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RESEARCH PAPER

The In Vitro Dissolution of Theophylline from Different Types of Hard Shell Capsules

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ABSTRACT

The in vitro dissolution of theophylline from two-piece hard shell capsules has been investigated using different types of capsule shells (gelatin, gelatin/polyethylene glycol, hydroxypropyl methylcellulose), different formulations, different capsule fill weights, and different tamping forces. Analysis of variance confirmed that the formulation and the capsule shell materials were the most important factors influencing drug dissolution. The maximum extent of drug dissolution was significantly increased when hydroxypropyl methylcellulose (HPMC) capsules were used. The mean dissolution time (MDT) was significantly reduced, indicating a faster dissolution rate of the drug from HPMC capsules. The addition of microfine cellulose to the formulations as filler reduced the MDT in all cases, whereas the addition of lactose monohydrate did not enhance drug dissolution. The study confirmed that a change from gelatin hard shell capsules to gelatin/PEG or HPMC hard shell capsules should not pose problems with respect to drug absorption or bioavailability.

Key Words: *Drug dissolution; Gelatin capsules; Hydroxypropyl methylcellulose capsules; Two-piece hard shell capsules*

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INTRODUCTION

Solid oral dosage forms are well accepted by patients as a form of efficient and painless treatment. The introduction of the two-piece hard shell capsule allowed the administration of powdered materials as single unit dosage forms, even if these could not be compacted. Other advantages of powder-filled hard shell capsules are, for example, taste masking and enhanced drug dissolution. The latter is one key factor in the pharmacological performance of a drug.

With the recent introduction of hydroxypropyl methylcellulose (HPMC) hard shell capsules as an alternative to conventional gelatin hard shell capsules, problems involved in the filling of hygroscopic and moisture-sensitive drugs and drugs causing cross-linking of gelatin molecules can be overcome.[1] However, for HPMC capsules to be accepted as a replacement for gelatin hard shell capsules, proof is required that the drug dissolution is not hindered from such two-piece hard shells. Chiwele et al.[2] compared the shell dissolution time of various empty hard capsules under different test and storage conditions. They found that in water and dissolution media similar to gastric fluids at 37°C the shell dissolution time of HPMC capsules was only slightly longer than that of gelatin or gelatin/PEG capsule shells. However, while gelatin and gelatin/PEG capsule shells dissolved first at their weakest points, i.e., at the shoulder of the round ends, HPMC capsules dissolved evenly across the shell.

The aim of this work was to assess the dissolution of a poorly water-soluble drug, theophylline, from different types of two-piece hard shell capsules. The influence of the shell composition was compared with other factors known to modulate the dissolution of drugs, i.e., tamping force, fill weight, and formulation. Any capsule shell could prolong the dissolution of a drug from the enclosed powder plug to a certain degree, which can be estimated either from the dissolution time of the empty shell, or by using powder plugs without encapsulating them, as control. The shell dissolution time of different types of hard shell capsules can be investigated easily,[2] whereas to produce powder plugs of sufficient mechanical strength to handle without their protective shell, yet of a porosity high enough to be relevant for use in capsules, is impossible in most cases. Also, in this paper emphasis is placed on a comparison of alternative types of capsule shells with the traditionally used gelatin shells to investigate whether the new shells could pose problems in terms of a reduced bioavailability. Hence, powder-filled gelatin capsules were used as control in the studies. All dissolution tests were performed in water, as it has been shown previously[2] that at 37°C the shell dissolution times of the different types of capsules were not different in 0.1 M HCl and water. Furthermore, the Pharmacopoeias do not prescribe the use of buffered media, when studying rapid release dosage forms.

EXPERIMENTAL

Drug and Excipients

Theophylline anhydrous (batch 95658, Knoll AG, Ludwigshafen, Germany), lactose monohydrate (Pharmatose 110M®, batch 025512, DMV, Veghel, Netherlands), microfine cellulose (Vivacel A300®, batch 070809111, Rettenmeier & Sons, Ellwangen-Holzmühle, Germany), and magnesium stearate (batch 1691198, Medex Pharmaceuticals, Naseby, U.K.) were used as received. All capsule shells were supplied by Shionogi Qualicaps, S.A. (Alcobendas, Spain).

