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A new enteric tablet of acetylsalicylic acid.
I. Technological aspects

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Summary

The aim of this study was to develop a multiple-units enteric tablet of acetylsalicylic acid (ASA). ASA crystals were coated with acrylic latex (Eudragit L30D) and then compressed into tablets. Depending on both structure and concentration of plasticizer used, we obtained tablets with good gastric resistance properties. Propyleneglycol (PROP) at a 30% level (w/w compared to the polymer) could be recommended as plasticizer. The analysis of Heckel's plots recorded during compression of ASA crystals was in agreement with the results of the gastric resistance tests.

Introduction

In an earlier publication (Dechesne et al., 1982) we drew some conclusions on the use of aqueous dispersions of enteric polymers: first, the coating conditions had little influence on the properties of applied films, and secondly, both structure and concentration of plasticizer markedly influenced the characteristics of Eudragit L30D films. In a review article, Bechgaard (1982) has demonstrated the advantages of multiple-unit controlled-release dosage forms compared to single-unit dosage forms. Because of the advantages of both multiple-units dosage forms and the use of aqueous dispersions of enteric polymers, the purpose of this study was to coat acetylsalicylic acid (ASA) crystals with aqueous latex and to compress them in order to obtain a "microdispersed" enteric tablet.

Materials and Methods

Coating conditions

ASA crystals (230–700 μm; Bayer Leverkusen, F.R.G.) were coated in a fluidised bed (Uniglatt) with 15, 22.5 and 30% of Eudragit L30D. Plasticizers used were triacetine (TRIA) and propyleneglycol (PROP). Composition of the solution:

Eudragit L30D	800 g
Plasticizer	10 or 30% (w/w compared to the polymer)
Talc	56 g
Water	400 g.

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Spraying solution feed: 12 g/min/kg.
Exhaust air and tablet bed temperature: 30–35 ° C.
Spraying air pressure: 30 N/cm^2.
Drying air temperature: 60 ° C.
Final drying time: 20 min.

ASA content

An accurately weighed amount of coated crystals corresponding to 350 mg of ASA was dissolved in 100 ml of NaOH 0.5 N. After 15 min on a shaker, 2 ml were filtered and diluted with 100 ml NaOH 0.5 N. Quantitative determination of ASA content was performed on this solution by UV spectrophotometry at 300 nm. Hydrolysis of ASA and determination of salicylic acid content at 300 nm were performed to avoid polymer and/or plasticizer interferences. Based on ASA content, it was possible to estimate percentages of applied polymer (Table 1).

Salicylic acid content

Because of the use of an aqueous coating dispersion, it was important to know if ASA was hydrolysed during the coating process or during conservation. Concentrations of free salicylic acid in coated crystals were measured using a high-performance liquid chromatographic (HPLC) method. Salicylic acid was extracted with freshly distilled methanol. After filtration, portions (20 μl) of this solution were injected into the HPLC system which consisted of an automatic injector (Rheodyne, model 7120) and pump (Pye-Unicam type LC-XPD) fitted with a variable wavelength ultraviolet monitor (Pye-Unicam model 4020) operated at 298 nm. The stainless-steel column (25 cm × 0.4 cm i.d.) was prepacked with μBondapak C18 (mean particle size, 7 μm). Chromatography was performed with a mobile phase of methanol (50% v/v) in phosphoric acid (0.05 M) at a flow rate of 1 ml/min. Salicylic acid was eluted with a retention time of 7.1 min.

Testing of ASA crystals

Each batch was tested for gastric resistance and for intestinal dissolution. For the gastric resistance test, crystals were kept 3 h in a USP II apparatus filled with HCl 0.1 N. For the intestinal dissolution, enteric-coated crystals were first maintained in gastric juice for 1 h and then the pH was adjusted to pH 6.5.

The concentration of ASA in dissolution medium was determined by direct spectrophotometry at 276 nm. When the pH was 6.5, ASA release was measured indirectly by U.V. spectrophotometry at 300 nm after hydrolysis of ASA into salicylic acid.

