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STUDIES ON THE DELIVERY MECHANISMS OF THEOPHYLLINE FROM A SUSTAINED RELEASE TABLET

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ABSTRACT

The in-vitro and in-vivo release of theophylline from an oral sustained release tablet (Theograd^{R}) was studied.

The in-vitro release profiles were determined by means of the rotating basket method, the paddle method and the modified disintegration method, described in the USP XX as apparatus 1, 2 and 3 respectively. Besides a stationary basket-rotating paddle method was used.

It was demonstrated that in the stationary basket-rotating paddle apparatus and in the paddle apparatus at low rotational speeds of the paddle, mild agitation conditions were created. Under these conditions the release of theophylline from the sustained release tablet appeared to be matrix controlled. The leached matrix was found to be structurally very weak. For a matrix type

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of sustained release tablet this is probably beneficial as it would be less likely to cause accumulation and gastro-intestinal obstruction.

In contrast the conditions of agitation in the rotating basket apparatus and in the disintegration apparatus were found to be rather severe. This was partly due to mechanical abrasion of the dosage form caused by the gauze of the basket and the basket-rack respectively, and partly the result of high solvent agitation, especially in the disintegration apparatus. Under these conditions it appeared that the empty matrix of the sustained release tablet eroded during the release process. This was confirmed by the results of studies under non-dissolving circumstances of the drug which showed that in this case only the leached matrix of the sustained release dosage form eroded and not that part of the dosage form from which the drug had not yet been dissolved.

The in-vivo absorption appears to relate to the in-vitro release. When the Theograd^{R} tablet was taken on an empty stomach, it appeared that the absorption rate could succesfully be simulated by means of the stationary basket-rotating paddle method and the paddle method, both at low rotational speeds of the paddle. It was very likely that in this case the in-vivo release from the sustained release tablet was matrix controlled too. Under these conditions the bioavailability was found to be 65% compared with an oral solution of the drug. In contrast, when the Theograd^{R} tablet was taken after a meal, a relative bioavailability of 90% was observed. It was made plausible, that the greatly enhanced bioavailability, observed on postprandial administration of the tablet, was due to partial erosion of the leached matrix. This erosion was caused by the food induced increased motility of the gastro-intestinal tract. Based on the results of this study it is recommended to take Theograd^{R} tablets after a meal.

INTRODUCTION

Nowadays it is recognized that many drugs for chronic administration should be dosed in a schedule that maintains the plasma concentration within a safe and effective range. For the drug with a relatively short elimination half life and a narrow therapeutic index this obviously results in frequent dosing. In this case the use of sustained release dosage forms can be advantageous, because such preparations may reduce dosing frequency, fluctuations in drug levels and side effects[1-3]. Moreover, it is likely that patient compliance

will increase and that the pharmacological respons will be more uniform. There has been a remarkable increase in interest in this type of dosage forms, with the result that many substances are now available in sustained release preparations.

During the period of development of sustained release dosage forms, one of the drugs which has been in the centre of interest is theophylline. In an abundance of literature the in-vivo absorption rate and bioavailability of this drug has been described extensively.[3-7] However it appeared that both external factors, such as time of administration of the dosage form and food, and physiological factors such as gastric emptying rate, pH, gastrointestinal motility and transit time, mostly influenced the absorption rate of the drug to a great extent.[8-11] Consequently it is not surprising that nowadays there is a growing need for information about the release mechanisms of the different sustained release dosage forms, so it will become possible to predict the influence of external and physiological factors on the absorption rate and bioavailability of the drug.

Recently in a single dose as well as in a chronic dose study of the bioavailability of a matrix type of sustained release tablet (Theograd^{R}), it is demonstrated that the bioavailability of the drug was greatly enhanced when the tablets were taken after a meal.[12,13]

Data about the in-vitro release characteristics of this sustained release tablet are extremely scarce.[14]

In the present study the in-vitro release characteristics will be investigated in more detail, with the purpose of getting a better understanding of the release mechanism of the sustained release tablet. Besides some of the characteristic in-vitro release profiles will be compared with the in-vivo absorption rate.

MATERIALS AND METHODS

Drugs

A matrix type of theophylline sustained release tablet (Theograd^{R}-250 mg), Abbott Laboratories, Lot no. 37-001 VH02) was studied. The tablets were composed of 250 mg of anhydrous theophylline plus excipients to give a total weight of the tablets of 300 mg. The tablets are film-coated with a water

soluble coating. The matrix consists of the copolymer methylacrylate-methylmethacrylate. At all physiological pH's the pure copolymer is insoluble in water.