Formulations

Three different formulations (see Table 1) were compared in this study: (a) formulation "T," i.e., theophylline (99.5%) and magnesium stearate (0.5%); (b) formulation "T + L," i.e., theophylline (50%), lactose monohydrate (49.5%), and magnesium stearate (0.5%); and (c) formulation "T + C," i.e., theophylline (50%), microfine cellulose (49.5%), and magnesium stearate (0.5%). All powder mixtures were prepared using a mortar and pestle as follows. The appropriate weight to produce 20 capsules was placed into the mortar except for the magnesium stearate. The powders were mixed for 10 min, with the mortar wall being scraped clean at 1-min intervals. The required amount of magnesium stearate was added and mixed for 2 min only. The use of drug without addition of magnesium stearate as a control was not possible due to the stickiness of the powder to the die and the tamping pin of the powder plug estimator used to produce the powder plugs (see below).

Individual amounts of powder mixture were weighed to ±0.001 g (Sartorius analytical balance,

Table 1

Factors and Factor Levels (Classification Numbers Indicated in Brackets) Used in Experiments and ANOVA

Factor	Levels	
Capsule shell material	Gelatin (1)	
	Gelatin/PEG (2)	
	HPMC (3)	
Formulation	T (1)	
	T+L (2)	
	T+C (3)	
Capsule fill weight and tamping force	450 mg (1)	104.5±4.6 N (1)
		72.6±2.5 N (2)
	425 mg (2)	81.9±1.7 N (2)
		52.9±1.9 N (3)
		33.4±2.1 N (4)
	400 mg (3)	52.0±2.0 N (3)
		23.0±4.0 N (4)

T=mixture of theophylline (99.5%) and magnesium stearate (0.5%); T+L=mixture of theophylline (50%), lactose monohydrate (49.5%), and magnesium stearate (0.5%); T+C=mixture of theophylline (50%), microfine cellulose (49.5%), and magnesium stearate (0.5%).

Göttingen, Germany) and placed into the die of a Höfliger and Karg powder-plug estimator,[3] which was instrumented with a load cell and an electronic micrometer (Mitutoyo, Tokyo, Japan). The tamping force used varied between 23.1 and 104.5 N, i.e., the typical range of forces achieved in modern tamp-filling machines.[4,5] The plugs formed were transferred into capsule shells, size 0, using a transfer plunger, whereby the die containing the plug was accurately centered above the capsule body. The latter was mounted into a special holder, which also allowed the replacement of the cap and closing of the capsules to the correct closed joined length of 21.8 mm.

Dissolution Tests

Drug dissolution was studied in an ERWEKA Dissolution tester (Pharmatest PTWS, Heusenstamm, Germany) using 1000 mL distilled water at 37°C and a paddle speed of 50 rpm. The drug concentration was monitored by UV spectrophotometry at a wavelength of 273 nm every 3 min up to 30 min, and then every 5 min up to the final observation time of 60 min. Capsules were placed into basket sinkers to prevent flotation. The saturation solubility of anhydrous theophylline in water is 8 g/L. Hence, even at the highest dose of 450 mg, sink conditions were maintained throughout the experiment.

Experimental Design and Statistical Analysis

For a plug to fit fully the body of a size 0 capsule, the plug length should not exceed 18.5 mm. Depending on the capsule fill weight, densification of the powder plug using a defined tamping force is required. The force should be large enough to form a plug, which can be transferred easily into the capsule body. However, the plug density should not exceed that of the tap density of the powder mixture to allow rapid deaggregation of the particles forming the powder plug.[6] Industrial use of capsule-filling machinery has shown that the plug length should fill preferably at least 80–90% of the capsule body to avoid large variability in capsule fill weight. This could be due to the ratio between plug length and diameter in underfilled capsules being too small, which will prevent arching and hence result in a plug collapse during transfer from the nozzles or dosing bores into the capsule body. Hence, for each capsule size the tamping force required to fill a specific weight will increase as the fill weight increases. Therefore, to study the influence of fill weight on drug dissolution, the

tamping force was adjusted in the experiments. All results are the mean and standard deviation of six replicates. Multifactorial analysis of variance (ANOVA) was used to study the influence of the individual formulation factors tested and their two-way interactions (SPSS 10.0, SPSS Inc., Woking, U.K.). Table 1 lists the different factors employed in this study and their levels in the ANOVA.

