

The Shell Dissolution of Various Empty Hard Capsules

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The shell dissolution properties of gelatine, gelatine/polyethylene glycol (PEG) and hydroxypropyl methylcellulose (HPMC) capsules were studied as a function of temperature, dissolution medium, and after different storage conditions. In any dissolution medium with a pH below or equal to 5.8, HPMC capsule shells dissolved rapidly, and there was no difference in the time in which dissolution occurred in the tested temperature interval of 10 to 55 °C. Gelatine and gelatine/PEG capsule shells, generally, did not dissolve at temperatures below 30 °C. The shell dissolution time of all capsules tested was prolonged and more variable in mixed phosphate buffer pH=6.8. The addition of enzymes (pepsin, pancreatin) to any dissolution medium was found not to enhance the differences between the different types of capsules investigated. In practical terms, the results indicated that capsule formulations should not be taken with drinks from the carbonated Cola-type. Gelatine containing capsules should preferably be administered with a warm drink, whereas HPMC capsules could be given with cold or warm drinks. The latter type of capsules should also be preferred for preparations to be taken in the fasted state. A short storage of gelatine containing capsules under hot humid tropical conditions appeared not to alter the dissolution properties of the shells, and changes in disintegration times and dissolution times of formulations filled in such capsules might be a reflection of changes of the powders incorporated rather than of the capsule shells. However, a short storage of HPMC capsules under such conditions appeared to influence the capsule shell matrix.

Key words gelatine capsules; hydroxypropyl methylcellulose capsules; shell dissolution; two-piece hard shell capsules

Lehuby first patented the two-piece hard shell capsule in 1846. These capsules were made from starch or tapioca, sweetened with some sucrose and coloured with 'fish silver.' Several additions to the patent followed, describing the use of various materials and mixtures including gelatine. Gelatine has been the material of choice for the manufacture of hard shell capsules for a long time. Gelatine is a material widely used in food industry. It is readily soluble in biological fluids at body temperature and is a good film forming material. Its suitability for producing capsules is related to its ability to form a thermally reversible gel. However, some properties of gelatine films are disadvantageous for their use as a capsule shell material. For example, gelatine capsule shells exposed to low relative humidity of the storage air become brittle, which also occurs when they are filled with formulations containing hygroscopic materials. It was found that exposure to tropical conditions, with high relative humidity above about 60—70%, increased the minimum temperature for dissolution of gelatine films from 31 °C to over 50 °C and even up to more than 97 °C.¹⁾ Cross-linking between gelatine proteins due to the presence of aldehyde groups in the filling material can also reduce the solubility of the capsule shells.^{2,3)} Hence, it appears beneficial to be able to use different materials for manufacturing two-piece hard shell capsules. To make the process economic such capsule shells should be manufactured on similar machines, as used for gelatine capsules, and they should have the same performance on conventional filling equipment.

Several materials have been tested in the last decades to replace fully or modify gelatine as the capsule shell material. These attempts often either failed due to difficulties in large-scale manufacture, because the capsules could not be used on conventional filling machines, or the capsules had *in vivo*-solubility problems. However, two new varieties of capsule shells, which were developed in Japan, fulfil all the require-

ments for two-piece hard shell capsules in terms of their manufacture and filling properties:

(1) Five percent of polyethylene glycol (PEG; molecular weight 4000) has been added to the gelatine. These 'gelatine/PEG'—capsules show a minimised brittleness when exposed to air of low relative humidity during storage.⁴⁾ They can also advantageously be used for filling of hygroscopic formulations.

(2) Hydroxypropyl methylcellulose (HPMC) was used as major film forming agent. Carrageenan and potassium chloride were added in small quantities to lower the thermal gelation temperature of HPMC and to promote gelation, respectively.⁵⁾ These 'HPMC' capsules should show no incompatibilities with most filling materials or powders, as the only incompatibility currently known for HPMC is the interaction with some oxidising agents.⁶⁾

On a laboratory scale, cross-linked dextran has been successfully used to form two-piece hard shell capsules by the usual dipping procedure.⁷⁾ Such capsules could be used for the delivery of drugs to the colon without the need to coat them with a polymer film. Experience of their large-scale manufacture, however, is currently not available.

The aim of this work was to compare the shell dissolution properties of ordinary gelatine hard capsules with gelatine/PEG and HPMC capsules in different dissolution media, independent of their capsule content, at different temperatures and after different storage conditions in order to evaluate their suitability as a solid oral dosage form.

