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EFFECT OF STORAGE ON THE PROPERTIES OF ACETYLSALICYLIC ACID TABLETS COATED WITH AQUEOUS HYDROXYPROPYL METHYL-CELLULOSE DISPERSION

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ABSTRACT

The objective of this study was to investigate whether the properties of acetylsalicylic acid tablets coated with aqueous hydroxypropyl methylcellulose dispersion using glycerol or polyethylene glycol 6000 as plasticizer change during storage at 25° or 40°C. Titanium dioxide was used as pigment. The tablets were coated in a fluid bed apparatus. The disintegration time and the release of acetylsalicylic acid during two hours were determined for both uncoated and coated tablets immediately after their preparation and after different storage periods.

When the tablets were stored at room temperature (25°C) the coat protected the core efficiently against changes in the measured parameters as compared with uncoated tablets. However, at higher temperature (40°C) some unfavorable phenomena occurred in the coat and after storage of 48 months, the disintegration time was

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longer and the dissolution of acetylsalicylic acid slower than from uncoated tablets. Polyethylene glycol was found to be a better protecting agent than glycerol.

INTRODUCTION

Because of the flammability, toxicity and high cost of organic solvents, film coating of tablets is nowadays increasingly based on aqueous systems. The use of water based solutions or dispersions is not, however, without its drawbacks, e.g., moisture and heat during the procedure may influence the active ingredients. The results obtained by Pickard et al. (1) showed, however, no degradation of a moisture sensitive drug during the coating process. In this respect, water based and organic solvent systems were similar. This means, that tablets even with a relatively moisture sensitive active ingredient tolerate aqueous coating systems.

The physical properties of tablets may also change due to the coating. Rowe et al. (2) have noticed a prolonged disintegration time and Pickard et al. (3) reported, that the dissolution of acetylsalicylic acid is slower from coated than from uncoated tablets. However, only a few papers have been published concerning the changes in the technical properties of tablets due to different aqueous coating systems. This is even more the case when one considers possible ageing phenomena. Studies were therefore planned to establish differences in the rate of disintegration and dissolution of acetylsalicylic acid from tablets coated with various water based systems and to find out whether storage times and conditions affect these properties.

MATERIALS AND METHODS

Preparation of acetylsalicylic acid tablets

The tablet examined included 500 mg of acetylsalicylic acid (ASA). The composition of the tablet and the quality of raw materials are listed in table 1.
Maize starch and lactose were mixed and then granulated with gelatin solution with air suspension method in Glatt apparatus. The dried granules were sieved through 1.0 mm sieve and mixed with acetylsalicylic acid and modified starch in a fluid bed apparatus. The mass was compressed to tablets with a rotary press using punches with diameter of 11 mm and curvature radius of 16.0 mm. The weight of the tablet was adjusted to 650 mg and the hardness to appr. 9 kg as measured with the Pfizer hardness tester.

TABLE 1

The composition of the tablets

Ingredient	Quality and source of the ingredient	
Acetylsalicylic acid cryst.	Ph.Eur.	Bayer AG, West-Germany
Maize starch	Ph.Eur.	CPC Industrial Product, Denmark
Lactose	Ph.Eur.	Zuid Nederlandse Melkindustrie b.v., Netherland
Gelatin	Ph.Nord.	Rousselot, France
Modified starch	USP XX	Sta-RX 1500™, Colorcon Ltd., Great Britain
Purified water	Ph.Eur. Ph.Nord.	Farmos Group Ltd., Finland

Coating of acetylsalicylic acid tablets

The tablets were coated with aqueous hydroxypropyl methylcellulose dispersion using glycerol or polyethylene glycol as plasticizer and titanium dioxide as pigment. The composition of coating solutions and the quality of raw materials are listed in table 2.

Coating solutions were prepared as follows:

Hydroxypropyl methylcellulose was dispersed into cold purified water, plasticizer was added into the dispersion, glycerol as such and polyethylene glycol dissolved into a small amount of purified water. Titanium dioxide was mixed thoroughly into the coating solution. The coating solution was allowed to stand overnight. It was

TABLE 2

The composition of coating solutions

Ingredient	Amount (%) solution 1	Amount (%) solution 2	Quality and source of the ingredient	
Hydroxypropyl methylcellulose 15 cp	5.0	5.0	USP XX	Methocel™E15 Premium, Colorcon Ltd., Great Britain
Glycerol (85%)	1.0	-	Ph.Eur.	Henkel International GmbH, West Germany
Polyethylene glycol 6000	-	1.0	Ph.Nord.	Hoechst AG, West Germany
Titanium dioxide	0.4	0.4	USP XX	Kemira, Finland
Purified water	ad 100.0	ad 100.0	Ph.Eur. Ph.Nord.	Farmos Group Ltd. Finland
Symbol	HPMC-GLY	HPMC-PEG		

mixed thoroughly before use and slightly also during the coating operation.