To provide a single normalized value to characterize the percentage release–time profiles, the mean dissolution time (MDT) was determined from each individual dissolution profile using the trapezoidal rule.[7,8]

RESULTS AND DISCUSSION

Total Amount of Drug Dissolved

The relative amount of drug dissolved after 60 min is compared in Figs. 1–3. Analysis of variance indicated that all factors and their two-way interactions were highly significant ($P \leq 0.002$), except for the interaction between capsule shell material and tamping force, which was insignificant. The dominant factor appeared to be the formulation ($F=334.09$), and also the capsule shell material was found to have a larger effect ($F=168.47$) than all other factors ($F < 20$). This is also reflected in the figures. When the dissolution values for the maximum fill weight are examined (Fig. 1), any addition of fillers, i.e., lactose or microfine cellulose, produced a significantly higher drug dissolution when compared to that of theophylline alone. Both excipients are hydrophilic. They promote water penetration into the powder plug, and in addition lactose enhances wetting of the drug particles. Either effect should result in improved drug dissolution. For HPMC capsules, the dissolution of all formulations after 60 min was greater than for the other two capsule types, whereas there appeared to be no difference between gelatin and gelatin/PEG capsules. There was also no difference in the shell dissolution time of gelatin and gelatin/PEG capsules in water at 37°C,[2] suggesting that the dissolution behavior here is mainly governed by the dissolution of the shells. With one exception, the addition of either filler resulted in a similar increase in the maximum drug dissolution. A comparable influence of capsule shell material was observed at

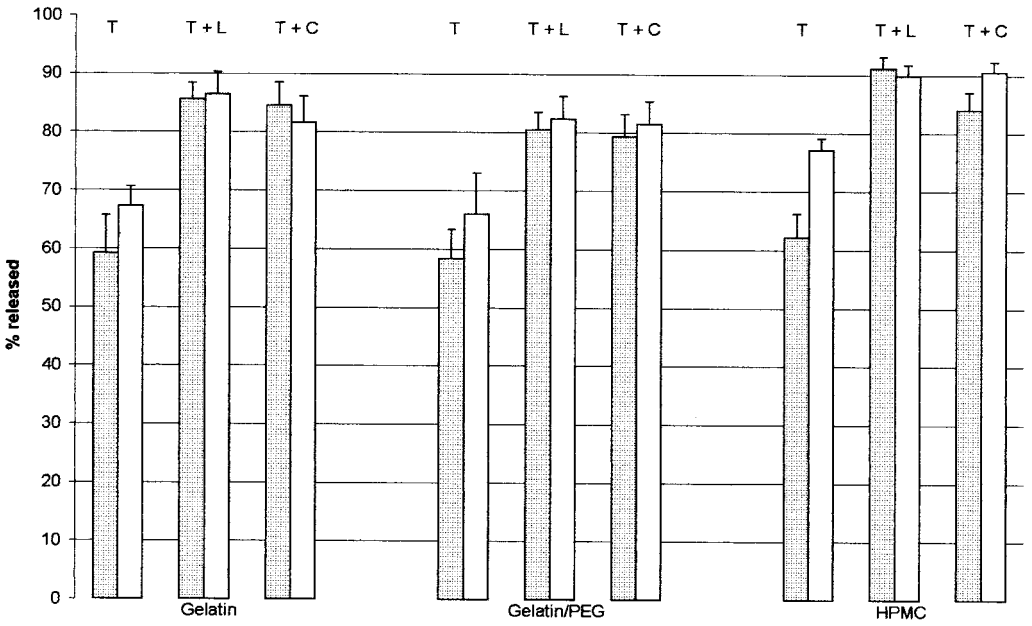

Figure 1. Percentage drug released after 60min from different hard shell capsules containing different formulations ($\bar{x}+s$, $n=6$) and a fill weight of 450mg. T=mixture of theophylline (99.5%) and magnesium stearate (0.5%); T+L=mixture of theophylline (50%), lactose monohydrate (49.5%), and magnesium stearate (0.5%); T+C=mixture of theophylline (50%), microfine cellulose (49.5%), and magnesium stearate (0.5%). Tamping force: shaded=72.6 N, white=104.5 N.