Experimental

White opaque two-piece capsule shells made from gelatine, HPMC and gelatine/PEG (Shionogi Qualicaps, S.A., Alcobendas, Madrid, Spain) of size 0 and 3 were used in this study. Water, produced by a combination of demineralisation and reverse osmosis was freshly made over night. Pancreatin (pig pancreas), pepsin A powder (biochemical grade), anhydrous disodiumhydrogen orthophosphate, potassium-dihydrogenorthophosphate, sodium

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chloride and 5 M hydrochloric acid were obtained from Merck (BDH, Poole, U.K.). Sodium taurocholate hydrate (97%) was purchased from Avocado Research Chemicals Ltd. (Heysham, U.K.).

The following dissolution media were prepared according to British Pharmacopoeia (1998, see Appendices XIIB-A187 and IA-A46): 1) 0.1 M hydrochloric acid, pH=1.0; 2) mixed phosphate buffer, pH=6.8; 3) artificial gastric juice. Artificial intestinal juice was prepared from mixed phosphate buffer by adding 0.5 g sodium taurocholate hydrate and 10.0 g pancreatin per final volume of 1000 ml. Solutions containing enzymes, *i.e.* artificial gastric and intestinal juice, were freshly prepared every day.

The determination of the shell dissolution time of the hard capsules followed a method described by Boymond⁸ as modified by Jones and Cole.⁹ In each capsule shell, a steel ball bearing (non-corrodable grade) was placed, and the capsules were closed to their specified closed joined length. For size 0 capsules, the diameter of the ball bearings used was 6.344 mm, and for size 3, steel ball bearings with a diameter of 4.990 mm were used. Special metal holders in the form of a strip of stainless steel were suspended across 800 ml glass beakers. The holders contained holes, through which the capsule body could pass, but not the cap. The holes were spaced 5 mm apart. The liquid level in the glass beaker was kept so that the liquid surface touched the lower surface of the metal holders, but did not cover the top surface. The glass beakers were placed in a water bath (Grants Instruments, type SB 20, Barrington, Cambridge, U.K.) providing thermostatic control of temperature of $\pm 0.5^\circ\text{C}$. The liquid inside the glass beakers was stirred at 37 rpm (Heidolph Laboratory Stirrer, type 12ZR1, Germany). The paddle was kept 1 cm above the base of the glass beakers, and 5 mm from the metal holders. The end point of capsule shell dissolution was defined as the time when the steel ball bearing was released from the capsule body and hit the base of the glass beaker. Results are the mean and standard deviation of ten capsules, tested with five units at a time. In those experiments, where the capsule shells did not release any of the steel ball bearings during 120 min, only 5 capsules were studied, and the experiment was terminated at this point.

Capsules were stored either under ambient room conditions ($19 \pm 1^\circ\text{C}$, 35–40% relative humidity of the air), or under conditions defined as 'tropical' ($37 \pm 0.5^\circ\text{C}$, 75% relative humidity of the storage air¹⁰). To achieve the latter, a desiccator containing a saturated solution of sodium chloride was placed into an incubator set at 37°C (B & T Unitemp, U.K.).

Analysis of Variance (ANOVA) was performed using SPSS 9.0 (SPSS, Woking, U.K.).

Results and Discussion

Water is commonly used as dissolution medium in major Pharmacopoeias. It is also recommended as a drink to patients when taking a solid oral dosage form. In this case, 150 ml is usually recommended. In the current experiments the temperature range was between 10° and 55°C , and a $\sqrt{2}$ geometric progression of test temperatures from room temperature (19°C) upwards was used. The lowest value of 10°C was chosen to represent the taking of the dosage form with a cold drink. In preliminary experiments, placing a 200 ml beaker filled with 150 ml water of 10°C in a 37°C thermostatically controlled water bath had shown that it can take up to 7 min, before temperature equilibrium is achieved, depending on the rate of movement of the outer water mantle. Such a comparatively long time span could influence the initial *in vivo* shell dissolution and consequently the release and dissolution of the capsule formulations. The upper temperature limit of 55°C corresponded to the average drinking temperature of coffee or tea, as determined on such drinks from 10 volunteers using a thermometer.

