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# MICROAGGREGATED EGG ALBUMIN PARTICLES CONTAINING PARACETAMOL FOR TABLETING PROCESSES.

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## ABSTRACT

Microaggregated egg albumin particles containing paracetamol were prepared by a new microencapsulation method. Thus, paracetamol was suspended into an ovalbumin solution and then heated to coagulate the protein. The paracetamol crystals were entrapped into the new protein structure and as a consequence microaggregated egg albumin particles were obtained. This novel microencapsulation method improved the flow properties of paracetamol powder that are normally poor. The flow characteristics of the microaggregated particles depended on the paracetamol concentration and the particle size. Furthermore, the bitter taste of paracetamol was masked by this microencapsulation method and the microaggregated particles were used to produce chewable and non

chewable paracetamol tablets. The "in vivo" oral relative bioavailability of these two kinds of tablets of microencapsulated paracetamol in six volunteers were 99.5 and 92.5%, respectively, as determined from the urinary accumulative excretion.



## INTRODUCTION.

Microencapsulation and other related processes have been employed in Pharmacy to enhance stability of drugs, to reduce incompatibilities between drugs, to disguise unpleasent taste, to reduce gastrointestinal irritation and to achieve a sustained release effect[1].

Microencapsulation processes are specially interesting for the preparation of chewable tablets. These tablets have a rapid pharmacological action and are mainly used for oral administration of antacids and analgesics[2].

Paracetamol is a popular analgesic with a bitter taste and poor powder flow characteristics. In previous works, egg albumin microspheres containing paracetamol were produced by an emulsion technique using olive oil[3]. Although it was possible to mask the unpleasent bitter taste of paracetamol, the produced microspheres powders had poor flow properties and did not rise to an optimum tableting process. The poor flow properties of the egg albumin microspheres powder containing paracetamol were probably due to the presence of residual oil in the particles.

Although vegetable oils are usually employed for the preparation of microencapsulated drugs by the emulsion method, a

liquid alkane, isooctane, has been used to microencapsulate erythromycin[4] and phenacetin[5]. Organic solvents, such as isooctane, are volatile, explosive and toxic products, so their practical application in the pharmaceutical industry should be avoided.

In the present paper a novel method for the production of ovalbumin microaggregated particles containing paracetamol is described. This method can easily be scaled-up. The effect of particle size and paracetamol content on the flow properties of the powder were studied by direct (flow rate) and indirect methods (Hausner factor and percentage compressibility). Chewable and non chewable tablets were made and their "in vivo" relative bioavailability studied in six volunteers from the urinary relative excretion.

## MATERIALS.

Paracetamol (Fisons, U.K.), Ovalbumin (Ovosec, Spain), Ac-Di-Sol and Avicel (FMC, U.S.A.). Mannitol, Saccharin and Magnesium stearate USP were supplied by Claudio Barcia (Spain). Other chemicals were analytical grade from Panreac (Spain).

## METHODS.

### Microencapsulation.

7.5, 15, 30, 60 or 120 g of paracetamol were added to 150 ml of a 20% (w/v) egg albumin solution. The suspension was stirred at 1500 rpm with a mechanical stirrer (Heidolph RZR 1)

for 15 minutes and then heated at 70°C for 30 minutes. Once the albumin was denaturated, the stirring was stopped and the mass of coagulated albumin microaggregated particles with paracetamol dried at 50°C for 12 hours and the final product screened through standard sieves.

Particle Characterization.

Size and shape. The size and shape of the paracetamol crystals and ovalbumin microaggregated particles with the different paracetamol content were characterized using an optic microscope (Optiphot Nikon, Japan).

Size separation by sieving. Sieves of 1.5, 0.84, 0.4, 0.25 and 0.075 mm (CISA, Spain) were used to separate the microaggregated particles into different size ranges.

Paracetamol assay. The paracetamol content of the microaggregated particles was determined by an spectrophotometric assay (Beckman DU-6, USA) at 244 nm .

