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Instability of drug release from anhydrous theophylline–microcrystalline cellulose formulations

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Summary

In the production of anhydrous theophylline–microcrystalline cellulose pellets, extrusion is preceded by wet granulation. Wet granulation also used in the tablet production causes a remarkable decrease in drug release rate accompanied by a conversion of anhydrous theophylline into theophylline monohydrate. Oven drying at 40 °C does not seem sufficient to restore this conversion. The formation of additional bindings may be responsible for the decrease in drug release rate instead of the crystal transition. The degree of the further decrease in drug release rate during storage depends on the humidity conditions and the packaging. This instability in pharmaceutical availability seems specific for the combination of theophylline and microcrystalline cellulose. A decrease in dissolution rate is also seen for dry compressed anhydrous theophylline–microcrystalline cellulose blends when stored at high humidity levels. Storage at low humidity levels or the use of another diluent seem to overcome this unpredictable change in drug dissolution rate.

Introduction

Microcrystalline cellulose is a widely used excipient in the production of pellets and tablets. The drug release rate of theophylline from pellets containing microcrystalline cellulose is influenced by the production parameters and is related to the amount of water used during the granulation step. Simultaneously a conversion of anhydrous theophylline in theophylline monohydrate is observed (Herman et al., 1988). As both theophylline polymorphs have a different dissolution rate, it is believed that the crystal transition is responsible for the change of drug dissolution rate.

To elucidate this change in drug release rate, simulated pellets and tablets of a different composition were produced and investigated for their dissolution profiles, crystal transitions and weight variations.

Finally, the influence of storage conditions and packaging on the stability of the dissolution rate is presented.

Materials and Methods

Formulation A was produced by direct compression of 60 mg anhydrous theophylline (micronised theophylline, Boehringer Ingelheim, F.R.G.) and 40 mg Avicel pH 101 (F.M.C. Philadelphia, U.S.A.). The powders were mixed for 10 min in a planetary mixer (Kenwood, type N 901). A com-

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pression force of 90 kg/cm^2 was applied in order to produce 7 mm flat tablets using an eccentric press (Korsch, Frankfurt, F.R.G.).

Formulation B contained theophylline monohydrate (Carlo Erba, Milano, Italy). The ratio 60/40 (w/w) of drug/Avicel pH 101 was calculated as anhydrous theophylline (without crystalline water). Tablets were made as described for formulation A.

Formulation C contained anhydrous theophylline and STA RX-1500 (Colorcon, Orpington, U.K.) (60/40 w/w). The powders were mixed in a planetary mixer (Kenwood, type N 901) for 10 min and granulated with 80% (w/w) water calculated on dry weight base. The wet powder mass was forced through a 1500 μm sieve in order to simulate the extrusion process. 500 mg wet granules were wet compressed on an eccentric press at a pressure of 90 kg $\cdot$ cm^{-2} using 7 mm flat punches. These wet tablets were finally oven-dried for 3 h at 40 °C.

Formulation D consisted of anhydrous theophylline and Avicel pH 101 and was treated as described in the production procedure of formulation C.

Storage conditions

Tablets A were stored unpacked at 90% R.H. whereas *tablets B* and *C* were stored unpacked at 30% R.H.

Tablets D were stored at different humidity levels (80% and 30% R.H.) both unpacked and filled in hard gelatin capsules or aluminum/polyethylene unit-dose bags.

Evaluation tests

After production, all tablets were subjected to a dissolution test in 900 ml water at 37 °C using the paddle method (USP XXI). The drug release was monitored continuously at 271 nm (Zeiss, PM6 UV spectrophotometer, F.R.G.).

X-Ray diffractions (Philips, PA25 equipped with a copper anticathode, 25 mA, 40 kV) and weight determinations were also performed on the freshly prepared tablets.

TABLE 1

Time of 50% drug release (h) and weight variation data, referred to the weight immediately after production (%, ±S.D.) of different simulated pellet formulations stored under different conditions for several weeks

U = unpacked; C = filled in hard gelatine capsules; AP = packed in aluminum/polyethylene unit bags.