The end point determination of the disintegration of hard capsules filled with, for example, powders or granules, as described in the major Pharmacopoeias is problematic. It is often not possible to separate the disintegration time of the powder plug from the time for the capsule shell to release the plug. The latter depends on the shell dissolution properties, but is strongly overlaid by the properties of the filling mater-

ial.¹¹ For example, some materials cause swelling of the powder plug on contact with moisture, which will cause opening of the two-piece capsule. In such cases, some of the plug is exposed early to the disintegration liquid, while some parts of the plug may be entrapped at the ends of the capsule shell. The ideal test method would determine the shell dissolution time and the disintegration time of the powder plug separately. As this cannot be achieved with the standard pharmacopoeial disintegration test, in this paper a method was sought, which removes the influence of the filling materials on the dissolution of the capsule shells. Steel ball bearings as filling material ensure that the capsule body remains suspended in the disintegration liquid, but do not dissolve, swell or alter their physical state in any other way. Hence, there is no influence of the filling material on the shell dissolution time. Dissolution of the capsule shell normally starts at the ends of the capsule. Tiny holes may be formed, which continually grow. The size of the ball bearings was chosen to match approximately the inner diameter of the capsule body. For the ball bearing to fall free requires a considerable growth of the dissolved area of the capsule shell, but at some point before this occurs, the capsule body can no longer support its weight and the ball bearing will drop out of the capsule. The authors believe that this test is a method, which is able to distinguish between shell dissolution times of capsules of different materials when tested under different conditions.

The shell dissolution times obtained for capsules of size 0, stored at ambient room conditions, are compared in Fig. 1a. Only HPMC capsules dissolved at the lower temperatures of 10° and 19°C , and their shell dissolution time appeared not to be influenced to any great extent when increasing the temperature up to the upper test limit employed. Gelatine and gelatine/PEG capsules, however, showed strong temperature dependence. Rapid shell dissolution only occurred at temperatures above 30°C . At temperatures below 25°C these capsules swelled and formed leather-like sacks (see Fig. 6), which did not release the ball bearings, unless the capsule cap separated from the capsule body. Modern capsules, however, have strong locking mechanisms between the two shell parts, preventing such opening. Similar trends were observed for all types of capsules using capsule size 3 (Fig. 1b). For HPMC capsules, the shell dissolution times were similar to those obtained for size 0 capsules up to a temperature of 30°C . From 37°C onwards, however, the shell dissolution times were significantly longer for capsules of size 3 (ANOVA, $p < 0.05$). This indicates a tendency of the material to form viscous gels at higher temperatures, which, in these cases, would not affect dosage form dissolution to a larger extent. Although some significant differences in shell dissolution time were also found for gelatine and gelatine/PEG at high temperatures, they were not systematically in one direction. Hence, they may only represent the larger variability of dissolution of these types of capsule shells.

In Fig. 2a, the relationships between shell dissolution time and temperature are illustrated for capsule size 0 using 0.1 M hydrochloric acid as the dissolution medium. The shell dissolution times for HPMC were not different from those obtained in water. For gelatine and gelatine/PEG capsules, however, the shell dissolution was found to be slower at 30°C . Melting and dissolution properties can be altered by pH, de-