Compression of ASA crystals

Compression was carried out on a single punch tablet machine (Courtoy AC/27) at 20 ± 0.1 kN in order to obtain tablets with a minimal crushing strength of 5 kg (Erweka) and a maximal dis-

TABLE 1

ASA contents of the batches of ASA-coated crystals

Experiment	Plasticizer		Applied polymer		ASA content %
	Nature	%	Theoretical %	Estimated %	
1A	TRIA	10	15.0	10.4	83.34
1B	TRIA	10	22.5	15.3	75.55
1C	TRIA	10	30.0	20.6	67.05
2A	TRIA	30	15.0	11.1	79.94
2B	TRIA	30	22.5	15.6	72.00
2C	TRIA	30	30.0	19.6	64.80
3A	PROP	10	15.0	9.9	84.23
3B	PROP	10	22.5	15.7	74.82
3C	PROP	10	30.0	21.4	65.82
4A	PROP	30	15.0	10.3	81.46
4B	PROP	30	22.5	14.8	73.33
4C	PROP	30	30.0	17.5	68.51

integration time of 2 min. Crystals were compressed alone or after the addition of 20% of microcrystalline cellulose (Avicel PH102). The die and punches were 12 mm in diameter and the punches were flat-flaced.

Weight was calculated to correspond to tablets containing 500 mg ASA. Tablets were tested, like crystals, for ASA content, gastric resistance and intestinal dissolution.

Results and Discussion

The characteristics of the batches are summarized in Table 1. Theoretical percentages were calculated based on a yield of 100% for the coating process. Estimated percentages were calculated based on ASA content determinations. Comparing estimated and theoretical percentages (100% yield) of applied polymers, it was observed that the yield of the coating process was approximately 68%. Salicylic acid content of ASA coated crystals (Table 2) was increased during twelve months. Despite this enhancement, salicylic acid percentages still remained within USP requirements (3% to the maximum for coated ASA).

Results of the gastric resistance tests are shown on Figs. 1–3. In agreement with Fick's first law, the coating thickness markedly influenced the diffusion of ASA in gastric fluid. Keeping in mind that the only specification about gastric resistance allows a maximum release of 10% of active materials within 2 h (Swiss Pharmacopoeia), it was observed that 22.5% of applied polymer was needed for satisfactory gastric resistance properties.

Plasticization, in general, refers to a change in the thermal and mechanical properties of a given polymer. As previously demonstrated (Dillon et al., 1953; Morton et al., 1954), a plasticizer dispersed in a synthetic latex, first forms an emulsion. As the system ages, the plasticizer diffuses from

TABLE 2

Salicylic acid contents of some batches of ASA-coated crystals (% compared to ASA content)

Time (months)	1C	2C	3C	4C
0	0.1663	0.1002	0.0982	0.1502
0.5	0.2651	0.1332	0.1198	0.2742
1	0.4362	0.2150	0.1257	0.4480
4	0.5134	0.3366	0.2951	0.6726
6	0.6354	0.5006	0.3048	0.7335
9	0.8431	0.8396	0.3611	0.9490
12	0.9242	1.0186	0.5020	1.0209

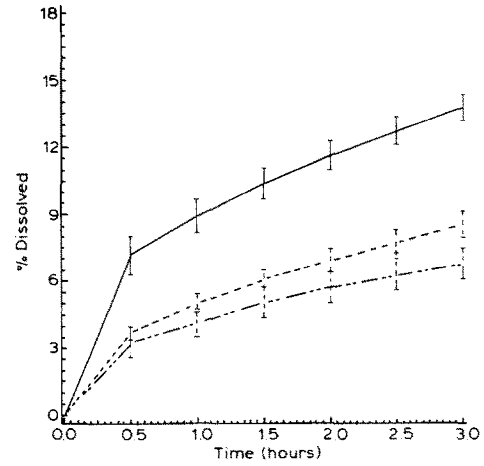

Fig. 1. Percentages of ASA dissolved against time during the gastric resistance test of coated crystals (each value is the mean ± S.E.M.); batches: (———), A; (- - - - -), B; (— — —), C.