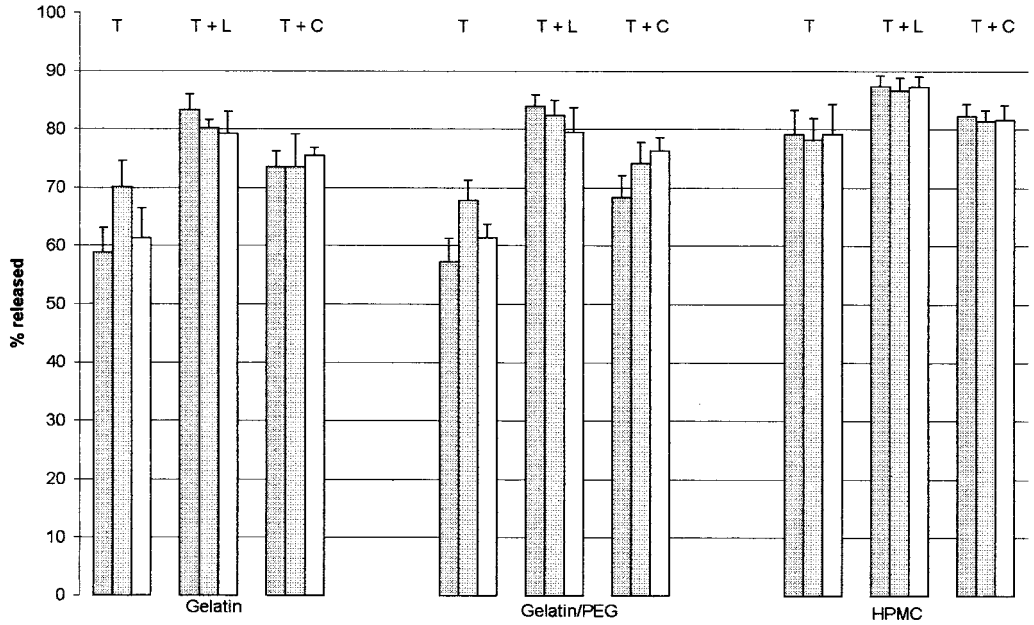

Figure 2. Percentage drug released after 60min from different hard shell capsules containing different formulations ($\bar{x}+s$, n=6) and a fill weight of 425mg. T=mixture of theophylline (99.5%) and magnesium stearate (0.5%); T+L=mixture of theophylline (50%), lactose monohydrate (49.5%), and magnesium stearate (0.5%); T+C=mixture of theophylline (50%), microfine cellulose (49.5%), and magnesium stearate (0.5%). Tamping force: dark shaded=33.4 N, light shaded=52.9 N, white=81.9 N.

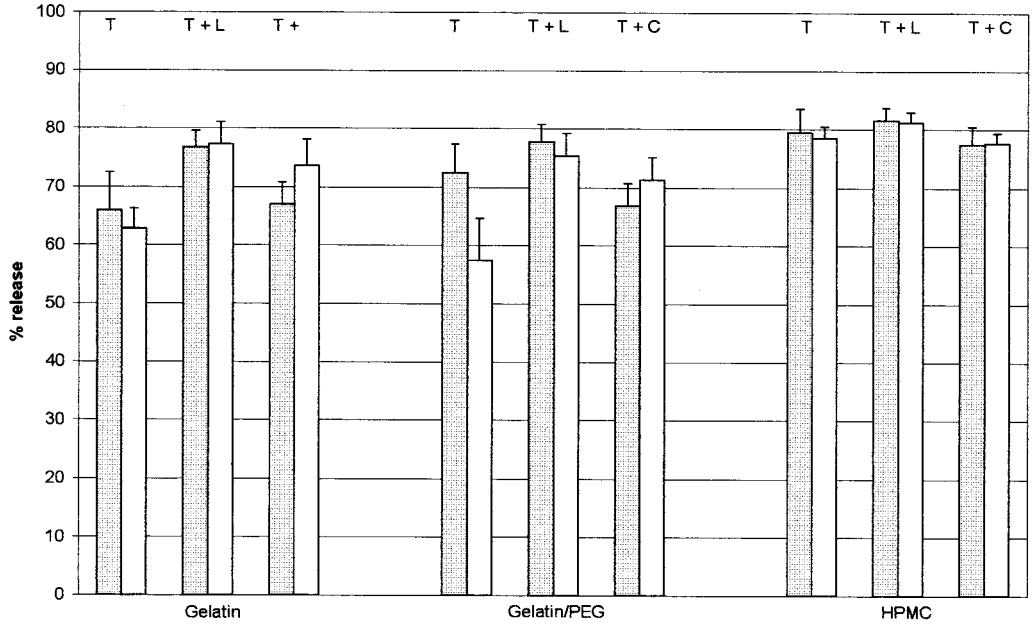

Figure 3. Percentage drug released after 60min from different hard shell capsules containing different formulations ($\bar{x}+s$, n=6) and a fill weight of 400mg. T=mixture of theophylline (99.5%) and magnesium stearate (0.5%); T+L=mixture of theophylline (50%), lactose monohydrate (49.5%), and magnesium stearate (0.5%); T+C=mixture of theophylline (50%), microfine cellulose (49.5%), and magnesium stearate (0.5%). Tamping force: shaded=23.1 N, white=52.0 N.

the lower fill weight of 425 mg (Fig. 2). However, in this case formulations containing lactose were found to promote drug dissolution more than those containing microfine cellulose. Due to the decrease in the total surface area of the powder plugs, lactose had a greater effect because of its combination of wetting and water penetration properties, as opposed to microfine cellulose which acts by swelling. This was also observed for the lowest fill weight of 400 mg (Fig. 3), but the influence of the capsule shell material was reduced.