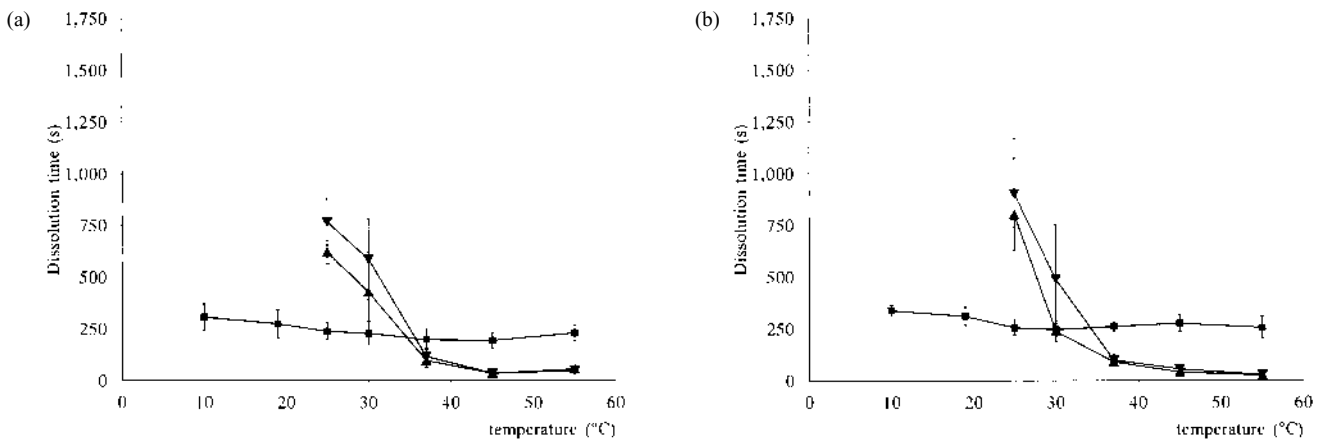


Fig. 1. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (1a) and Size 3 (1b) in Water as a Function of the Temperature of the Dissolution Medium after Storage under Ambient Room Conditions

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

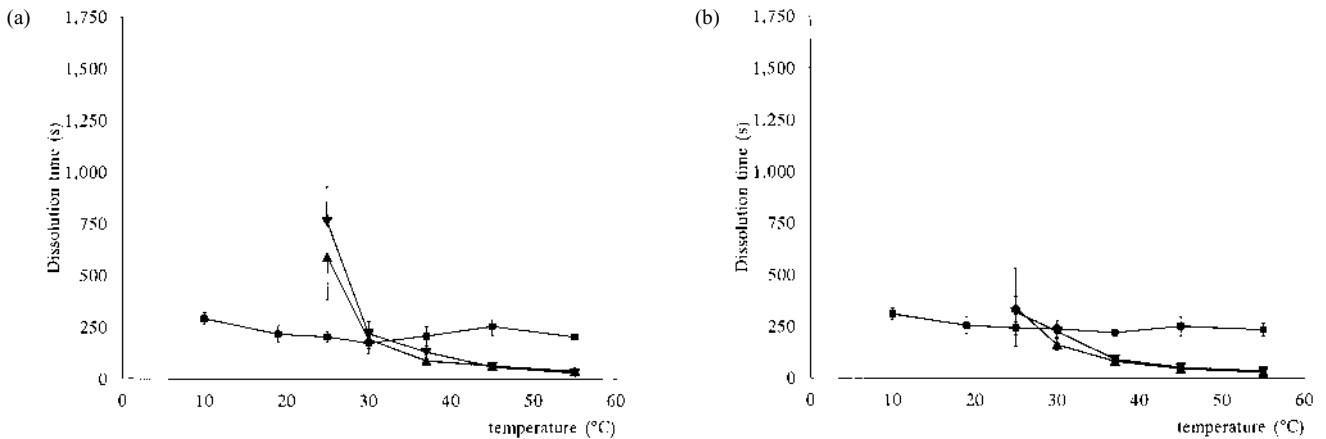


Fig. 2. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (2a) and Size 3 (2b) in 0.1 M Hydrochloric Acid as a Function of the Temperature of the Dissolution Medium after Storage under Ambient Room Conditions

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

pending on the origin of the gelatine.¹¹ The shell dissolution time of HPMC capsules size 3 was generally longer than for size 0 capsules (Fig. 2b), and, except for 10 °C, this difference was significant (ANOVA, $p < 0.05$). For gelatine and gelatine/PEG capsules, however, a tendency for the shell dissolution time to become shorter with the smaller capsule size was observed.

The shell dissolution time of HPMC capsules was significantly increased in mixed phosphate buffer (Fig. 3a; ANOVA, $p < 0.05$). Also, between 20° and 45 °C the shell dissolution time gradually increased, and the dissolution process became more variable. Above 45 °C, HPMC capsules dissolved only slowly *i.e.* it took about 1 h 20 min for size 0 and 1 h for size 3 capsules (Fig. 3b) to dissolve. This could be due to a distortion of the gel point by the pH of the buffer to a higher temperature. At low temperatures, HPMC capsules of size 0 dissolved more rapidly than size 3 capsules, but at a higher temperature the differences in dissolution time were mainly not significant (ANOVA). The pH of the mixed phosphate buffer has also significantly altered the shell dissolution properties of gelatine and gelatine/PEG capsules at temperatures below 37 °C, while at 37 °C and above shell dissolution was similar to that observed in water and 0.1 M

hydrochloric acid. The dependence of dissolution of gelatine capsule shells on pH was previously proposed to have caused great variability of tetracycline absorption in humans,¹² which gives some support to the findings reported here. Another reason could be the greater relative ionic strength of the mixed phosphate buffer. An increase in ionic strength of the dissolution medium was reported previously to prolong considerably the disintegration time of hard gelatine capsules, filled with lactose.¹³ However, both Elliott's and Hüttenrauch's observations were made at 37 °C, whereas in this paper the effect of pH and ionic strength applies only to temperatures below 37 °C. This might be due to slight differences in the manufacture of gelatine capsules in 1971/72 from today.

