International Journal of Pharmaceutics, 55 (1989) 47–52
Elsevier

IJP 01849

Effect of storage on tabletted microencapsulated aspirin granules

O.M. Al-Gohary, S.S. Al-Gamal *, A. Hammad and A.M. Molokhia

College of Pharmacy, Kind Saud University, Riyadh (Saudi Arabia)

(Received 15 February 1989)
(Accepted 20 March 1989)

Key words: Microencapsulation; Aspirin; Drug release; Aging

Summary

The antithrombotic effect of aspirin has been demonstrated through the use of small daily doses of the drug. Slow release formulations were shown to be adequate dosage form for this purpose. In this study, two sustained release formulations of aspirin were prepared and compared to plain aspirin tablets for their drug release and behavior upon storage at 40 °C/90% relative humidity (R.H.). The polyacrylate–polymethacrylate based polymers were found suitable for the preparation of a sustained release aspirin product. The release characteristics of the drug were adequate to meet its antithrombotic effect. Storage-related changes observed in this study should help in better understanding and proper treatment of such formulations for the sake of obtaining more stable products with predictable uniform drug release.

Introduction

Aspirin holds a unique position among all drugs in clinical medicine because of its general lack of adverse effects. The main problem in aspirin medication is the risk of gastric irritation and bleeding. Previous reports showed that aspirin in microencapsulated form was better absorbed, provided a prolonged stable plasma salicylates concentration, produced significantly fewer gastric ulcerations and was much more tolerated compared to raw or conventional aspirin (Lechat et al., 1967; Bell et al., 1966; Vignalou and Beck, 1967; Wiseman, 1969; Khalil and El-Gamal, 1973; Khalil and El-Gamal, 1971; Khalil et al., 1971). Slow releasing aspirin formulations were found ideal to provide the small doses of aspirin required for their antithrombotic effect (Roberts et. al., 1984; Roberts et al., 1986).

One of the most widely used polymers for the preparation of sustained release formulations is Eudragit retard (the less permeable, RS grade, and the more permeable RL grade). Beside its inertness to the digestive tract, it is pH-independent, insoluble in the digestive tract but swells to release the drug by diffusion (Jalsenjak et al., 1980). In a further study (Hannula and Harmia, 1982), sustained release aspirin tablets were prepared using Eudragit as binder. The effects of drug concentration, granulation time and granulating solution composition on the release kinetics of the prepared tablets were studied (Hannula and Harmia, 1982; Hannula, 1983).

In this report, two types of sustained-release aspirin tablets, RS and RL tablets, were prepared using Eudragit as a coating material to the aspirin

* *Present address*: School of Pharmacy, University of Alexandria, Alexandria, Egypt.
Correspondence: A. M. Molokhia, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

granules. The effect of storage at relatively high temperature and humidity of these tablets was studied and compared with the results obtained simultaneously for plain aspirin tablets.

Materials and Methods

Materials

Aspirin crystalline powder was obtained from Merck (Darmstadt, F.R.G.); starch powder from Fluka (Buchs, Switzerland); Eudragit RL-100 and the less permeable grade Eudragit RS-100 (polyacrylate–polymethacrylate copolymers with low quaternary ammonium groups) from Rohm Pharma (Darmstadt, F.R.G.); and polyisobutylene (PIB) from BASF (Ludwigshafen, F.R.G.). All other reagents were of pure grade and used as supplied.

Methods

Preparation of microcapsules

Aspirin-Eudragit RS and Aspirin-Eudragit RL microcapsules were prepared using the phase separation method (Benita et al., 1985). A 20 g quantity of 8% w/w polymer solution was prepared in chloroform to which PIB (6% w/w) was added to prevent aggregation of the prepared microcapsules. Five grams of aspirin powder (particle size 250–315 μm) were dispersed in the above solution and stirred at 200 rpm. An adequate volume of cyclohexane was added to the dispersion dropwise at a rate of 10 ml/min at room temperature until complete phase separation was achieved. The microcapsules were separated by decantation followed by filtration and washing with 2 aliquots each of 100 ml cyclohexane to remove excess PIB. The product was dried under vacuum at room temperature for 24 h. Microcapsules were subjected to sieve separation and fractions having a particle size of 315–800 μm were used for the preparation of tablets. A known weight of the microcapsules was dissolved in methanol and assayed for aspirin content spectrophotometrically. The UV absorbance at 278 nm was measured in a Pye Unicam SP 8800 Spectrophotometer (Cambridge, U.K.). Blank experiments showed no interference from Eudragit in methanol at the above wavelength.