Storage time (weeks)	Formulations								
	A	B	C	D					
	Storage and packaging conditions								
	90%	30%	30%	80%			30%		
	U	U	U	U	C	AP	U	C	AP
Dissolution time									
0	0.07	0.07	2.1	3.2	3.2	3.2	3.2	3.2	3.2
	(0.03)	(0.02)	(0.1)	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)
1	0.38	0.08	2.2	7.0	4.7	3.6	3.2	3.6	3.0
	(0.08)	(0.02)	(0.2)	(0.6)	(0.9)	(0.2)	(0.8)	(1.2)	(0.8)
3	0.52	0.08	2.0	6.9	6.3	4.4	3.4	4.0	3.6
	(0.08)	(0.04)	(0.2)	(0.6)	(0.7)	(0.6)	(0.4)	(0.8)	(1.1)
6	1.08	0.08	2.1	6.9	6.4	4.3	3.4	3.8	3.5
	(0.11)	(0.04)	(0.2)	(0.3)	(0.7)	(0.8)	(0.8)	(0.7)	(0.7)
Weight variation									
1	15.5	−2.8	1.4	7.0	2.3	0.3	0.5	1.2	0.5
	(0.6)	(0.1)	(0.3)	(0.1)	(0.2)	(0.0)	(0.0)	(0.1)	(0.0)
3	17.0	−4.8	1.3	7.2	6.4	0.3	−0.4	0.5	0.3
	(0.7)	(0.2)	(0.1)	(0.6)	(0.3)	(0.0)	(0.0)	(0.1)	(0.0)
6	19.0	−7.6	1.3	7.3	7.3	0.3	−0.9	−0.2	0.2
	(0.9)	(0.3)	(0.1)	(0.5)	(0.4)	(0.0)	(0.1)	(0.0)	(0.0)

All test were carried out in triplicate and replicated after 1, 3 and 6 weeks of storage.

Results and Discussion

Initially, formulation A consisting of directly compressed anhydrous theophylline and microcrystalline cellulose, showed a fast drug release (Table 1). After one week of storage at a high humidity level (90% R.H.) the unpacked tablets A showed a dramatic decrease in release rate. X-Ray diffractions indicated that the anhydrous theophylline was completely converted into the monohydrate form. Also the tablet weight increased for more than 15%. These data indicate that tablets A stored at high humidity levels absorb water causing a conversion of anhydrous theophylline into theophylline monohydrate which was believed to be responsible for the decrease in release rate (Herman et al., 1988).

Considering previous results, in contrast to what one might expect freshly prepared tablets B, containing theophylline monohydrate, showed a similar drug release rate to freshly prepared tablets A containing anhydrous theophylline. After storage at 30% R.H., X-ray diffractions of tablets B revealed a conversion of theophylline monohydrate to anhydrous theophylline in function of time which was accompanied by a gradual loss of weight. Although anhydrous theophylline has a higher dissolution rate than theophylline monohydrate (Shefter and Higuchi, 1963), a decrease in drug release rate was seen after one week storage time at 30% R.H. (Fig. 1). This observation and the similarity in the initial release rate of tablets A and B indicate that the formation of theophylline monohydrate is not responsible for a decrease of the drug release rate. The free water created by the crystal transition may initiate the formation of additional bonds between theophylline and microcrystalline cellulose which could be responsible for the small decrease in drug release rate.

Tablets C, containing anhydrous theophylline and STA RX-1500 instead of microcrystalline cellulose and prepared by wet granulation, did not disintegrate in water resulting in a relatively slow drug release. No change in release rate was observed during storage at 30% R.H. X-Ray diffractions showed the presence of theophylline monohydrate just before the oven-drying step. During oven-drying, the theophylline monohydrate was completely converted into the anhydrous form which is in contrast to tablets D where oven-drying (40 °C, 3 h) was not able to reconvert theophylline monohydrate into the original anhydrous form. This indicates that the inability of reconversion after wet granulation is related to the presence of microcrystalline cellulose. These data allow us to suppose that apart from the theophylline crystal transition, humidity might induce the formation of additional bindings between theophylline and microcrystalline cellulose causing a decrease in drug release rate.