From the results shown in Figs. 1—3 some practical conclusions can be drawn. First, neither type of capsules should be taken with drinks such as a carbonated Cola-type drink to avoid slow down of the dissolution of the capsule shell, because these drinks contain considerable amounts of phosphates. Also, the pH dependence of the shell dissolution process suggests that gelatine or gelatine/PEG hard shells should not be used for preparations, which require the patient to take the capsules in the fasted state *i.e.* without intake of

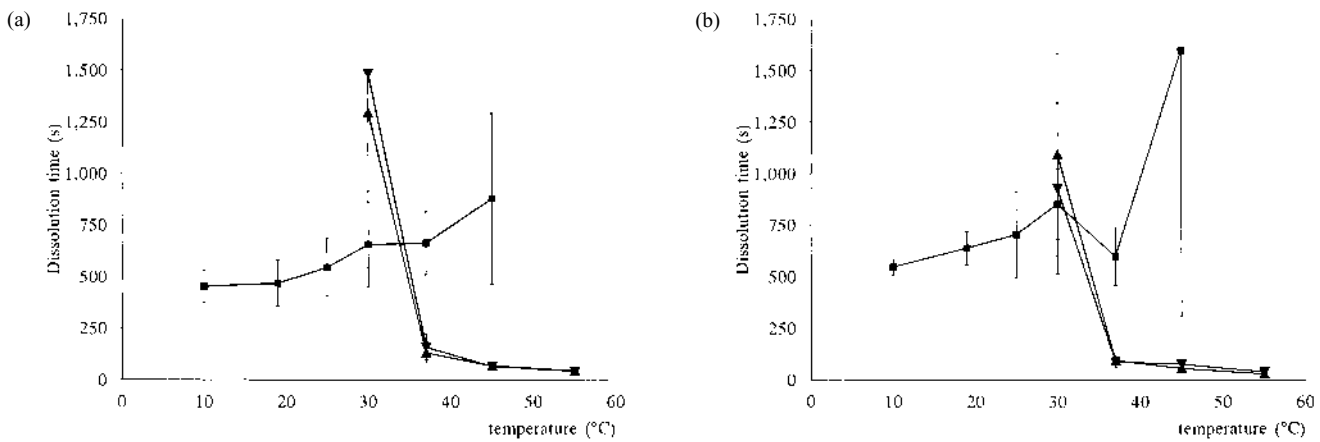


Fig. 3. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (3a) and Size 3 (3b) in Mixed Phosphate Buffer (British Pharmacopoeia, Values for HPMC at 55 °C Not Included; Size 0: 4694 ± 1061 s; Size 3: 3289 ± 316 s) as a Function of the Temperature of the Dissolution Medium after Storage under Ambient Room Conditions