Preparation of tablets

Aspirin microcapsules were mixed with 10% starch disintegrant and directly compressed in a single-punch machine (Erweka, Type EKD, Frankfurt, F.R.G.). Tablet weight was adjusted to contain approximately 250–300 mg of aspirin. The hardness was measured in kg in a hardness tester (Erweka, Type TB24, Frankfurt, F.R.G.) and was adjusted to the range of 4–6 kg. The tablets were then packed in groups in paper bags and stored in a humidity chamber maintained at 40 °C/90% R.H. Plain aspirin tablets (Aspro, Nicholas Laboratories, U.K.) with more than 4 years remaining in their shelf-life were also packed and stored under the same conditions.

Individual packs were sampled after 0, 2, 5 and 9 weeks and examined for disintegration (6 tablets), drug release (2 tablets) and aspirin and free salicylic acid content (4 tablets). Disintegration was determined in double-distilled water in a USP apparatus (Erweka, Type ZT4, Frankfurt, F.R.G.). Aspirin release in 0.05 M acetate buffer, pH 4.5, was measured in a USP dissolution apparatus (Erweka, Type DT, Frankfurt, F.R.G.) according to the USP XX method. Samples were withdrawn at different time intervals, filtered through a 0.45 μm pore size filter, properly diluted with the dissolution medium and assayed for aspirin by measuring UV absorption at 265 nm. Aspirin content in tablets was determined by the same method used to determine aspirin in the microcapsules. The free salicylic acid was determined by chloroform extraction from crushed tablets in presence of sulphuric acid. The chloroform extract was treated with ferric nitrate aqueous solution. The aqueous layer was then separated and absorbance was measured at 530 nm. A standard solution of salicylic acid in chloroform was used as a reference.

Results and Discussion

Results of aspirin content determination carried on the 3 types of aspirin tablets tested in this

TABLE 1

Aspirin content before storage

Tablet no.	Aspirin (mg)		
	Aspro	RS coated	RL coated
1	325	269	271
2	308	258	260
3	282	252	254
4	290	262	270
5	317	259	262
6	303	273	250
7	298	248	276
8	305	256	276
9	308	258	267
10	312	246	255
Tolerance limits	255–345 *	220–296 **	225–303 **

* Based on label claimed drug content.

** Based on mean drug content in compressed tablets.

study immediately before storage are shown in Table 1. According to the USP specifications for tablet content uniformity, the commercial brand as well as the two microencapsulated aspirin tablets were found to comply with the requirement. The effect of storage on aspirin and free salicylic acid contents was followed by examining 4 tablets of each formulation for both ingredients. The data are presented in Figs. 1–3. The plain aspirin tablets (Fig. 1) showed a decrease in the average acetyl salicylic acid content of up to 6% during the period of storage. This result was expected because of the high relative humidity and temperature to which the tablets were exposed. The free salicylic acid content, however, increased

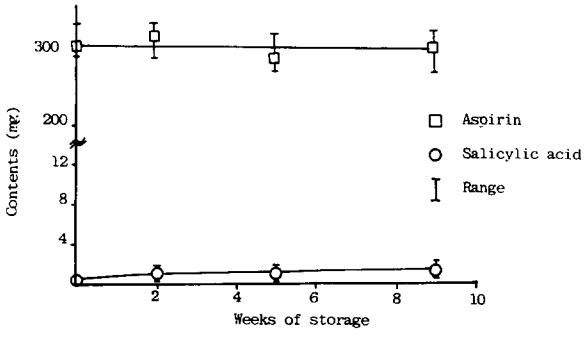

Fig. 1. Effect of storage on aspirin and salicylic acid contents of Aspro tablets.

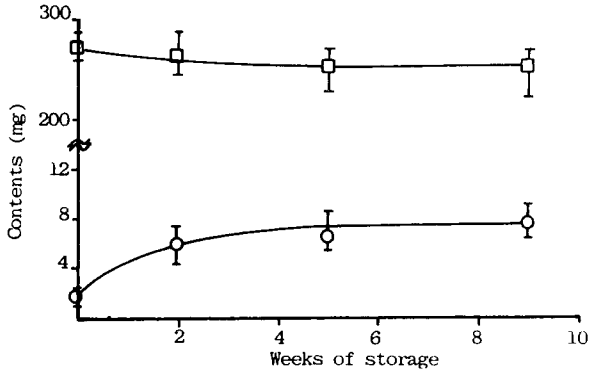

Fig. 2. Effect of storage on aspirin and salicylic acid contents of RS coated tablets.

only from 0.16% to 0.3% after the first 2 weeks of storage and remained constant thereafter. Probably, most of the salicylic acid produced from aspirin decomposition sublimed under the conditions of storage leaving a small amount in the tablets.