Moisture content. Moisture content of the different particles was measured using a Karl-Fisher apparatus (Metrohm, 658 KF processor and 665 dosimeter) and standard procedures.

Characterization of Powder Flow.

Flow rate. A simple shutter was placed below a funnel outlet (1.4 cm) and the hopper was filled with 100 g of particles. The shutter was then removed and the time taken for the particles to discharge completly was recorded[6].The flow rate was obtained by dividing the discharged powder mass by the time.

The process was repeated at least 20 times and the results taken as the mean.

Bulk density measurements. The bulk densities of the microaggregated particles and of the paracetamol used as raw material were determined according to the method described by Saleh and Stamm[7]. 50 g of particles were allowed to flow freely into the measuring cylinder. Tapping was carried out onto a wood surface from a height of 1 inch at 2 seconds intervals. The initial bulk density ($d_0$) and the bulk density after repeating 500 times the procedure ($d_{500}$) were calculated by dividing the weight (m) by the original volume (Vo) or the final volume ($V_{500}$). The process was repeated at least 3 times in each case.

$$d_0 = \frac{m}{Vo} \qquad d_{500} = \frac{m}{V_{500}}$$

Bulk densities ($d_0$ and $d_{500}$) were used to study the powder flow properties of the micoaggregated paticles by two indirect methods: The Hausner factor (H.F.) and the percentage compressibility (% compressibility), according to Rabasco et al.[8]

$$H.F. = \frac{d_{500}}{d_0} \quad ; \quad \% \text{ compressibility} = \frac{d_{500} - d_0}{d_{500}} \times 100$$

Tablet formulation:

Chewable tablets of paracetamol were produced by using microencapsulated paracetamol with a particle size range from 0.25 to 0.4 mm and a content of 70.5% w/w of paracetamol. Manni-

tol, saccharin, Ac-Di-Sol (FMC) and magnesium stearate were used as excipients.

Non chewable tablets of microencapsulated paracetamol were produced in order to study the possible application of albumin microaggregated particles for sustained release formulations. For this purpose, microencapsulated paracetamol particles (range size between 0.25 and 0.4 mm) with a content of 33.1% (w/w) of paracetamol were used as the active ingredient and magnesium stearate was used as a lubricant.

Tableting. An Eccentric tablet press (Bonals, Spain) was used to produce the different tablets.

Evaluation of Tablets.

Uniformity of weight. The uniformity of weight was evaluated according to the USP XXI.[9]

Thickness. The crown thickness of at least 10 tablets was measured with a micrometer.

Hardness. The hardness of at least 10 tablets was determined with an Erweka tester.

Friability. The friability was evaluated by calculating the loss in weight of 10 tablets (expressed as percentage) using an Erweka friabilator during 5 minutes at 25 rev/min. The experiment was repeated 3 times.

Disintegration. The disintegration was measured according to the USP XXI.

The dissolution was performed according to the USP XXI[9] for paracetamol tablets using phosphate buffer pH 5.5.

Bioavailability.

Six healthy (4 males and 2 female) volunteers, age range 24-27 years and weight range 55-75 kg, participated in the study which was conducted in a randomized and crossover manner. Three different tablets of paracetamol in doses of 500 mg were administered orally with 150 ml of water: Formulation 1, reference formulation consisting of 1 tablet of Panadol (Sterling Winthrop S.A.); Formulation 2, 2 chewable tablets of microencapsulated paracetamol (250 mg each); Formulation 3, 2 non chewable tablets of microencapsulated paracetamol (250 mg each).

Urine samples were taken at 0, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing. The volume of urine was measured and recorded. An aliquot was taken and maintained at - 20°C until it was assayed.

Paracetamol concentration in urine samples. The method used for the determination of total paracetamol was a modification of the spectrophotometric assay described by Sotiropoulus et al.[10] 5 ml of 3 N HCl was added to 2 ml of urine and the mixture was boiled for 1 hour, cooled and filtered. 2 ml of the filtered solution was transferred to a 50 ml volumetric flasks, 10 ml of 5 % vanillin in isopropanol was added and then the system was mixed. Their absorption was measured at 395 nm against a blank.