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

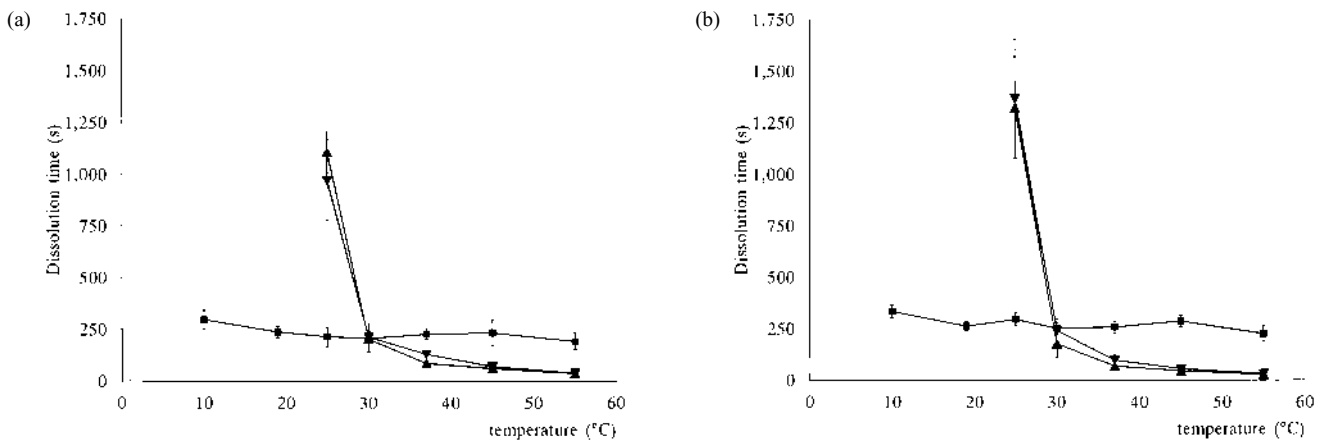


Fig. 4. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (4a) and Size 3 (4b) in Artificial Gastric Juice (British Pharmacopoeia) as a Function of the Temperature of the Dissolution Medium after Storage under Ambient Room Conditions

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

food, unless given with a warm drink. Care should be taken with HPMC capsules and hot drinks, but with a cold drink shell dissolution problems could be overcome. Secondly, for gelatine and gelatine/PEG capsules a warm drink such as coffee or tea could promote drug release, whereas a cold drink should be avoided. As long as the pH of the drink is below or equal to that of demineralised water (pH=5.8 in these experiments), HPMC capsules can be taken with any form of drink.

Courts¹⁴ reported that the rate of peptic hydrolysis of gelatine by pepsin was comparatively slow, yet was three times faster than a thermal degradation at 37 °C. However, the results for artificial gastric juice (Figs. 4a, b) were similar to those obtained using 0.1 M hydrochloric acid. The shell dissolution of gelatine containing capsules in artificial gastric juice is therefore not related to the presence of the enzyme. This also applies to HPMC capsules. It is consistent with findings reported by Shiu *et al.*¹⁵ These authors compared dissolution media containing enzymes with enzyme-free media with respect to the drug release profiles from ordinary gelatine capsules in comparison to cross-linked gelatine capsules. Advantage was gained from the addition of enzymes

only for the cross-linked capsules.

The addition of pancreatin and bile salts to mixed phosphate buffer reduced the shell dissolution time of the gelatine and gelatine/PEG shells slightly, but there was still no dissolution below 30 °C (Figs. 5a, b). Courts¹⁴ did not study pancreatin, but some of its components, namely trypsin and chymotrypsin. These enzymes were found to cause heavy proteolysis of alkali-processed ox-bone gelatine. One reason for the absence of effect in this study could be that the dissolution process is the rate limiting process, and consequently enzymatic degradation, although occurring, did not play a significant role. The addition of pancreatin and bile salts changed the shell dissolution properties of HPMC capsules to a limited extent. However, the shell dissolution times were sometimes below and sometimes above those found in mixed phosphate buffer solution. These variations were also not consistent for capsule sizes 0 and 3, and hence, the deviations might reflect the variability of the dissolution process only; they appear not to be enzyme related.

The storage under tropical humid conditions (37 °C and 75% relative humidity of the storage air) for 24 h resulted in a softening and stickiness of all capsules when still warm.

However, after removing them from the storage chamber, they were allowed to cool down for 15 min in a closed 20 ml polyethylene bottle. After that time, they had regained their firmness, and stickiness was minimal. As before, for HPMC capsules the shell dissolution values in artificial gastric juice were consistently longer for size 3 capsules (Fig. 7b) compared to size 0 shells (Fig. 7a), and the difference was in almost all cases statistically significant (ANOVA, $p < 0.05$). The shell dissolution times for HPMC capsules, which had been stored under tropical conditions, in artificial intestinal juice (Figs. 8a, b) were significantly reduced for temperatures between 10° and 30°C (ANOVA, $p < 0.05$). Above 37°C, however, shell dissolution times were increased, and at 55°C these capsules did not dissolve during a time span of two hours. During the storage the HPMC capsules took up moisture, which could have led to a hydration of the capsule shell walls. Water penetration through the hydrated material might be slower and thus the capsule shells would not dissolve readily. The change in dissolution behaviour observed for HPMC capsule shells appears to be in contrast to findings reported by Matsuura and Yamamoto,⁵⁾ who used a similar humidity to store antibiotic filled HPMC capsules and did not

report any changes in capsule disintegration. They employed longer storage times and used a storage temperature of 60°C, higher than normally used in such trials in Europe. The discrepancy between the two findings can only be explained by the deficiencies of the standard disintegration test applied as discussed above.

