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# NANOENCAPSULATION OF ACETYL SALICYLIC ACID WITHIN ENTERIC POLYMER NANOPATICLES

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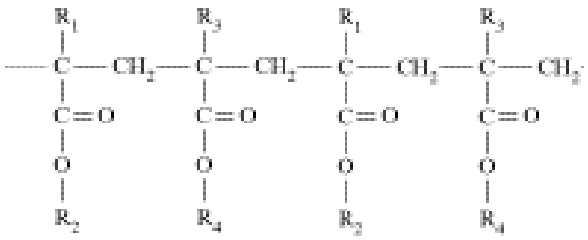
**Abstract.** Nanoencapsulation of Acetyl Salicylic Acid (ASA) was carried out by a modified double emulsion, using an enteric coating of the copolymers Eudragit L-100 and L -30 D-55 as polymeric matrix. Nanoparticles (NPs) were obtained with different amounts of surfactant (20-40 mg) and stirring rates (12000-15000 rpm) at *p*H between 1 and 2. The average size of the NPs was around 300 nm. The best results of the nanoencapsulation NPs process were reached with the combination of the copolymer Eudragit L-100 and L-30 D-55, showing nanoparticles yield and encapsulation efficiency higher than 90% and release profiles with smaller burst. The release profiles indicate that the matrix used is suitable to prevent the contact of the active principle with the gastric medium and that this device could achieve a more efficient release in the intestine.

## 1. INTRODUCTION

Nowadays, most of the analgesics are obtained using materials that allow the release of the drug in the intestine and not in the stomach. These systems are specially important for patients that present cardiovascular diseases and need a daily consumption of a stablished dose. This is the case of the Aspirin that could produce gastrointestinal bleedings in the long run, originating an iron deficit and also producing gastric ulcers among other symptoms [1-3].

Numerous works have been developed to obtain microparticles, including the method of solvent evaporation [4-10] with different polymeric matrix and different morphologies of the particles have been obtained using different experimental conditions. Several polymers are sensitive to pH changes. These polymeric materials have the characteristic of protecting the drug of the action of the enzymes and gastric fluids, which are in fact very acidic (pH = 1-2) [11-17].

The polymers Eudragit L-100 and L-30D-55 developed by Röhm Pharma Polymersbelong; the chemical structures of these polymers is:



Eudragit L-100 where $R_1$, $R_3$ = $CH_3$, $R_2$ = H, $R_4$ = $CH_3$

Eudragit L-30D-55 where $R_1$, $R_3$ = H, $R_2$ = H, $R_4$ = $CH_3$

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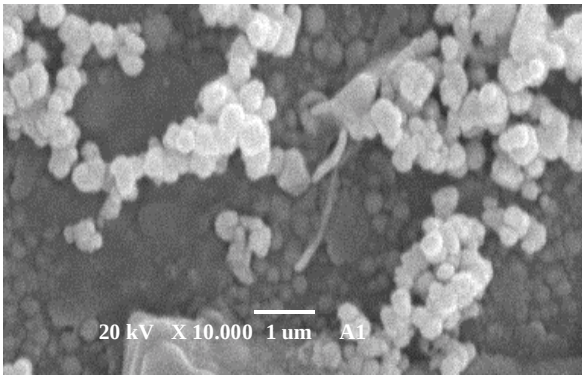