Relative bioavailability in urine (RBU). It was estimated using the following formula:

$$RBU\ (\%) = \frac{(\%\ \text{recovered in urine 24 h})\ \text{sample} \times \text{dose reference}}{(\%\ \text{recovered in urine 24 h})\ \text{reference} \times \text{dose sample}} \times 100$$

## RESULTS AND DISCUSSION.

Fig. 1.A. shows the shape of paracetamol crystals used as raw material. When these crystals are microencapsulated with ovalbumin they tend to form agglomerated particles that can be processed as conventional granules. Figure 1.B., 1.C. and 1.D. shows how the microencapsulated paracetamol particles become more spherical in shape as the ratio of paracetamol:ovalbumin decrease i.e. the less paracetamol content in the particles. The microencapsulated particles obtained by the method reported in this paper are not as spherical in shape as the ovalbumin microcapsules obtained by the emulsification method with vegetable oils.

Table 1 shows the flow characteristics of paracetamol powder used as raw material and ovalbumin microaggregated particles (microcapsules) with different paracetamol content.

Paracetamol as raw material is a powder with poor flow properties (table 1). It was impossible to measure its flow rate since the paracetamol powder showed no flow through the funnel used for the experiment. Powder flow was also studied by two indirect methods: Hausner factor and percentage compressibility.