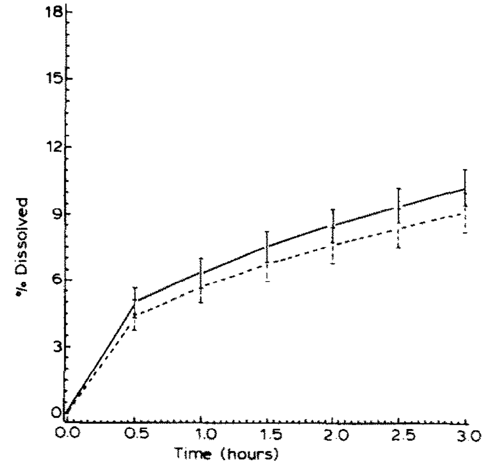

Fig. 2. Percentages of ASA dissolved against time during the gastric resistance test of coated crystals (each value is the mean ± S.E.M.); % of plasticizer: (———), 10%; (- - - - -), 30%.

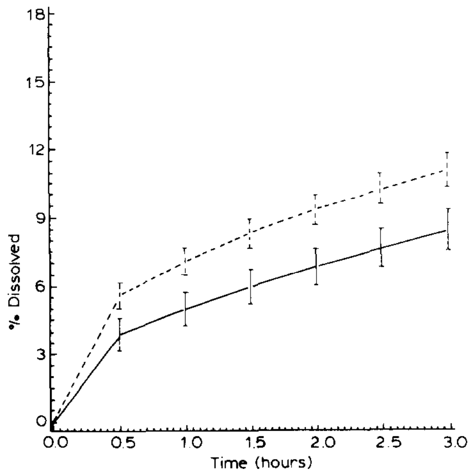

Fig. 3. Percentages of ASA dissolved against time during the gastric resistance test of coated crystals (each value is the mean ± S.E.M.; plasticizer: (———), PROP; (- - - - -), TRIA.

the emulsion droplets through the water and is absorbed by the polymer particles. It has been demonstrated (Masilungan and Lordi, 1984; Rowe et al., 1984) that depending on their nature, the plasticizers decreased the glass transition temperature (T_g) or the softening temperature of some common cellulose polymers. Also the effect of plasticizers on latex was influenced by their nature. Indeed two mechanisms permit the polymer to become plasticized: either the latex particles and plasticizer are brought together during the drying process or the latex particles absorb the plasticizer while in the latex state and thus are plasticized before the film is cast.

The extent of each phenomenon depends on the nature of plasticizer (solvent power, compatibility, permanence). Thus the nature of the plasticizer also influenced the percentages of ASA dissolved. The use of PROP instead of TRIA seemed to be a good solution to obtain low diffusion of ASA in artificial gastric fluid. That could be correlated with the highest effect of PROP on T_g of Eudragit L30D (Dechesne et al., 1984).

Finally, in agreement with some studies on free films (Fites et al., 1970; Donbrow and Friedman, 1974, 1975), an increase of the plasticizer concentration induced a decrease of the diffusion of ASA, especially when PROP was used as plasticizer. From Fig. 2, the relevance of this last comment was not obvious but this particular effect of PROP was demonstrated by a statistical analysis based on the FANOVA method (Gollob, 1968). Explanation of the use of this method and the results obtained with the data of the gastric resistance tests will be discussed in a future paper. For all batches, some differences appeared during the test of intestinal dissolution. In most cases, more than 80% of ASA were dissolved within the first 20 min of the intestinal dissolution test.

Table 3 summarizes the results of gastric resistance tests for some batches after compression with 20% microcrystalline cellulose. It was observed that:

- when the coating contains 10% of plasticizer, the gastric resistance characteristics were markedly modified by compression. Indeed, more than 20% of ASA were dissolved within the first two h of the gastric resistance test.
- when the coating contains 30% of plasticizer, after compression, there was a little increase in ASA diffusion, but the gastric resistance properties still remained satisfactory (less than 10% within 2 h).