Figs. 2 and 3 show that the microencapsulated aspirin tablets gradually decreased in potency during the first 5 weeks of storage then remained almost stable thereafter. On the other hand, because of the entrapment within the granule polymer shell, the free salicylic acid content increased from 0.3% up to about 3% after 5 weeks of storage with no indication of further increase. Such stabilization benefit is expected to be more pronounced after long-term storage.

Table 2 shows the effect of storage on disintegration. Plain aspirin tablets showed no signifi-

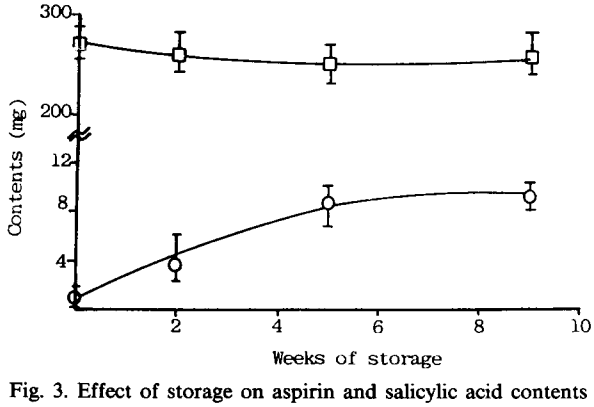

Fig. 3. Effect of storage on aspirin and salicylic acid contents of RL coated tablets.

TABLE 2

Effect of storage on disintegration

Weeks of storage	Disintegration time (average of 3 readings)		
	Aspro (s)	RS (h)	RL (h)
0	32	0.87	0.85
2	42	2.25	2.33
5	62	> 3	> 3
9	35	> 3	> 3

cant change in disintegration time by storage. The average times recorded conform with the disintegration requirement for the uncoated aspirin tablets. Despite the presence of 10% starch in the other two formulations, disintegration was very slow (about 52 min). It was believed that the presence of the disintegrant in the formulation would lead to tablet disintegration with the liberation of the microencapsulated aspirin granules which, in turn, should result in a uniform drug release. However, upon storage, a further increase in disintegration time was observed with the tablets turning into a non-disintegrable mass after 2–5 weeks.

The storage effect on tablet disintegration was reflected on drug release. The plain aspirin tablets (Fig. 4) showed no change in the amounts of acetyl salicylic acid released after 20–30 min (about 100%) with a slight decrease in the initial

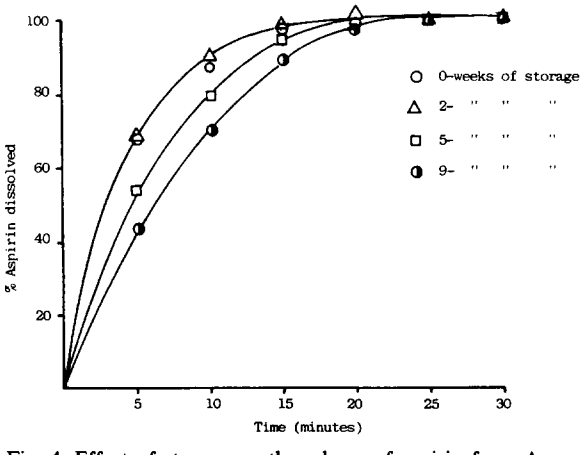

Fig. 4. Effect of storage on the release of aspirin from Aspro tablets.

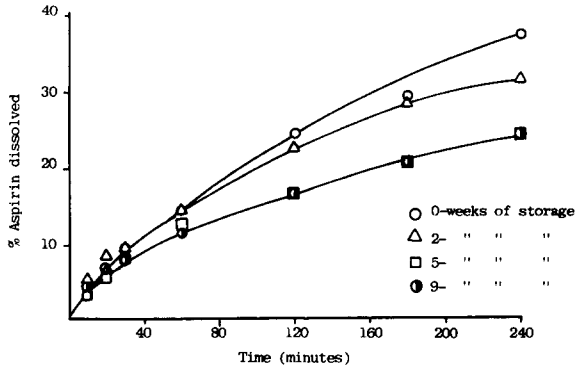

Fig. 5. Effect of storage on the release of aspirin from RS coated tablets.

