

## Ethylcellulose Microspheres containing Sodium Diclofenac: Development and Characterization

Marcelo A. BACCARIN<sup>1</sup>, Raul C. EVANGELISTA<sup>2</sup> & Ruth M. LUCINDA-SILVA<sup>1\*</sup>

<sup>1</sup> NIQFAR, Curso de Farmácia, CCS, UNIVALI, R. Uruguai, 458, CP 360, Itajaí, SC, 88302-202, Brazil

<sup>2</sup> Faculdade de Ciências Farmacêuticas, UNESP, Rod. Araraquara-Jaú, km 01,  
Araraquara, SP, 14801-902, Brazil

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**SUMMARY.** The objective of the present study was the development and characterization of ethylcellulose microspheres containing diclofenac and the determination of the *in vitro* drug release profile. Microspheres were prepared by emulsification/solvent evaporation method using ethyl acetate as solvent for the polymer and water as non solvent. The microspheres were characterized by morphologic and granulometric analyses. The amount of encapsulated drug as well as its release profile *in vitro* were also determined. The product obtained was microparticles with smooth surface and narrow size distribution, about 50% of the particles being smaller than 5 µm. The methodology used allowed drug encapsulation with a good yield and the system provided a controlled release of diclofenac.

**RESUMEN.** "Microesferas de etilcelulosa conteniendo diclofenaco: desarrollo y caracterización". El objetivo del este estudio fue el desarrollo y la caracterización del microesferas de etilcelulosa contiendo diclofenaco y la determinación del perfil de la liberación del fármaco *in vitro*. Las microesferas fueron preparadas por el método de emulsificación/evaporación del solvente, usando como disolvente polimérico el acetato de etilo y como no disolvente el agua, y fueron caracterizadas por análisis morfológicos y granulométricos. Fueron determinados el tenor de encapsulación y el perfil de la liberación del fármaco *in vitro*. Las microesferas obtenidas presentaron superficie plana y distribución de tamaño pequeña, siendo aproximadamente el 50% de las partículas más pequeñas que 5 µm. La metodología usada hizo posible la encapsulación del fármaco y el sistema usado proveyó un perfil de la liberación controlada del mismo.

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### INTRODUCTION

Drugs are usually administered by the most common routes vehiculated in conventional dosage forms. Intervals during the administration regimen can be inconvenient for the patient and, on the other hand, some drugs can be partially deactivated or neutralized in the GIT, causing low bioavailability, requiring the administration of higher doses of the drug to guarantee its efficacy, therefore increasing the probability of adverse side effects to appear. Such limitations have motivated the development of different strategies aiming the optimization of the drug. Several approaches have been experimented in order to solve such problems. Among them, the development of innovative pharmaceutical dosage forms, which can transport

pharmacological active molecules to specific target sites throughout the body and/or can be able to control the drug release rate is probably the most promising. Such pharmaceutical systems can modify the drug bioavailability profile without altering the structure of the moiety being transported. Important examples of these modern dosage forms are microcapsules/microspheres, in which it is possible to incorporate lower amounts of a molecule for a therapeutic or diagnostic goal within a polymeric appropriate structure for oral as well as intravenous administration of the drug<sup>1,2</sup>.

Although a very great number of polymers can be used, natural or semisynthetic polysaccharides, such as cellulose derivatives, play an important role in microencapsulation processes<sup>2</sup>.

**KEY WORDS:** Diclofenac; Ethylcellulose; Microencapsulation.

**PALAVRAS CHAVE:** Diclofenaco; Etilcelulosa; Microencapsulación.

\* Autor a quien dirigir la correspondencia. E-mail: rlucinda@univali.br

For example, ethylcellulose (EC) is a very useful substance and has been traditionally employed in the preparation of oral administered dosage forms, *e.g.* coated and matrix tablets<sup>3,4</sup>. Its film forming ability allows the formation of micro and nanocapsules<sup>5-7</sup>, beads<sup>8</sup> and other coated solid pharmaceutical dosage forms<sup>9,10</sup>.

Since they present important adverse side effects, antiinflammatory drugs are very good candidates to be encapsulated in such delivery systems<sup>11</sup>. The present work describes the development and characterization of microspheres containing the non steroidal antiinflammatory drug sodium diclofenac (SD), using EC as the matrix forming polymer and aiming the controlled release of the drug.

## MATERIAL AND METHODS

### Material

EC of practice grade was purchased from Sigma (St. Louis, USA), SD of pharmaceutical grade was purchased from Galena (São Paulo, Brazil). Solvents and other substances used were of analytical grade.

### Preparation of microspheres containing sodium diclofenac

EC microspheres were prepared by an emulsion/solvent evaporation method, using water as non solvent. The drug was added at different concentrations (1:1, 1:2, and 1:4 drug:polymer) into a 0.1% solution of EC in ethyl acetate. This polymeric solution containing the drug was dropped under agitation into an aqueous 1% polysorbate 80 solution at a 1:3 ratio between oil and water phases.