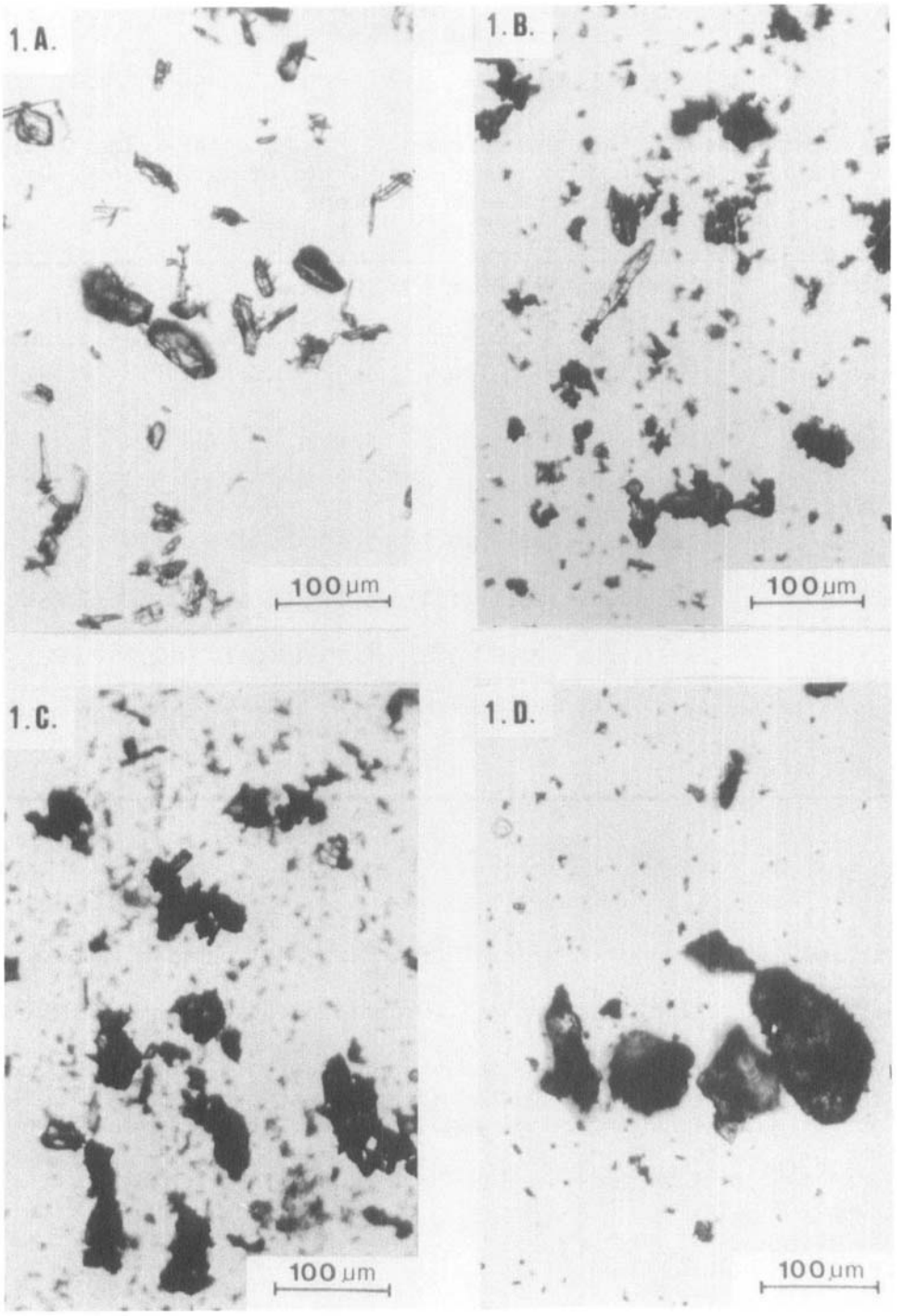


FIGURE 1.

Paracetamol Crystals (Figure 1.A.) and Egg Albumin Microaggregated Particles with Different Paracetamol Content: Fig. 1.A. 100% ; Fig. 1.B. 66% ; Fig. 1.C. 50% and Fig. 1.D. 33% of Paracetamol.

TABLE 1.

Flow Properties of Paracetamol used as Raw Material (size < 0.1 mm) and Egg Albumin Microaggregated Particles (size 0.4 > Ø > 0.26 mm) with different Paracetamol Content.

| Material | Paracetamol content (%) | Flow rate (g/s) | Hausner factor | % compressibility |
|---|---|---|---|---|
| Paracetamol | 100 (-) | No flow | 1.92 (0.06) | 47.8 (1.54) |
| MICROCAPSULES | 80.7 (4.2) | 16.6 (0.4) | 1.14 (0.02) | 12.6 (1.68) |
| | 70.5 (1.4) | 17 (0.7) | 1.18 (0.01) | 14.9 (0.73) |
| | 54.5 (0.4) | 18.1 (1.7) | 1.19 (0.01) | 16 (0.86) |
| | 29.7 (1.7) | 23.8 (0.6) | 1.15 (0.01) | 12.7 (0.88) |
| | 20.7 (4.1) | 23.5 (1.8) | 1.17 (0.01) | 14.8 (0.81) |

Particles with high interparticle friction and cohesive powders have Hausner factor greater than 1.6 and percentage compressibility values higher than 40, whereas powders with a Hausner factor of approximately 1.2 and percentage compressibility between 5 and 15 can be clasified as free-flowing[11] powders . Table 1 shows that paracetamol as raw material has a Hausner factor and a percentage compressibility insufficient for a direct tableting process. On the other hand when the paracetamol is microencapsulated with ovalbumin, the microaggregrated ovalbumin particles obtained have good flow characteristics and according to Stani-

forth [11] microagglomerated ovalbumin particles have excellent powder flow properties. Table 1 shows that the larger the amount of paracetamol in the particles the lower the flow rate of the microaggregated ovalbumin particles (microcapsules). This is probably due to the less spherical shape of the microencapsulated paracetamol (see figure 1) as well as to the decrease in the density of the particles when the amount of paracetamol present in the microaggregated particles increased.

The flow characteristics of microagglomerated ovalbumin particles of different size ranges were studied in order to clarify the effect of particle size on the flow properties of the microagglomerates.

Table 2 shows that particles with a size range between 0.25 and 0.4 mm have an optimum flow rate. For this reason, they were chosen for the production of tablets. Microagglomerated particles of size range between 0.075–0.25, and 0.4–0.84 mm also have good powder flow properties, while particles larger than 0.84 and lower than 0.075 mm have poorer flow characteristics.