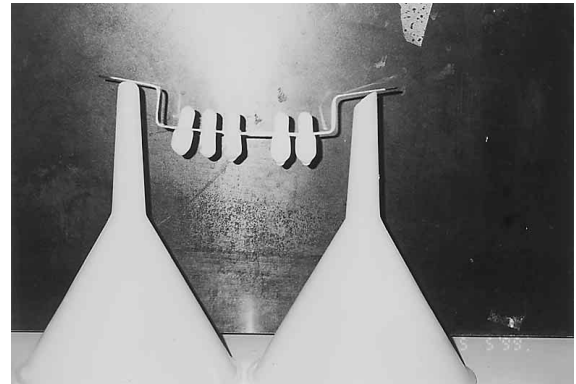


Fig. 6. Gelatine Capsules after Exposure to Water of 19°C as Dissolution Medium

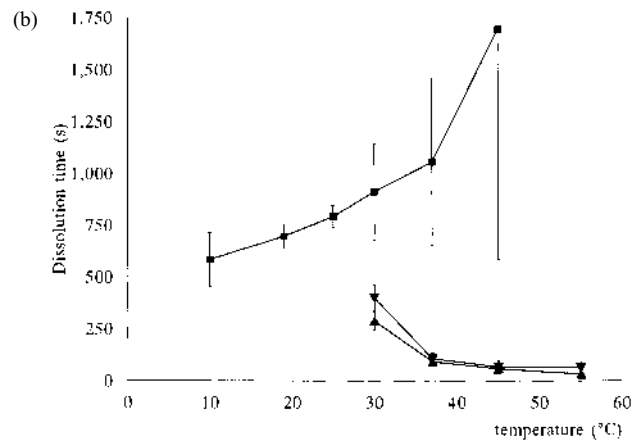
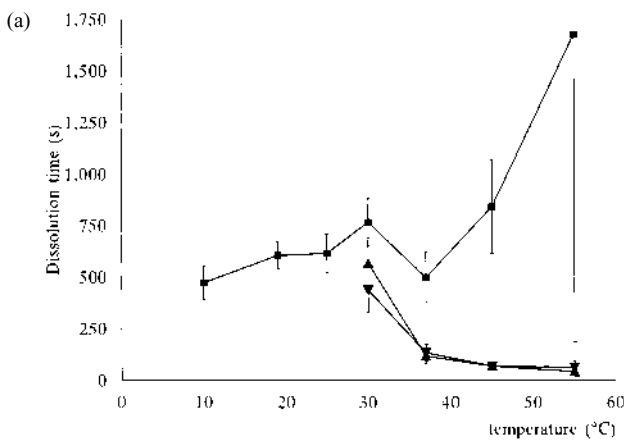


Fig. 5. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (5a) and Size 3 (5b) in Artificial Intestinal Juice (Boymond *et al.*⁸⁾) as a Function of the Temperature of the Dissolution Medium after Storage under Ambient Room Conditions

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

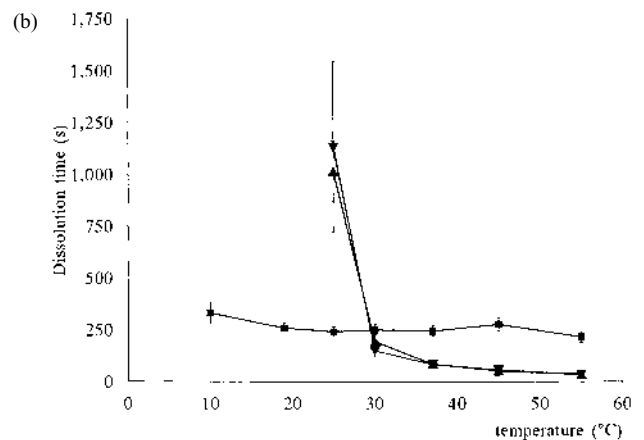
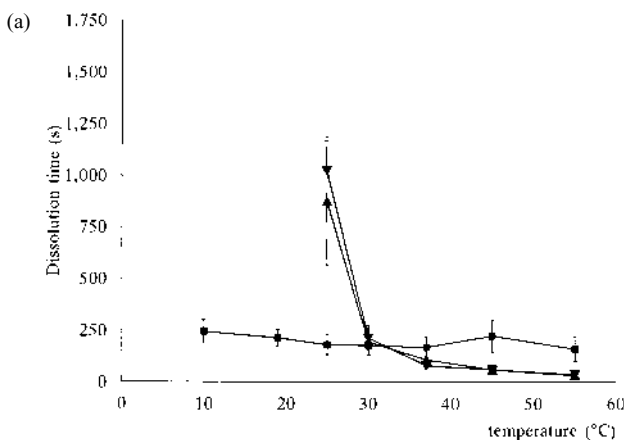