After the emulsification, the solvent was evaporated at 30°C under stirring during 5 h. After that, the microspheres were isolated by centrifugation, washed twice with distilled water and freeze-dried.

### Determination of drug content

Weighed samples of microspheres were left in contact with 5 mL of phosphate buffer solution 0.1 M for 4 hours under stirring, then they were filtered through analytical paper and the drug was spectrophotometrically assayed at 276 nm.

### In vitro drug release

The *in vitro* release of diclofenac was determined in dissolution apparatus (Erweka DT 32) using an adaptation of the USP XXIII' dissolution test 1. Aliquots of 2.5 mL were collected

from the release medium (400 mL of simulated enteric juice) maintained at 37 °C at established time intervals (0.25; 0.5; 1; 2; 4; 6; 7; 11; 23; 28; 30 h) and the drug absorbance was measured at 276 nm.

### Morphological analyses

Optical microscopy was used to follow the microparticles formation during all steps of the process. Morphological analyses were carried out by scanning electron microscopy (Jeol, mod. T330A) of samples of dried microspheres placed on metallic supports and covered with colloidal gold under vacuum.

### Size distribution analysis

Particles size distribution was performed under optical microscopy (Olympus SZ 40) using *Leica Image Analysis System* software. The Feret diameter at 0° was used as measuring parameter.

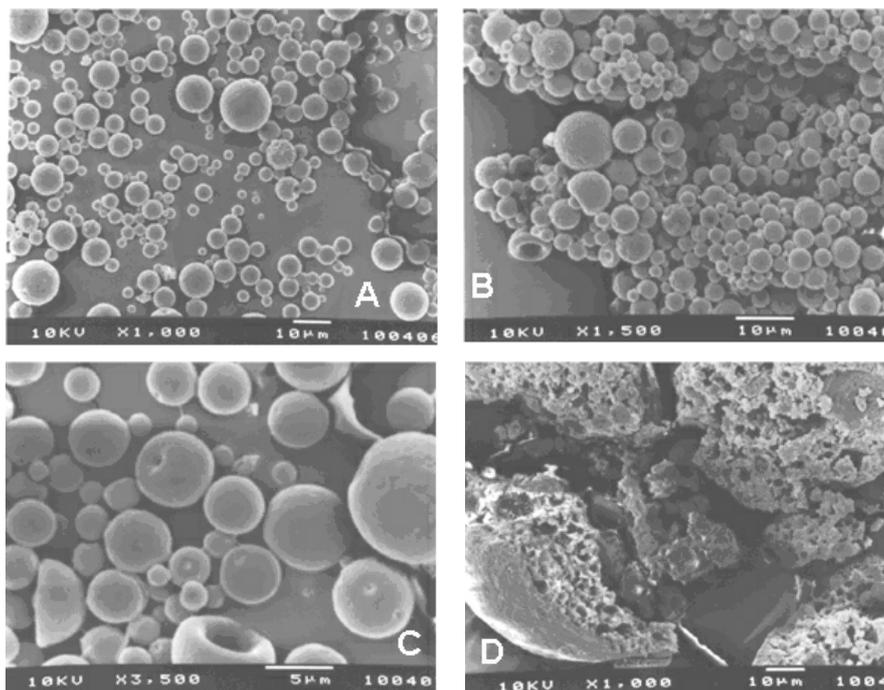
## RESULTS AND DISCUSSION

EC is probably the insoluble polymer the most used in pharmaceutical coating processes due to its good property of film formation<sup>9,10,12</sup>. Its physicochemical properties, especially its differentiated solubility in organic and aqueous solvents, allows it to be used in the preparation of microspheres by the emulsification/solvent evaporation method<sup>7</sup>.

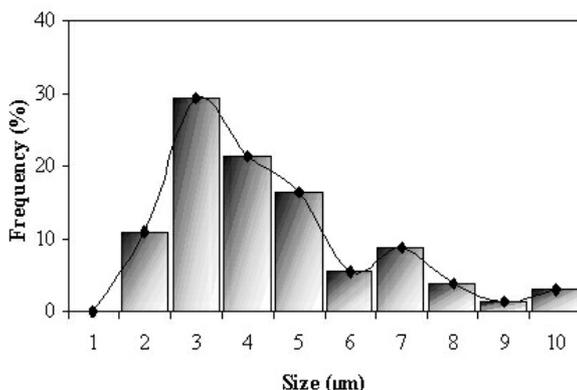
Ideally, in this method both the polymer and the drug are dissolved in an organic solvent of low boiling point and immiscible with water. This polymeric solution is then added to an aqueous solution of a surfactant, under stirring, to form an O/A emulsion system. After the emulsification is completed, the mixture can be heated to allow the solvent to be removed, resulting polymeric microparticles suspended in water.