TABLE 3

Gastric resistance test of tablets: % ASA dissolved

Experiment	Time (h)						
	0	0.5	1.0	1.5	2.0	2.5	3.0
1C	0	12.1 ± 0.172	17.8 ± 0.233	22.7 ± 0.363	> 27		
2C	0	3.0 ± 0.291	4.9 ± 0.310	6.3 ± 0.306	7.5 ± 0.290	8.6 ± 0.272	9.5 ± 0.272
3C	0	8.3 ± 0.330	14.5 ± 0.477	19.6 ± 0.580	24.1 ± 0.690	> 27	
4C	0	2.5 ± 0.169	4.0 ± 0.225	5.3 ± 0.329	6.5 ± 0.383	7.6 ± 0.474	8.6 ± 0.546

Each value is the mean ± S.D. of 3 replicates.

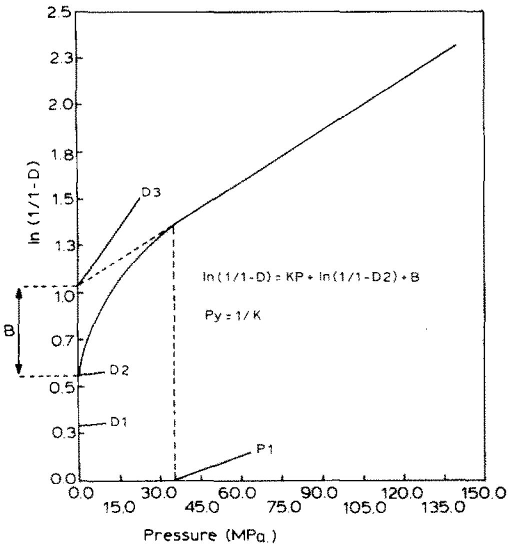

Fig. 4. Heckel's plot.

– PROP seemed to be the best plasticizer since it gave the less permeable applied films.

To understand what happened during compression, both forces and displacements of both upper and lower punches were recorded during compression. Using the modified Heckel's equation (Heckel, 1961a and b; Humbert-Droz et al., 1982) a set of parameters was defined (Fig. 4):

$$\ln\left(\frac{1}{1-D}\right) = K \cdot P + \ln\left(\frac{1}{1-D_2}\right) + B$$

P = applied pressure
D = relative density
P_y = mean yield pressure = $1/K$
D_1 = relative density before compression
D_2 = relative density of precompression
D_3 = characteristic relative density of the powder
P_1 = limit pressure; above this pressure, all diminution of the porosity is the consequence of plastic deformations.
$B = \ln(\frac{1}{1-D_3}) - \ln(\frac{1}{1-D_2})$

The parameter P_1 was estimated by non-linear regression. The model used was as follows:

$$\text{if } P \leqslant P_1\text{: } \ln\left(\frac{1}{1-D}\right) = a_0 + a_1 \cdot P + a_2 \cdot P^2$$

$$\text{if } P > P_1\text{: } \ln\left(\frac{1}{1-D}\right) = K \cdot P + D_3$$

with $K = a_1 + 2a_2 \cdot P_1$ and a_0, a_1, a_2 = parameters of the polynomial regression.

The true density of powders was evaluated by an air comparison pycnometer (Beckman model 930). Tablet weights corresponded to tablets with a thickness of 3 mm at theoretically zero porosity. Values of parameters for different substances are given in Table 4.

Densification of ASA was principally achieved by plastic deformation (low value of P_y: 13.5 MPa.) but, in agreement with Humber-Droz et al. (1982) ASA underwent some fragmentation as shown by parameter B (0.177).