Fig. 7. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (7a) and Size 3 (7b) in Artificial Gastric Juice (British Pharmacopoeia) as a Function of the Temperature of the Dissolution Medium after Storage of the Capsules at 75% Relative Humidity and 37°C for 24 h

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

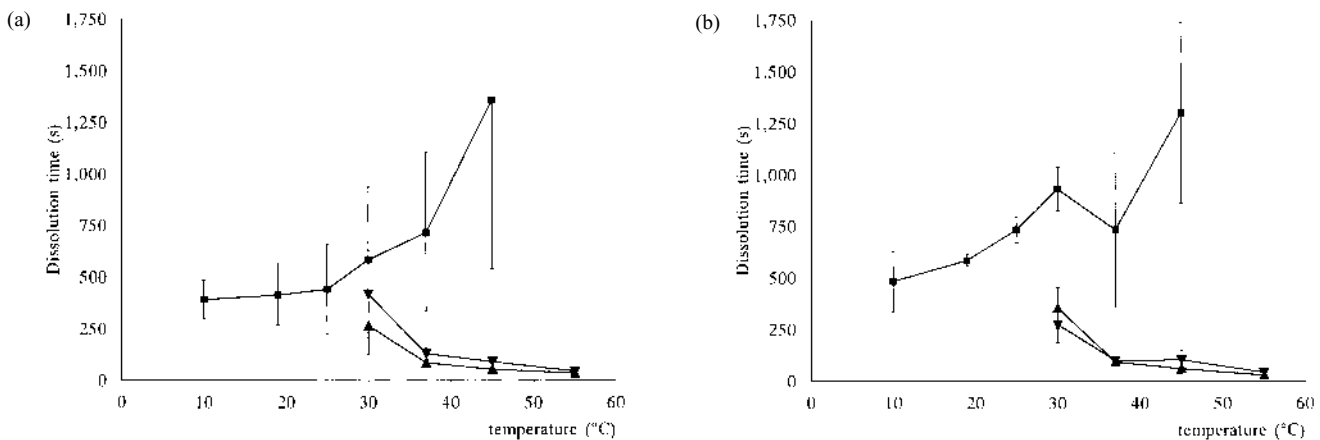


Fig. 8. Shell Dissolution Times of Two-Piece Hard Shell Capsules Size 0 (7a) and Size 3 (7b) in Artificial Intestinal Juice (Boymond *et al.*⁸) as a Function of the Temperature of the Dissolution Medium after Storage of the Capsules at 75% Relative Humidity and 37 °C for 24 h

■, HPMC capsules; ▲, gelatine capsules; ▼, capsule shells made from a mixture of gelatine and PEG.

Conclusions

In any dissolution medium with a pH below or equal to 5.8, HPMC capsules dissolve rapidly and the shell dissolution is independent of temperature between 10 ° and 55 °C. Gelatine containing capsule shells, however, do not dissolve at temperatures below 30 °C in such dissolution media, and their shell dissolution times are dependent upon temperature. Mixed phosphate buffer appears not to be a suitable dissolution liquid to test the dissolution of capsule shells, because shell dissolution is more variable and prolonged. The addition of enzymes to any dissolution medium does not enhance the differences between the different types of capsules. In practical terms, the results indicated that capsule formulations should not be taken with drinks from the carbonated Cola-type, because these drinks contain a considerable amount of phosphates. Gelatine containing capsules should preferably be administered with a warm drink, whereas HPMC capsules could be given with cold or warm drinks. The latter type of capsules should also be preferred for preparations to be taken in the fasted state *i.e.* without intake of food. A short storage period of gelatine containing capsules under hot humid tropical conditions appears not to alter the dissolution properties of the shells, and changes in disintegration times and dissolution times of formulations filled in such capsules might be a reflection of changes of the powders incorporated rather than of the capsules. However, a short storage period of HPMC capsules under such condi-

tions appears to influence the capsule shell matrix, and hence, care should be taken when this type of capsules is exposed to hot and humid tropical conditions.

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