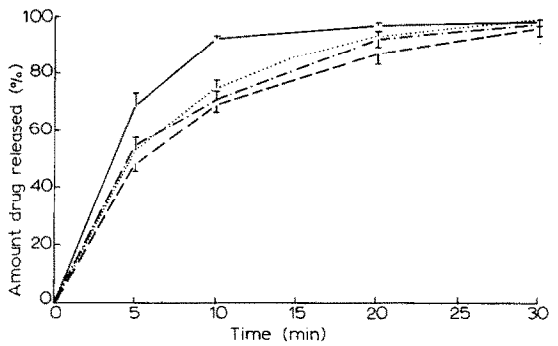

Fig. 1. Drug release of directly compressed simulated tablets containing theophylline monohydrate and microcrystalline cellulose, immediately after production (———) and after 1 (· · · · · ·), 3 (------) and 6 (· – · – ·) weeks of storage at 30% R.H. The dissolution medium was water at 37 °C. The vertical bars indicate S.D. ($n = 3$).

As a consequence of these findings, the drug release of tablets D stored at 80% and 30% relative humidity levels was examined. Tablets D were unpacked, filled in hard gelatin capsules and in aluminum/polyethylene unit-bags, respectively, and were stored for 6 weeks at different humidity levels as indicated in Table 1. Compared to formulation A produced by direct compression, the release rate of wet compressed tablets D was lower immediately after production. These observations confirm the results reported by Herman et al. (1988) (Fig. 2). After one week, the release rate of the unpacked tablets D, stored at 80% R.H., was lower than the release rate observed immediately

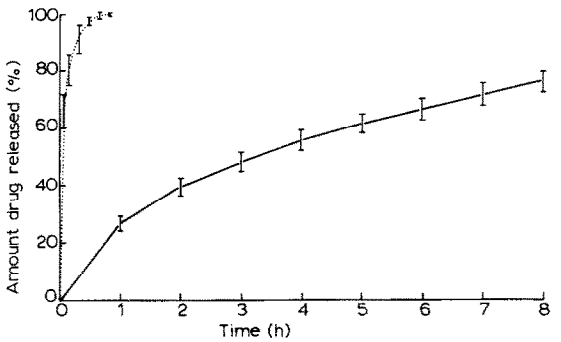

Fig. 2. Drug release of freshly prepared tablets containing anhydrous theophylline and microcrystalline cellulose, produced by direct compression (· · · · · ·) and by wet compression (———) ($n = 3$).

after production. For tablets filled in hard gelatin capsules, a similar decrease in release rate was observed after a period of 3 weeks storage. This indicates that the hard gelatin capsules seem to hinder the transport of water vapor. This was confirmed by the difference in gradual weight increase of the tablets packed in hard gelatin capsules, compared to the unpacked samples. Tablets packed in aluminum/polyethylene unit-bags showed only a minor decrease in release rate.

The drug release rate of tablets D, packed or unpacked, did not change after a storage for 6 weeks at 30% R.H.; neither did the tablet weight, in comparison to freshly prepared tablets D. All X-ray diffraction patterns of tablets D, whether they were stored at 30% R.H. or 80% R.H. confirmed the presence of theophylline monohydrate instead of the initially used anhydrous theophylline. This indicates that neither the oven-drying after the wet compression step, nor a 6-week exposure at 30% R.H. were sufficient to reconvert theophylline monohydrate into the anhydrous form.

In contrast to STA RX-1500, microcrystalline cellulose seems to hold water during oven-drying preventing the crystal conversion of theophylline monohydrate to the anhydrous form during oven drying at 40 °C.

Because of the excess of water held in these tablets containing microcrystalline cellulose and prepared by wet granulation, no water of crystalization must be consumed for the formation of additional bindings as reported for formulation B.

Conclusion

The drug release rate of tablets or pellets containing anhydrous theophylline and microcrystalline cellulose is decreased by an aqueous granulation procedure or storage in humid conditions. Although this phenomenon is accompanied by the formation of theophylline monohydrate, this crystal transition does not seem to be responsible for a change in dissolution rate. The real cause of the decrease in release rate might be the formation of additional bindings between theophylline and microcrystalline cellulose in the presence of moisture. The drug release rate of these formulations varied as a function of the storage conditions and packaging materials. A stable release rate as a function of storage time could only be guaranteed in humidity levels not exceeding 30% R.H. These stability problems can be avoided by using a diluent as STA RX-1500 instead of microcrystalline cellulose.

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