rate of release. The RS and RL tablets (Figs. 5 and 6) showed slow rates of drug release with only 8% and 11% of the total aspirin content released after 30 min and 37% and 49% released after 4 h, respectively. The rate of release decreased upon storage until a minimum rate was reached after 2–5 weeks with no further decrease. Apparently, the polymer coat is slowing drug release from the granules with the diffusion across the polymer layer as the rate-determining step for the release process. After storage for 5–9 weeks the amounts of aspirin released within 4 h for the RS and the RL tablets were almost the same (23%). The observed decrease in the release rate upon storage of these two formulations is probably due to changes

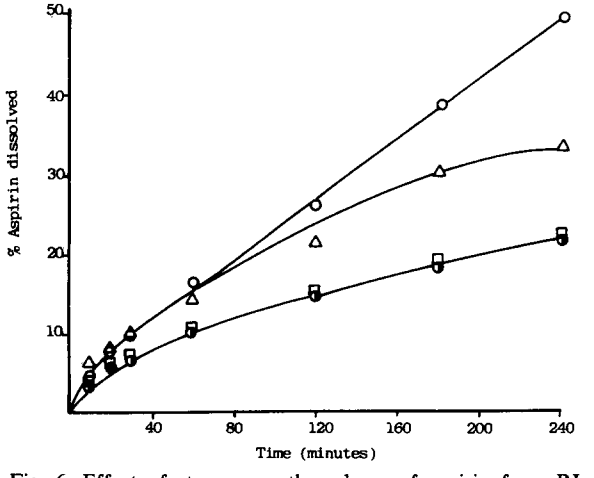

Fig. 6. Effect of storage on the release of aspirin from RL coated tablets.

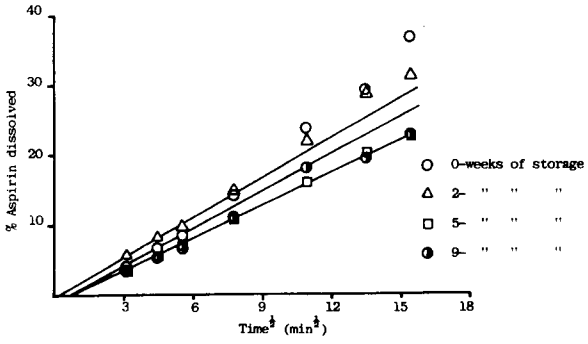

Fig. 7. Effect of storage on the relationship between aspirin release and $t^{1/2}$ for the RS coated tablets.

in the polymer film. Cross-linking of the polymer molecules enhanced by the conditions of storage may have resulted in perfection of coverage to the aspirin granules and/or increase in the film resistance to drug diffusion.

This view is supported by the plots of amounts released versus $t^{1/2}$ (Figs. 7, 8) which show a positive deviation from linearity after about 2 h in the dissolution experiment for tablets before storage and after 2 weeks of storage. Similar positive deviation was previously observed (Baveja et al., 1985) and was attributed to surface attrition with decrease in diffusional path length for the drug.

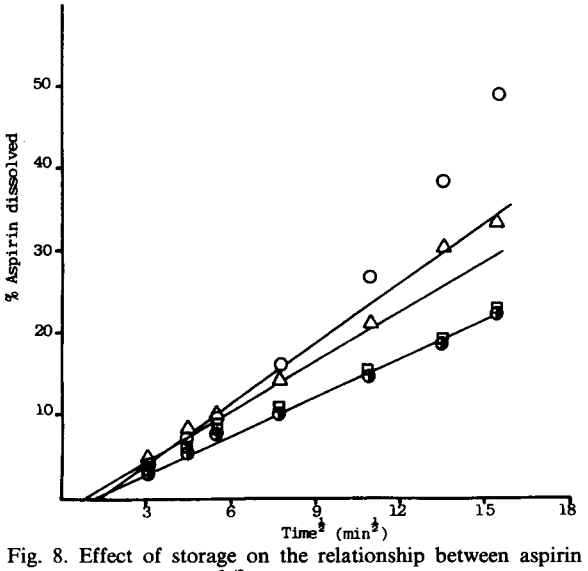

Fig. 8. Effect of storage on the relationship between aspirin release and $t^{1/2}$ for the RL coated tablets.

Such change probably takes place at weakly covered spots and disappears as coverage is strengthened. The prolongation of the tablet disintegration time followed by the inability to disintegrate may also be related to physical changes in the matrix with strengthened bonds between the polymer molecules.