**Fig. 1.** Scanning electron micrographs of ASA NPs (sample A1).

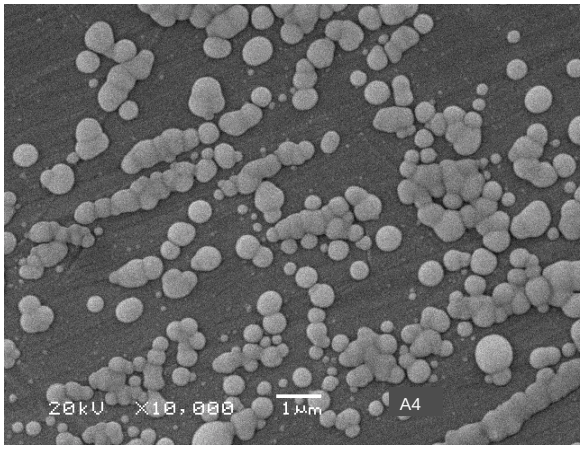


**Fig. 2.** Scanning electron micrographs of ASA NPs (sample A4).

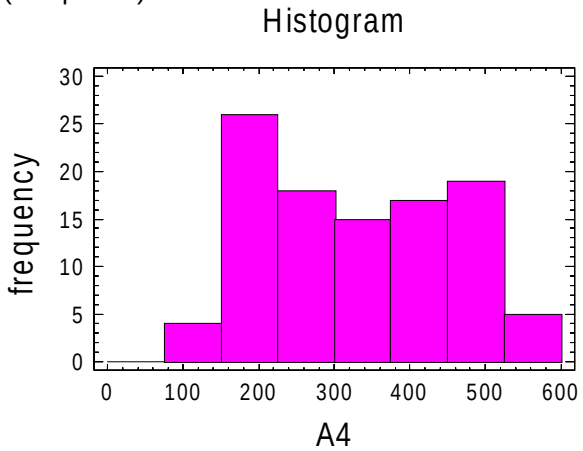


**Fig. 3.** Frequency diagram of the nanoparticles diameter for the sample A-4.

The specific aim of the present work consists in developing a procedure of nanoencapsulation of the (ASA) using the copolymers Eudragit L-100 and L-30D-55 as polymeric matrix of enteric coating; another task was to evaluate the advantages of such a nanodevice.

## 2. EXPERIMENTAL

### Reagents

- Acetyl salicylic acid (ASA): from BASF was analyzed according to the USP 27.
- Eudragit® L-100: Anionic copolymers of methacrylic acid and methyl methacrylate (1:1), MW: 135.000, *Tg* > 150 °C, supplied by Röhm Pharma Polymers.
- Eudragit® L-30 D-55: Is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate (1:1), *Tg* 110 °C supplied by Röhm Pharma Polymers.
- Tween 80®, viscosity 375-480 mPas, $n^{20}_{D}$ 1,472. supplied by the Fluka Chemie AG (93781).
- Solvent: Pure ethanol supplied by MERCK.

Dissolution medium used for release determinations:

- Hydrochloric acid 0.1 M (Merck);
- Sodium tribasic phosphate 0.2 M (Merck).

### Instrumentation

- Ultra Turrax homogenizer (Modelo T- 25 IKA), Germany.
- Scanning Electron MicroscopE (JEOL JSM 6060LV).
- U. V. Spectrophotometer (UV- Vis / Jasco V-530).

### Encapsulation procedure

The general procedure used was as follows: An alcohol solution (2 ml), containing an amount of the drug (ASA), was added dropwise to a solution that contained the polymer dissolved in a buffer of *p*H=7 (20 ml). The mixture was homogenized using the Ultra Turrax for 5 min. The dispersion obtained in this first step was emulsified over buffer solution (*p*H=2) containing Tween 80® at stirring rates ranging from 12800-15000 rpm/min for 15 min. Finally, NPs were collected by centrifugation and washed several times with small amounts of acidic water to eliminate the surfactant and dried under vacuum for 8 h.

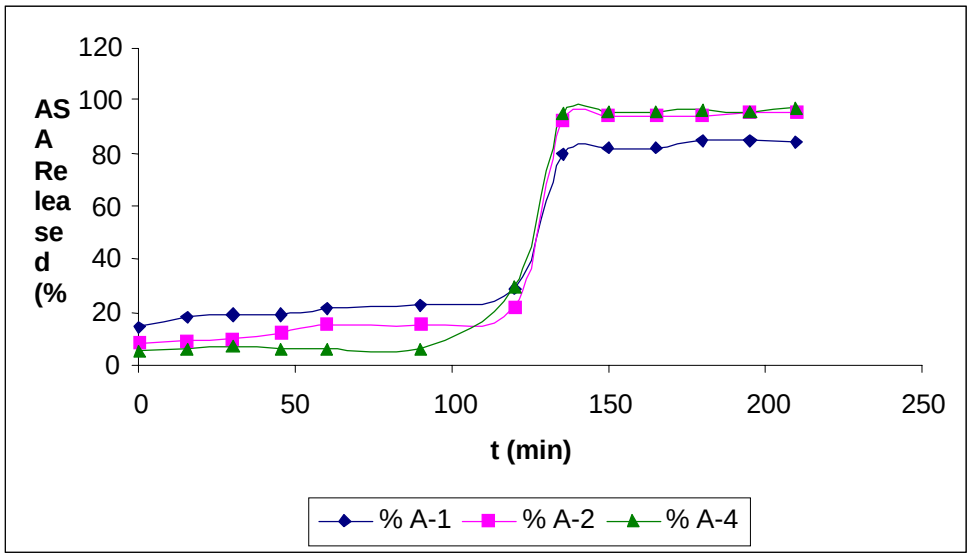


**Fig. 4.** Release profiles of the nanoparticles.

**Table 1.** Experimental conditions for ASA nanoencapsulation.

| Sample | ASA amount, (mg) | Polymer type | Surfactant amount, (mg) | Stirring rate, (rpm/min) |
|---|---|---|---|---|
| A1 | 20 | Eudragit® L 100 | 20 | 12800 |
| A2 | 20 | Eudragit® L 100 | 40 | 15000 |
| A3 | - | Eudragit® L 100 | 40 | 15000 |
| A4 | 20 | Eudragit® L 100: Eudragit L-30 D-55 | 40 | 15000 |