Figure 1 presents SEM images of the microspheres obtained. Some parameters, such as surface aspect, roundness, and size uniformity could be assessed by microscopy and granulometry. The internal structure of the particles is a porous matricial system, as can be seen in Figure 1D, that shows a fractured particle. This type of structure, essentially matricial with the drug highly dispersed within the matrix, is typical from particles, in this case called microspheres, obtained by the emulsification/solvent evaporation method<sup>13</sup>.

Figure 2 shows that the particles sizes were between 1 and 10 µm, 50% of them being shorter than 5 µm. The narrowness of the size distri-



**Figure 1.** Photomicrographs of ethylcellulose microspheres. **A.** without drug; **B.** 1:2 drug:polymer ratio; **C.** 1:1 drug polymer ratio; **D.** Internal structure of microspheres.



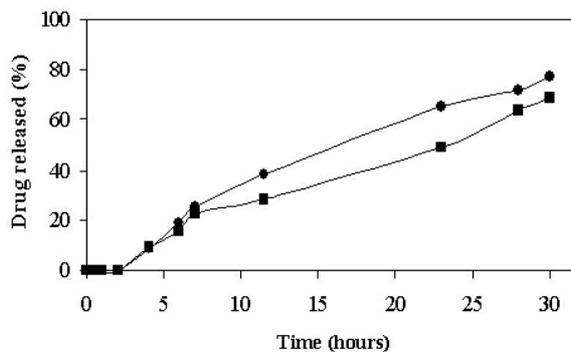
**Figure 2.** Size distribution of ethylcellulose microspheres containing diclofenac.

bution, *i.e.*, the size homogeneity of the particles obtained confirm the efficacy of the method used in obtaining microspheres. This size uniformity is related to the use of an emulsified system, the size and uniformity of the internal phase of the emulsion being responsible for the granulometry of the final solid particles<sup>14,15</sup>.

The entrapment efficiency was directly related to the drug amount in the environment and conditions studied. Some different initial drug amounts were tested in order to optimize the encapsulation efficiency. The highest entrapment efficiency was 4.33% when a 1:1 drug to polymer ratio was used. This value was greater than those obtained with 1:2 and 1:4 drug to polymer ratio. This relative low value is certain-

ly related with the hydrosolubility of sodium diclofenac, which allows the drug dissolution and diffusion into the external phase when the organic solution is dropped into the aqueous solution. The process of solvent removal as well as the washing steps to which the particles are submitted also contribute to the drug partition from the matrix into the water.

Figure 3 shows the *in vitro* release of sodium diclofenac from the microparticles of 1:2 and 1:1 drug:polymer ratio. Similar drug release profiles are observed for both microspheres, except for the percentual released amount after 30 h of assay. The particles containing 1:2 drug to polymer ratio released 68% of drug where as the 1:1 particles released 77%. The *in vitro* release assay



**Figure 3.** Release profile *in vitro* of microencapsulated sodium diclofenac, using simulated enteric media. ● 1:2 drug:polymer ratio; ■ 1:1 drug:polymer ratio.

showed that the EC microspheres are able to release sodium diclofenac in a gradual and controlled way.

Table 1 shows the correlation coefficient data of the release curves compared with mathematical models of release kinetics of zero order (rate of drug released *versus* time), first order (log of rate of released drug versus time), and Higuchi's equation (drug released versus square root of time). For both systems analyzed the correlation coefficients were bigger than 0.94, the values for the Higuchi's model being the shortest, 0.9532 and 0.9448. Systems that do not follow the Higuchi's model are considered to exhibit drug release controlled not only by diffusion but also by erosion of the matrix <sup>2</sup>. The release profile of microspheres prepared at a 1:2 drug to polymer ratio showed correlation coefficients of 0.9946 for first order and 0.9820 for zero order kinetics, respectively. In such systems the drug release probably occurs not only by diffusion from the insoluble matrix but also by erosion of the matrix surface. Systems prepared at a 1:1 drug to polymer ratio exhibited shorter correlation coefficients, but the values were still greater than 0.98 for zero order and first order models.

Microspheres	Zero order	First order	Higuchi's equation
SD:EC 1:2	0.9820	0.9946	0.9532
SD:EC 1:1	0.9873	0.9809	0.9448

**Table 1.** Correlation coefficients the drug release data submitted to kinetics mathematical models.

## CONCLUSION

The physicochemical properties of EC, mainly its aqueous insolubility and film forming capacity, allowed the easy production of microspheres by the emulsion/solvent evaporation method. The particles showed smooth surface, high roundness and narrow size distribution. The entrapment efficiency for sodium diclofenac was 4.33% and the *in vitro* assay showed that the microparticles were able to control the drug release, about 70% of the drug being released after 30 h of assay. When the drug release data were submitted to kinetics mathematical models, it was observed that the systems seem to be governed by zero order and first order release kinetics, indicating that the release occurs by drug diffusion from the matrix as well as by other process, such as erosion of the matrix.

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