For a slow release dosage form any change in drug release rate should be accounted for and if possible corrected, before handling. In this research, the rate of release of aspirin from the RS and RL formulations although showing a marked decrease upon storage still released amounts within the therapeutic level required for its antithrombotic activity. Furthermore, it is possible that a prior exposure of the polymer-coated granules to conditions favoring strengthening of the polymer film without affecting the active drug before compression may result in a more stable and acceptable product with properly predicted drug release rate.

Conclusions

A slow release with prolonged action aspirin preparation is an ideal dosage form for patients seeking the antithrombotic effect of aspirin. A small daily dose of aspirin was found ideal for this purpose (Roberts et al., 1986). Few preparations of aspirin with slow release characteristics are marketed. The effect of storage on the release pattern from these formulations has not been carefully studied. In this study, two sustained release formulations of aspirin were prepared and tested for drug release and storage effect. The data suggest that: (a) Eudragit RL and RS are suitable polymeric materials for the preparation of slow release aspirin tablets with similar properties; (b) the tablets produced are more stable towards high temperature and humidity conditions compared to plain aspirin tablets; and (c) the storage-related changes in disintegration and drug release are in agreement and show that film resistance to drug release increases by storage.

Further studies are necessary to prove that film treatment under acceptable conditions would result in a storage-resistant product with a constant drug release rate.

Acknowledgements

This research was supported by the Research Center, College of Pharmacy, King Saud University. The authors are grateful to Mr. K. Abbas for manuscript typing.

References

Baveja, S.K., Rao, K.V. and Devi, K.P., Sustained release tablet formulation of diethylcarbamazine, Part III. *Int. J. Pharm.*, 27 (1985) 157–162.

Bell, S.A., et al., Drug blood levels as indices in evaluation of a sustained-release aspirin. *J. New Drugs*, 6 (1966) 284–293.

Benita, S., Hoffman, A. and Donbrow, M., Microencapsulation of paracetamol using polyacrylate resins (Eudragit retard), kinetics of drug release and evaluation of kinetic model. *J. Pharm. Pharmacol.*, 37 (1985) 391–395.

Hannula, A.M., Release kinetics of acetyl salicylic acid from tablets made with acrylic resin binder. Influence of granulation solution. *Acta Pharm. Fenn.*, 92 (1983) 45–56.

Hannula, A.M. and Harmia, T., Drug release from plastic matrix tablets granulated with drug solutions-the influence of concentration and granulating time. *Acta Pharm. Fenn.*, 91 (1982) 239–246.

Jalsenjak, I., Nixon, J.R., Senjkovic, R. and Stivic, I., Sustained-release dosing forms of microencapsulated isoniazid. *J. Pharm. Pharmacol.*, 32 (1980) 678–680.

Khalil, S.A.H. and El-Gamal, S.S., In-vitro release of aspirin from various wax-coated formulations. *J. Pharm. Pharmacol.*, 23 (1971) 72–74.

Khalil, S.A.H. and El-Gamal, S.S., Coating of pharmaceuticals by phase separation of cellulose derivatives: Preparation and in-vitro release. *Pharmazie*, 28 (1973) 385–388.

Khalil, S.A.H., El-Gamal, S.S., and Abdel Khalek, M.M., In-vitro release of phenobarbitone from gelatin micropellets. Effect of pH of preparation. *Acta Pharm. Suec.*, 8 (1971) 423–430.

Lechat, P., Ganter, P., Fontagne, J. and Flouvat, B., Experimental study on the gastric tolerance of aspirin in coated particles. *Therapie*, 22 (1967) 403–410.

Roberts, M.S., Joyce, R.M., McLeod, L.J., Vial, J.H. and Seville, P.R., Slow-release aspirin and prostaglandin inhibition (letter). *Lancet*, 1 (1986) 1153–1154.

Roberts, M.S., McLeod, L.J., Cossum, P.A. and Vial, J.H., Inhibition of platelet function by a controlled release acetyl salicylic acid formulation-single and chronic dosing studies. *Eur. J. Clin. Pharmacol.*, 27 (1984) 67–74.

Vignalou, J. and Beck, H., Clinical and biological study of 2 forms of aspirin. Estimation of gastric tolerance. *Therapie*, 22 (1967) 967–975.

Wiseman, E.H., Plasma salicylate concentrations following chronic administration of aspirin as conventional and sustained-release tablets. *Curr. Ther. Res.*, 11 (1969) 681–689.