The moisture content is an important parameter in tableting processes and stability of drugs. Figure 2 shows the moisture content of different kind of particles. Paracetamol as raw material was 0.2% at a relative humidity of 33±5 %. For the microaggregated particles containing paracetamol the moisture content depended on the amount of paracetamol in the particles. The moisture content decreased when the amount of microencapsulated

TABLE 2.

Flow Properties of Paracetamol used as Raw Material (size < 0.1 mm) and Egg Albumin Microaggregated Particles of Different Size.

| Material | Size of particles (mm) | Paracetamol content (%) | Flow rate (g/s) | Hausner factor | % compressibility |
|---|---|---|---|---|---|
| Paracetamol | Ø < 0.1 | 100 (-) | No flow | 1.92 (0.06) | 47.8 (1.54) |
| MICROCAPSULES | 1.5 > Ø > 0.84 | 54.8 (0.1) | 9 (0.2) | 1.12 (0.01) | 10.4 (0.73) |
| | 0.84 > Ø > 0.4 | 56.7 (1.6) | 14.9 (0.1) | 1.13 (0.01) | 11.2 (0.53) |
| | 0.4 > Ø > 0.25 | 54.5 (0.4) | 18.1 (1.7) | 1.19 (0.01) | 16 (0.86) |
| | 0.25 > Ø > 0.075 | 56.3 (1.5) | 16.7 (1.7) | 1.25 (0.01) | 20.2 (0.55) |
| | Ø < 0.075 | 69 (3.7) | No flow | 1.94 (0.02) | 48.4 (1.54) |

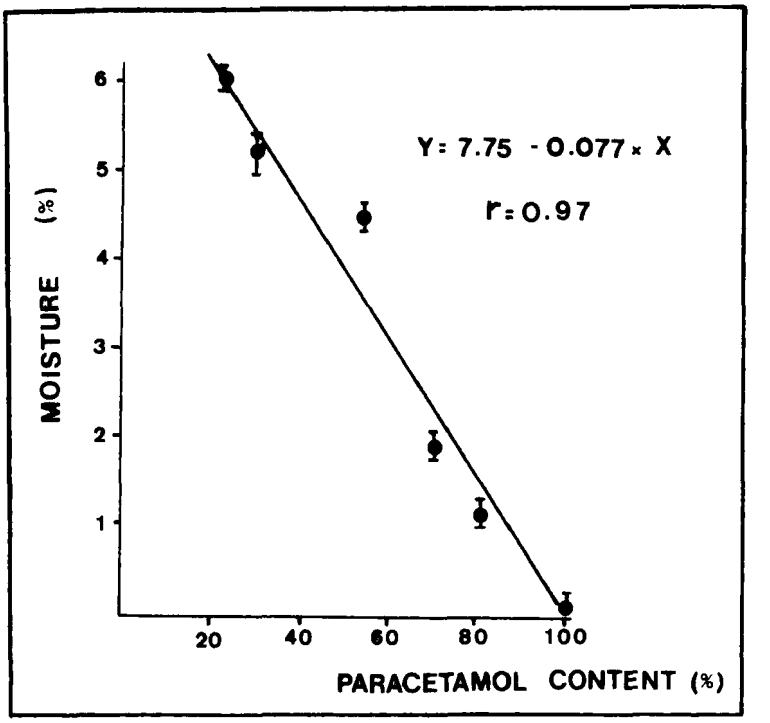


FIGURE 2.

Moisture (%) of Paracetamol used as Raw Material and of Microagglomerated Particles Containing Different Amounts of Paracetamol (%)At a Relative Humidity of 33±5 % (S.D.).

paracetamol increased, being 6.1% for a content of 20.7% paracetamol and 1.6% for a content of 80.7% paracetamol. Since albumin is a very hydrophilic material with a high water content, drugs susceptable to hydrolysis might not be suitable for preparation using this novel microaggregation technique.