On the basis of radial die wall pressure transmission, Carless and Leigh (1974) have demonstrated this double mechanism: considerable deformation and crushing at low pressures and plas-

TABLE 4

Parameters of compression

Material	P_y (MPa)	D_1	D_2	D_3	P_1 (MPa)	B ($D_3 - D_2$)
ASA crystals	13.5 ± 0.092	0.431 ± 0.003	0.582 ± 0.003	0.759 ± 0.003	9.98 ± 0.001	0.177 ± 0.005
Avicel PH102	39.6 ± 0.299	0.201 ± 0.002	0.263 ± 0.003	0.333 ± 0.001	11.33 ± 1.299	0.070 ± 0.003
Coated crystals						
1C	29.5 ± 0.392	0.546 ± 0.002	0.576 ± 0.004	0.712 ± 0.003	17.32 ± 2.134	0.136 ± 0.001
2C	24.7 ± 0.054	0.524 ± 0.002	0.536 ± 0.002	0.603 ± 0.002	10.42 ± 0.246	0.067 ± 0.002
3C	31.3 ± 0.253	0.526 ± 0.003	0.529 ± 0.003	0.694 ± 0.002	18.40 ± 0.246	0.165 ± 0.003
4C	26.0 ± 0.238	0.531 ± 0.001	0.539 ± 0.001	0.626 ± 0.001	10.78 ± 0.416	0.087 ± 0.002

Each value is the mean ± S.D. of 3 replicates.

TABLE 5

Parameters of compression of mixtures containing 80% ASA and 20% microcrystalline cellulose

Material	P_y (MPa)	D_1	D_2	D_3	P_1 (MPa)	B
Uncoated crystals	36.9 ± 0.122	0.422 ± 0.001	0.537 ± 0.002	0.681 ± 0.002	11.6 ± 1.226	0.144 ± 0.004
Batch						
1C	36.9 ± 0.067	0.473 ± 0.004	0.565 ± 0.003	0.613 ± 0.004	16.8 ± 0.708	0.048 ± 0.002
2C	32.9 ± 0.026	0.473 ± 0.002	0.554 ± 0.003	0.600 ± 0.004	10.2 ± 0.200	0.046 ± 0.002
3C	35.1 ± 0.096	0.465 ± 0.003	0.560 ± 0.002	0.589 ± 0.003	16.8 ± 1.035	0.029 ± 0.003
4C	34.6 ± 0.103	0.492 ± 0.003	0.590 ± 0.004	0.624 ± 0.003	10.1 ± 0.106	0.034 ± 0.001

Each value is the mean ± S.D. of 3 replicates.

tic deformation at higher pressures.

Coated crystals of ASA showed better flowing properties. Indeed, compared to uncoated crystals, an increase was observed of parameter D_1 which could be compared to the bulk density. D_1 was respectively 0.43 and 0.52–0.55 for uncoated and coated crystals. Comparing crystals coated with Eudragit L30D containing either 10% or 30% of plasticizer, a decrease of parameters B, P_y and P_1 was observed when 30% of plasticizer was used. A decrease of B (from 0.136 to 0.067 or from 0.165 to 0.087) and P_1 (from 17.3 to 10.4 and from 18.4 to 10.8) could be interpreted as a lowering of densification by fragmentation. As stated previously, a low value of P_y corresponds to high plastic properties. The decrease of P_y (from 29.5 to 24.7 and from 31.3 to 26.0) was the consequence of an increase of plastic properties when 30% of plasticizer were used. Values of compression parameters of mixtures containing 80% ASA-coated or uncoated and 20% microcrystalline cellulose are given in Table 5. In view of the inclusion of this Table, no difference appeared for parameter B, but the decrease of parameters P_1 and P_y still remained when plasticizer was used at a 30% level instead of 10%.

It was obvious that these results correlated well with gastric resistance tests on tablets. A decrease of plastic properties (10% plasticizer) combined with fragmentation phenomena resulted in more ASA dissolved during the gastric resistance test (> 27% within 2 h). Decrease of fragmentation during compression (30% plasticizer) correlated with low percentages of ASA dissolved (< 9% after 2 h) during the gastric resistance test.

It may be concluded that the use of Eudragit L30D latex as coating material makes gastric resistant crystal of ASA obtainable. The release of ASA in gastric fluid is markedly influenced by the nature and the concentration of plasticizer used. PROP at a 30% level (w/w compared to the polymer) may be recommended. When crystals are to be compressed in order to obtain tablets, a 30% level of plasticizer has to be employed, otherwise the gastric resistance properties of coated crystals will deteriorate.

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