The tablets were coated in a fluid bed apparatus (Glatt WSG 5) using an airborne spray system. The weight of coating batch was 6 kg and the amount of coating solution applied was 1.7 kg. The conditions employed were as follows:

temperature of inlet air 60°C
temperature of outlet air 44°C
air spray setting 2 kp/cm^2
coating time 35 minutes
drying time after tablets are coated 5 minutes.

Evaluation of physical parameters

Both the uncoated and HPMC-coated acetylsalicylic acid tablets were evaluated for disintegration time and dissolution profile immediately after their preparation and after storage for 1, 3, 6, 9, 12 and 48 months at 25°C and 40°C in HD-polyethylene bottles. The disintegration time was determined according to European Pharmacopea at 37°C in water using 18 tablets. The release of ASA during 2 hours was conducted according to the USP method with the rotating basket. The dissolution medium was 900 ml of USP artificial gastric juice without enzyme equilibrated at 37°C and stirred at 50 rpm. The drug released during two hours was analyzed and assayed by recording the absorbance at 278 nm. Twelve tablets were tested for each time point.

RESULTS AND DISCUSSION

The disintegration times of the tablets are listed in table 3 and the plots of these versus storage time are given in figure 1. The results obtained from tablets

TABLE 3

Disintegration time (min, sec) and relative standard deviation (per cent) of uncoated and cellulose coated acetylsalicylic acid tablets
(mean value of 18 tablets).

Storage time [months]		Uncoated		HPMC-GLY coated		HPMC-PEG coated	
		Storage temperature		Storage temperature		Storage temperature	
		25°C	40°C	25°C	40°C	25°C	40°C
0	mean	6'9''	6'9''	10'28''	10'28''	9'48''	9'48''
	s_{rel}	14.9	14.9	13.8	13.8	13.2	13.2
1	mean	7'35''	14'11''	12'10''	13'46''	10'46''	10'52''
	s_{rel}	17.6	20.3	11.4	17.4	12.7	16.1
3	mean	8'55''	17'	11'56''	11'40''	9'27''	9'8''
	s_{rel}	21.8	29.1	15.2	14.5	11.3	9.7
6	mean	9'6''	21'21''	12'53''	17'15''	11'22''	12'22''
	s_{rel}	15.9	16.9	12.4	16.9	15.6	14.8
9	mean	11'13''	18'6''	12'22''	21'57''	10'49''	14'2''
	s_{rel}	22.7	17.8	11.3	12.7	17.4	17.3
12	mean	11'22''	20'31''	12'33''	24'10''	10'26''	16'17''
	s_{rel}	19.1	21.4	9.6	15.1	11.2	14.5
18	mean	10'10''	19'26''	12'32''	28'27''	10'53''	19'53''
	s_{rel}	20.7	13.1	11.6	16.4	11.9	9.4
48	mean	15'57''	16'55''	14'27''	63'14''	10'1''	22'11''
	s_{rel}	21.7	14.1	17.7	11.7	13.1	10.5