Microaggregated egg albumin particles with different paracetamol content were processed into tablets. The compression properties of microaggregated albumin particles containing paraceta-

mol were studied using different proportions albumin:paracetamol. It was observed, that when the content of albumin was below 70% w/w and hence the paracetamol content above 30%, direct compression of microaggregated ovalbumin particles (0.4>Ø>0.25 mm) containing paracetamol was posible. However, direct compression of microcapsules with more than 70% of ovalbumin required the use of microcrystalline cellulose in the form of Avicel (FMC) to facilitate the tableting process.

The oral bioavailability of microencapsulated paracetamol tablets (chewable and non chewable) compared with a conventional marketed tablet of paracetamol was studied in a clinical trial. Table 3 shows the tablet characteristics of these three formulations. The six volunteers who participated in the "in vivo" study noticed that chewable tablets of microencapsulated paracetamol had a pleasant taste, however, a slightly bitter taste was still present.

The most important differences among the three formulations are: i) The use of microencapsulated paracetamol in two of the three formulations (formulation 2 and 3); and ii) the disintegration and dissolution characteristics. It should be noted that chewable tablets (formulation 2) due to the nature of administration will have an enhanced "in vivo" disintegration and dissolution as compared with the "in vitro" values. The "in vivo" disintegration and dissolution of the reference formulation (formulation 1) will be faster than the "in vitro" ones because

TABLE 3.

Tablets Characteristics of the Different Formulations: Formulation 1 - Reference, Formulation 2 - Chewable Tablets of Microencapsulated Paracetamol, Formulation 3 - Tablets of Microencapsulated Paracetamol.

| | Tablets | | |
|---|---|---|---|
| | Formulation 1 | Formulation 2 | Formulation 3 |
| Weight (mg) | 591.6 (0.08) | 913.6 (22.6) | 761.9 (8) |
| Uniformity of weight | conform to the USP specifications | | |
| Paracetamol content (mg) | 499.6 (7.1) | 239.9 (17) | 248.7 (9.6) |
| Thickness (mm) | 4.1 | 5.5 | 5.1 |
| Diameter (mm) | 13 | 13 | 13 |
| Hardness Erweka (kg) | 9.6 (1.5) | 8.4 (0.6) | 10.2 (0.7) |
| Friability (%) | 0.05 (0.05) | 0.74 (0.04) | 0.6 (0.7) |
| Disintegration (min) | 15 (3.4) | 27 (5.3) | 89 (22.1) |
| Dissolution (%) | | | |
| 5 min | 12.1 (2.2) | 20.6 (3.3) | 13.5 (6.4) |
| 10 min | 25.7 (7.9) | 24.5 (5.6) | 17.9 (2.5) |
| 15 min | 41.5 (5) | 29.4 (10.1) | 19.1 (3.3) |
| 20 min | 49.4 (6.4) | 38.2 (8.1) | 27.7 (7.2) |
| 25 min | 55.9 (7.8) | 53.7 (17.8) | 34.5 (9.8) |
| 30 min | 63.8 (8) | 69.5 (11.8) | 37.9 (15.3) |
| 480 min | 99.8 (0.5) | 98.7 (2.3) | 98.5 (1.5) |