Mean Dissolution Time

The maximum dissolution of drugs from dosage forms in a certain time period is not the only criterion related to drug absorption, although pharmacopoeial test methods would suggest this. The rate with which dissolution occurs is also very important and is often the rate-limiting process for drug absorption.[6] A calculation of the dissolution rate would require defining an appropriate kinetic law. However, here two processes overlap, namely the shell dissolution and the drug dissolution, and such a procedure would have to be viewed with skepticism. A model-independent approach is the use of the MDT.[7] The MDT reflects the dissolution rate and is shorter the faster the dissolution process progresses. The values for MDT are summarized in Table 2. Analysis of variance showed that the tamping force did not influence the MDT, nor were the two-way interactions between capsule shell material and fill weight or tamping force significant. From the other factors tested, the formulation proved again to be the most important variable (F=390.51), followed by the capsule shell material (F=43.83). To identify in which way the capsule shell materials influenced the MDT of the drug in these experiments, the Scheffé post hoc test[9] was employed in conjunction with the ANOVA. As indicated in Table 2, the MDT values of HPMC capsules were in several instances significantly smaller than those obtained using the gelatin or gelatin/PEG capsules. HPMC shell dissolution has been described as an even process proceeding simultaneously across the whole shell, whereas gelatin and gelatin/PEG capsule shells dissolve first at the shoulder of the round ends, and only later across the whole body.[2] When using HPMC shells the whole powder plug will hence be subjected to the dissolution medium earlier. The addition of microfine cellulose as the filler resulted in all cases in the shortest MDT, which in this case was independent of the capsule shell material. This might be due to the large swelling capacity of microfine cellulose.[10] However, if the capsules were filled with theophylline only or with the mixture containing lactose, drug release was significantly faster from HPMC capsules.

Table 2

Mean Dissolution Times (MDT, min) for Hard Shell Capsules Containing Theophylline Formulations for Different Fill Weights and Tamping Forces ($\bar{x}\pm s$, n=6)

Hard Shell Formulation	Gelatin			Gelatin/PEG			HPMC		
	T	T+L	T+C	T	T+L	T+C	T	T+L	T+C
450 mg									
104.5 N	20.0±3.1	18.6±2.8	10.2±1.4	20.1±2.2	19.4±3.3	11.0±1.5	20.4±0.8	14.4±1.9*	9.6±2.2
72.6 N	19.3±8.7	20.0±1.1	11.3±1.8	22.2±2.4	19.6±1.0	10.6±1.9	23.9±0.4	13.4±1.5***	10.7±1.8
425 mg									
81.9 N	19.9±0.4	19.3±2.0	9.5±1.1	20.1±1.7	21.2±2.0	9.7±1.0	16.2±1.4**	13.2±2.3***	9.5±1.9
52.9 N	18.2±1.5	18.5±2.5	10.5±1.7	18.9±1.8	19.2±1.8	11.9±3.0	16.8±2.4	13.5±1.5**	9.8±1.2
33.4 N	22.2±1.0	16.4±1.7	11.2±2.3	22.7±2.0	17.8±1.5	13.6±3.6	18.2±1.6***	12.6±1.7**	10.4±1.4
400 mg									
52.0 N	22.4±3.0	18.3±3.0	9.9±0.8	22.2±2.1	18.4±1.2	11.9±2.1	16.5±2.4**	13.9±1.6*	9.9±0.9
23.1 N	17.4±1.2	18.1±2.6	9.8±0.4	15.4±1.0	17.4±1.9	12.0±1.8	14.5±2.0*	14.6±1.6*	10.3±1.3

T=theophylline+0.5% magnesium stearate; T+L=50% theophylline+49.5% lactose+0.5% magnesium stearate; T+C=50% theophylline+49.5% microfine cellulose+0.5% magnesium stearate. Significance levels in Scheffé post hoc tests: *P<0.05, **P<0.01, ***P<0.001.

This indicates that the use of HPMC capsule shells could be advantageous for low solubility drugs. Overall, the general trend observed when comparing the total amount of drug dissolved in 60 min and the MDT values is similar. It is logical that a formulation that shows less drug release in the given time period, i.e., takes longer to dissolve the full drug content, will have a larger value for the MDT.

The study confirmed that a change from gelatin hard shell capsules to gelatin/PEG or HPMC hard shell capsules should not pose problems with respect to drug absorption and bioavailability. On the contrary, a slight advantage might be gained from using HPMC hard shell capsules instead of conventional gelatin capsule shells.

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