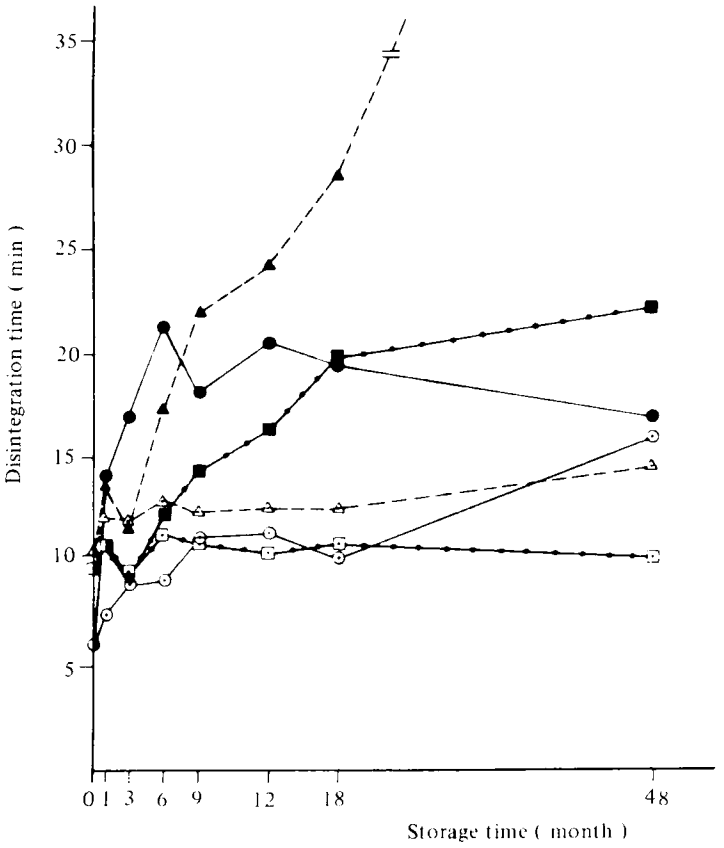

FIGURE 1

Disintegration time of uncoated and cellulose coated acetylsalicylic acid tablets after aging at 25°C and 40°C. Key: ○ , ● , uncoated tablet; △ , ▲ , HPMC-GLY coated tablet; □ , ■ , HPMC-PEG coated tablet. Open data points represent 25°C and closed data points represent 40°C.

immediately after their preparation indicate, that hydroxypropyl methylcellulose films disintegrate or dissolve rapidly and do not markedly prolong the disintegration time of acetylsalicylic acid tablets.

When the tablets were stored at 25°C the disintegration time of uncoated tablet lengthened from 6 to 16

minutes during storage for 48 months. The change for HPMC-coated tablets was very small, only 1-2 minutes. When the tablets were stored at 40°C the largest change in disintegration time of uncoated tablet occurred during the first month. After storage for one year, the changes were quite small. The disintegration times of coated tablets were prolonged during the whole storage period of 48 months at 40°C. The changes were markedly greater for HPMC-CLY coated tablets than for HPMC-PEG coated tablets.

The amount of acetylsalicylic acid dissolved from uncoated and HPMC-coated tablets are listed in table 4 and the plots of drug dissolution at 2 hours time versus storage time are given in figure 2. The theoretical amount of ASA in the tablet was 500 mg i.e. 2.77 millimoles. According the results obtained the drug did not dissolve totally during the two hour test, since the released amount of ASA from uncoated tablet after its preparation was appr. 480 mg i.e. 2.65 millimoles. During the 48 months storage at 25°C, the amount of the drug dissolved from uncoated tablet dropped nearly 40 per cent. The changes at 40°C were only slightly larger but they were faster, for the amount ASA released dropped appr. 50 per cent during the first six months. The coating procedure did not change the dissolution profile, because the amount of acetylsalicylic acid released from coated tablets after their preparation was similar as from uncoated tablet. When the HPMC-GLY coated and HPMC-PEG coated tablets were stored at 25°C for 48 months the amount of the drug released dropped only a few per cent. Conversely, storage at 40°C changed the dissolution profile markedly. After nine months, the amount of acetylsalicylic acid dissolved from the coated tablets had dropped 45-50 %, the amount being equivalent to that from uncoated tablets. After the storage of 48

TABLE 4

The amount of acetylsalicylic acid dissolved (millimol) and relative standard deviation (per cent) from uncoated and celluloce coated tablets during two hours (mean value of 12 tablets).

Storage time [months]		Uncoated		HPMC-GLY coated		HPMC-PEG coated	
		Storage temperature		Storage temperature		Storage temperature	
		25°C	40°C	25°C	40°C	25°C	40°C
0	mean	2.65	2.65	2.56	2.56	2.59	2.59
	s_{rel}	4.8	4.8	6.5	6.5	5.9	5.9
1	mean	2.56	1.83	2.65	2.45	2.57	2.34
	s_{rel}	6.3	24.1	6.4	6.6	6.5	11.3
3	mean	2.37	1.61	2.62	2.24	2.55	2.31
	s_{rel}	10.7	19.3	3.4	6.9	8.1	10.9
6	mean	2.36	1.33	2.61	1.74	2.65	1.80
	s_{rel}	11.5	9.3	6.2	18.3	4.5	19.2
9	mean	2.22	1.35	2.57	1.32	2.64	1.46
	s_{rel}	8.3	9.0	7.0	17.1	9.0	11.4
12	mean	2.17	1.26	2.50	0.75	2.68	1.16
	s_{rel}	17.7	16.6	7.9	7.8	5.1	16.7
18	mean	1.81	1.30	2.46	0.45	2.48	0.85
	s_{rel}	13.2	9.9	9.1	29.2	8.4	21.9
48	mean	1.65	1.51	2.28	0.14	2.60	0.20
	s_{rel}	10.9	11.8	5.9	5.8	6.0	3.8

