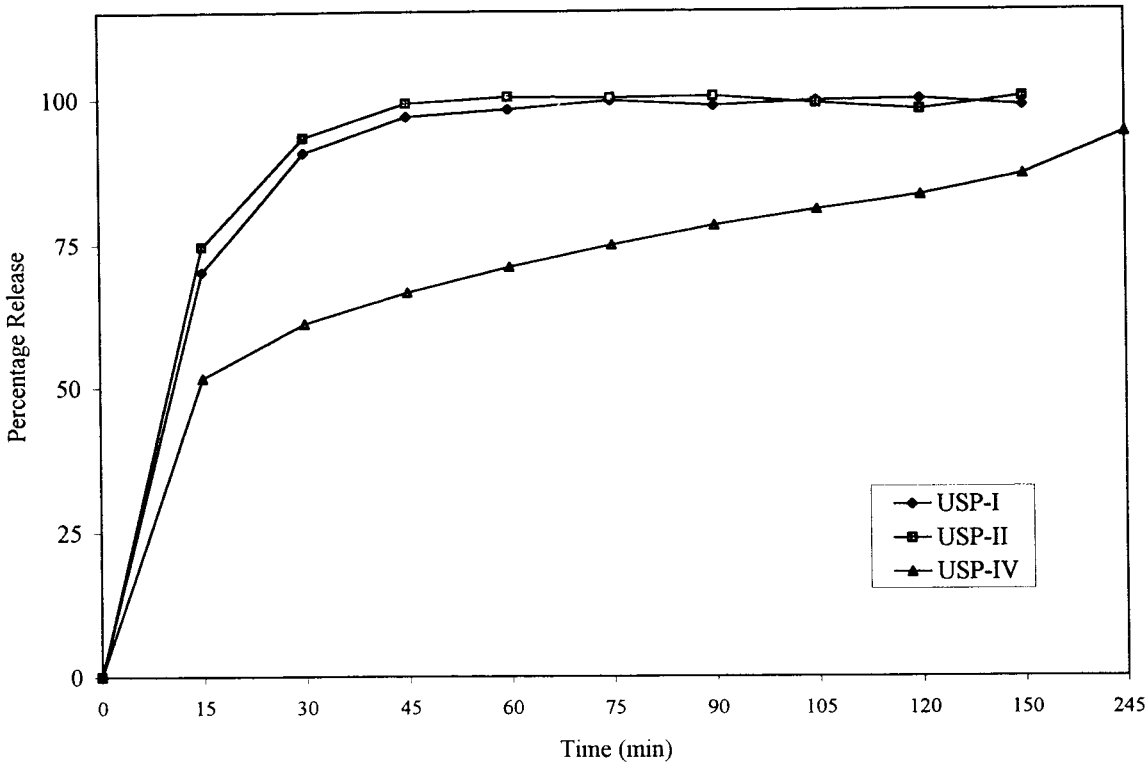

Figure 4. Dissolution profiles of the diclofenac sodium obtained with the three systems.

Table 5

Device	Agitation speed	t_{50}	t_{75}	t_{90}	t_{100}
USP—I	100 rpm				
t% (hr)		—	—	0.50	1.25
CV (%)		—	—	3.37	0.72
USP—II	50 rpm				
t% (hr)		—	0.25	0.50	1.00
CV (%)		—	5.75	2.01	0.41
USP—IV	4 ml/min				
t% (hr)		0.25	1.25	1.50	4.00
CV (%)		4.61	2.63	3.12	2.41

Table 6

	USP—I (100 rpm)	USP—II (50 rpm)	USP—IV (4 ml/min)
DE (%)	91.03	92.14	78.59
Zero-order	0.67921	0.60820	0.91111
First-order	0.66284	0.60196	0.83986
Higuchi	0.77594	0.71138	0.97397
Hixon-Crowell	0.66170	0.60407	0.86710
Wagner	0.68903	0.50495	0.99412

CONCLUSIONS

Regarding the dissolution characteristics of diclofenac sodium, we can conclude that the best "in vitro" conditions for our microcapsules are:

Media: pH > 6.5
Temperature: 37° ± 0.5°C
Device: paddle apparatus
Agitation speed: 50 rpm

Nevertheless, to study the degree of protection against gastric juices of one or another polymer or of the microencapsulation process itself, another test must be taken into consideration.

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