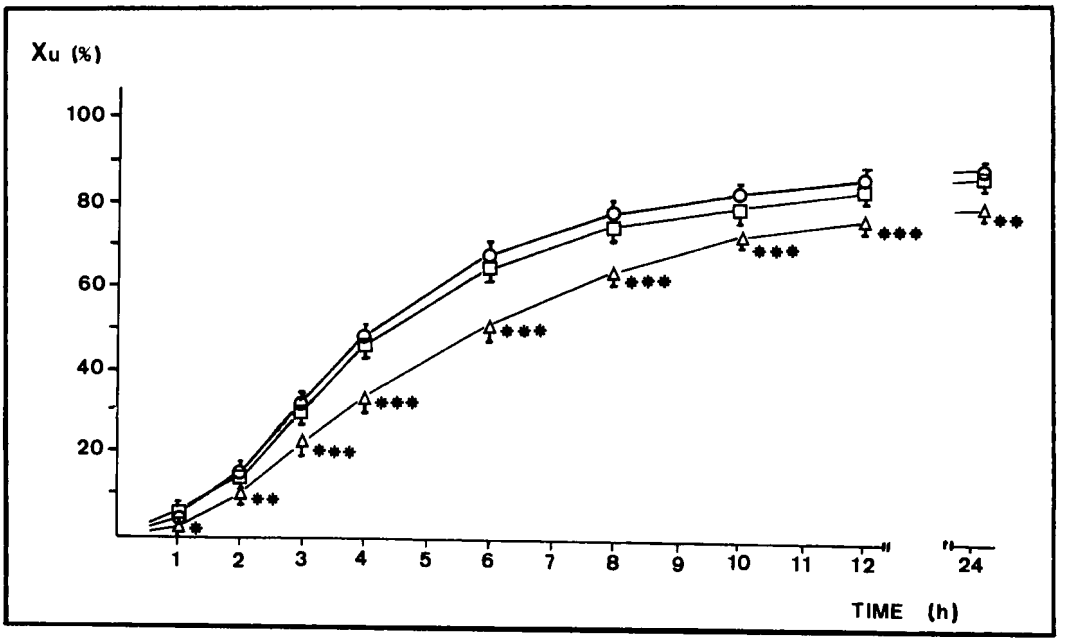


FIGURE 3.

Accumulative Excretion of Total Paracetamol of Three Different Tablets of Paracetamol. Key: ○—Formulation 1, □—Formulation 2 and Δ—Formulation 3.
Significant (ANOVA): *p<0.1, **p<0.05 and ***p<0.01

disintegration and dissolution of this formulation at pH 3 (pH in stomach is about pH 2-3) is faster than at pH 5.4 (pH of the dissolution test for paracetamol tablets, USP XXI). For all these reasons, formulation 3 must provide a slower absorption than formulations 1 and 2.

The urinary excretion and relative bioavailability of the three formulations are shown in figure 3 and table 4.

Figure 3 shows that there are no statistically significant differences in urinary excretion ($p<0.01$) between the reference

TABLE 4.

Mean Values of Urinary Excretion after 24 Hours ($Xu^{24}$) and Urinary Relative Bioavailability (URB) of the Three Different Formulations; Formulation 1 - Reference, Formulation 2 - Chewable Tablets of Microencapsulated Paracetamol, Formulation 3 - Tablets of Microencapsulated Paracetamol.

| | $Xu^{24}$ (%) | URB (%) |
|---|---|---|
| Formulation 1 | 94.3 (4.3) | -- |
| Formulation 2 | 90.1 (2.8) | 99.5 (8.2) |
| Formulation 3 | 86.9 (5.4)** | 92.5 (7.6) |

** Significant $p<0.05$ (ANOVA)

formulation (formulation 1) and the chewable tablets of microencapsulated paracetamol (formulation 2), but there is a statistically significant delay ($P<0.05$) in the urinary excretion of the non chewable microencapsulated paracetamol tablets (formulation 3) compared with the other two formulations. However, it was surprising that the urinary excretion of paracetamol for the formulation 3 were not so delayed as the "in vitro" disintegration and dissolution results indicated. This was probably due to the "in vivo" effect of certain enzymes (pepsin and trypsin) which can break the protein structure of the ovalbumin and enhance the dissolution of microencapsulated paracetamol. For this reason, it seems that the protein particles are not an optimal formulation for obtaining sustained release.

Table 4 shows the oral bioavailability of chewable and non chewable tablets of microagglomerated ovalbumin particles containing paracetamol as calculated for the 24 hours time period. These results agree with the good oral bioavailability of egg albumin microcapsules containing erythromycin reported by Farhadieh[4].

It can be concluded from the present work that egg albumin microaggregated particles can mask the bitter taste of paracetamol and overcome its poor powder flow properties. For these reasons, they are useful for the formulation of chewable tablets of paracetamol. However, the possible practical application of microencapsulated paracetamol for oral sustained release formulation is doubtful due to the oral "in vivo" degradation of heat denaturated proteins.



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