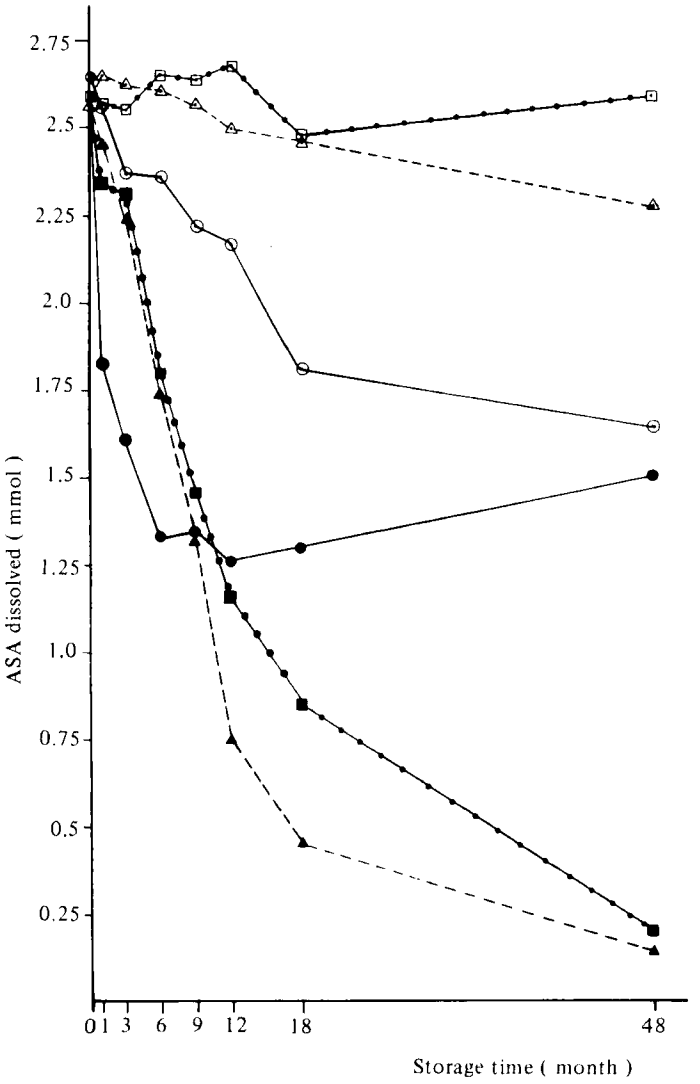

FIGURE 2

The amount of acetylsalicylic acid dissolved at two hours after aging at 25°C and 40°C. Key: ○ , ● , uncoated tablet; △ , ▲ , HPMC-GLY coated tablet; □ , ■ , HPMC-PEG coated tablet. Open data points represent 25°C and closed data points represent 40°C.

months, the amounts of the drug dissolved were only 5-8 % from the initial values.

Both the disintegration times and the dissolution data obtained indicate, that the HPMC-films protected the acetylsalicylic acid tablet, when the tablets were stored at 25°C. The observation, that the dissolution profile did not change during the storage at 25°C is in accordance with the results which Pickard et al. (3) obtained from HPMC-coated acetylsalicylic acid tablets stored at 20-21°C for one year. When the tablets were stored at elevated temperature, 40°C, some kind of ageing phenomenon for both uncoated and coated tablets was observed. The reason for changes of parameters measured for uncoated tablet might be some kind of hardening of the core. The changes in disintegration time and dissolution profile correlate quite well with each other, because both parameters changed markedly during the first six months, remaining nearly unchanged after this period. The protecting effect of HPMC-films can be observed at the beginning of the storage at 40°C, because the dissolution data for coated tablets are better for nine months than for uncoated tablet. The reason for that phenomenon is probably the elevated temperature, which changes the texture or gelation properties of HPMC-films. As with uncoated tablets, the changes in disintegration times and dissolution profile of coated tablets correlate quite well with each other. When the disintegration times of HPMC-GLY coated and HPMC-PEG coated tablets are correlated it can be seen, that the storage at 40°C prolonged noticeably more the disintegration time of HPMC-GLY coated tablet than that of HPMC-PEG coated tablet. The reason for this difference might be the thinner and noncontinous coat observed for HPMC-PEG coated tablet. This thinner and noncontinu-

ous film cannot withstand the mechanical stress in the disintegration test as well as the thicker continous film. The plasticizers used, glycerol and polyethylene glycol 6000, have different effects on film formation and the gelation properties of the film. It is well known, that glycerol lowers the gelation temperature of aqueous hydroxypropyl methylcellulose solution, but polyethylene glycol increases it (4). Since the amounts of plasticizers were relatively low, it is difficult to decide, whether the quality of plasticizers has an effect on the difference between the disintegration times.

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