**Table 2.** Determination of the nanoparticles diameter.

| Simple | Average Diameter. (nm) | Standard Deviation. (SD) |
|---|---|---|
| A1 | 724 | 169.7 |
| A2 | 422 | 123.9 |
| A3 | 252 | 70.3 |
| A4 | 328 | 124.7 |

## Morphology and distribution of particles sizes

The NPs morphology was analyzed by Scanning Electron Microscopy (SEM). Samples were recovered by sputtering with a layer of gold of approximately 20 nm using an EMS 550 Sputter coater. For each sample, one hundred particles were measured and the particle mean diameters were estimated using an appropriate software.

**Table 3.** Nanoparticles yield and encapsulation efficiency of ASA.

| Sample | Co-Polymer | Nanoparticles yield (%) | Encapsulation efficiency (%) |
|---|---|---|---|
| A1 | Eudragit® L 100 | 71± 0.8 | 86.0 |
| A2 | Eudragit® L 100 | 80 ± 0.4 | 92.0 |
| A3 | Eudragit® L 100 | - | - |
| A4 | Eudragit® L 100: Eudragit L-30 D-55 | 91± 0.6 | 95.0 |

## In vitro drug release

In vitro releases of the NPs were performed at laboratory scale, according to the USP XXVII. NPs were suspended in 100 ml of HCl ((0.1 mol $dm^{-3}$) for 2 h to simulated the gastric fluid (*p*H 1-2), and later the solution was replaced with 100 ml of HCl (0.1 mol $dm^{-3}$) / $Na_3PO_4$ (2 mol $dm^{-3}$) (3:1) (*p*H 6.8), the dissolution medium was kept under stirring at 100 rpm. All the experiments were carried out at 37 °C ± 0.2 °C. Samples (3 ml) were assessed at appropriate time intervals, and the ASA release was measured spectrophotometrically at 280 nm against a calibration curve. The calibration curve used was *C*= 0.1511A + 0.1134. Encapsulation efficiencies were also spectroscopically estimated.

## 3. RESULTS AND DISCUSSION

Table 1 summarizes the mean values of duplicate experiments for the experimental conditions used to obtain the NPs and the effect of these parameters on the morphology and particle diameter are provided in Table 2 and Figs. 1,2, and 3.

Sample A1 is different from the others because of the use of a smaller amount of surfactant and also due to a lower stirring rate, which lead to greater diameters, spheroidal particles and agglomeration of the particles. This sample produces a smaller particle yield and lesser encapsulation efficiency (see Table 3) and also a profile release with the greater burst observed for all the samples (see Fig. 4), due to an excessive accumulation of the drug on the surface of the particles.

The effect of the presence of drug inside the particles can be appreciated by comparing sample A2 (with) to sample A3 (without drug), and it is reflected on the particles size (see Table 2).

Sample A4 is characterized by an adequate particle size, broad distribution (Fig. 3) and sphericity but some agglomeration is observed. Furthermore, a new morphology, not present in any of the other samples, appears in this case. Some particles and compacted, forming short linear chains consisting of six to eight particles. To obtain this sample Eudragit L30 D-55, a copolymer of ethyl acrylate and methacrylic acid, was utilized, in contrast to the Eudragit L-100 which is a copolymer of methyl methacrylate and methacrylic acid. It is well known the glass temperature of acrylates is lower than that of the corresponding methacrylates [18]. Thus, the blend formed between these copolymers during the co-precipitation should posses a lesser glass transition. This fact could be a reasonable explanation of the compaction observed in Fig. 2, as well as the lesser burst observed for this sample, as seen in the release profile of Fig. 4. The lower glass temperature of this material should produce a lesser stiff material that favours the encapsulation. In fact, the suppliers of these pure copolymers indicate that the glass transition for the Eudragit L-100 is >150 °C and 110 °C for Eudragit L30 D-55. It must be noticed that the high *Tg* of these copolymers is attributed to the methacrylic acid, since the *Tg* of its polymer is much higher (228 °C) [19].

## 4. CONCLUSIONS

A procedure was designed for the nanoencapsulation of ASA in a polymeric enteric matrix using a modified double emulsion approach. The chemical composition of the matrix and the control of the parameters of the process lead to nanoparticles with a quite good performance as sensitive to the pH device. The best results were obtained using a blend composed by the copolymer Eudragit L-100 and the Eudragit L30D-55. Adequate release in vitro profiles and encapsulation efficiencies higher than 90% were obtained. All these results indicate the possibility of improv-

ing absorption and releasing rates avoiding side effects in future in vivo tests by using nanoparticles.

## ACKNOWLEDGEMENTS

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