Theophylline monohydrate (European pharmacopeia grade) was obtained from Brocacef, Maarssen, The Netherlands. Anhydrous theophylline was prepared by heating the monohydrate at a temperature of about 105° until constant weight.

The hydrated, anhydrous drug and Theograd® tablets were submitted to X-ray diffraction analysis (Guinier-Hägg). It was demonstrated that the diffraction patterns of the anhydrous form and the drug in the Theograd® tablets were identical.

Dissolution

Release rates of theophylline from the sustained release tablet were determined by means of the rotating basket method, paddle method and modified disintegration method, described in the USP XX as apparatus 1,2 and 3, respectively. Additionally a method with a stationary basket and rotating paddle was used. The apparatus is simular to the paddle assembly described in the USP as apparatus 2, with the exception that the dosage unit is not allowed to sink to the bottom of the beaker, but is placed in a basket. The basket, which is simular to that employed in the USP method 1 apparatus, is situated in such a way that the distance between the axis of the basket and the vessel wall is 2.5 cm and that the distance between the basket and the plane through the lowest point of the vessel perpendicular to the axis of the vessel is 7.5 cm. The theophylline sustained release tablet is placed in the centre of the bottom of the dry basket. The basket is lowered into position before rotation of the paddle is started. The temperature was thermostatically controlled at 37.0 $\pm$ 0.1°. Samples were taken at convenient time intervals through membrane filters (0.8 µm pore diameter) and analysed spectrophotometrically at 270 nm. Distilled water, 0.1 N hydrochloric acid and 0.025 molair phosphate buffer pH 6.8 were used as dissolution media.

To study the influence of the surface tension of the dissolution medium on the release rate of the drug, experiments were carried out in which 0.01% polysorbate 20 was added to the dissolution medium.

All the values presented for the dissolution experiments were the average of three to six replicate determinations.

Solubility

The saturated theophylline monohydrate and anhydrous theophylline solubilities were determined by placing excess solute in a water-jacketed beaker filled with 900 ml of water. Stirring was achieved with a paddle rotating at 100 r.p.m. The experiments were continued untill no increase in the amount of drug dissolved could be measured. Samples were taken at convenient time intervals through membrane filters and analysed spectrophotometrically. To prevent drug precipitation all glass syringes, pipettes and the filter apparatus were prewarmed. To achieve a fast saturation of the solvent, small solid particles (37 to 53 μm) were used. This fraction was isolated by sieving theophylline monohydrate by means of a air jet sieve (Alpine, Ausburg, West Germany). To prevent possible mechanical activation of the anhydrate, caused by the sieving procedure, this form was prepared from the sieved fraction of the monohydrate as described previously, and was subsequently aged for at least three month before use.

Erosion

Erosion of the theophylline sustained release tablet was studied under non-dissolving as well as under dissolving conditions for the drug. Erosion under non-dissolving conditions was determined in the rotating basket dissolution apparatus. The erosion was characterized by determining the weight loss of of the tablet as a function of the time in saturated solutions of theophylline monohydrate at different temperatures. After a convenient time interval the tablet was removed from the test medium and dried at 105^{o} until constant weight. Corrections were made for the amount of drug present in the saturated solution adherent to the surface of the tablet when it was taken from the medium. The presented values are the average of six replicate determinations.

The coating of the tablets studied is soluble in water at temperatures below about 45^{o}. Because some of the erosion experiments were carried out at higher temperatures, prior to all erosion experiments the coating of the theophylline sustained release tablets was removed. This could easily be accom-

plished by tearing off the coating film with the aid of a small knife and a pair of tweezers.

Erosion under dissolving conditions was studied simultaneously with the dissolution rate determinations. Because these experiments were carried out at a temperature of 37°, the coating was not removed.

Hydrodynamic Conditions in the Dissolution Apparatus

Some essential hydrodynamic conditions in the dissolution models were characterized by measuring the dissolution rates of non-disintegrating theophylline tablets placed at different positions in the dissolution apparatus.[15] The tablets, 10 mm in diameter and 3 mm thick, were prepared by compressing 250 mg of the powdered drug in a die at a load of 20 kN for 10 min. Samples were taken at appropriate time intervals and analyzed spectrophotometrically at 270 nm.

In-Vivo Absorption

The in-vivo absorption was studied in seven healthy volunteers, five females and two males, aged 37 ± 11 years and weighing 70 ± 16 kg. All subjects were non-smokers.

The Theograd^{R}-250 mg tablet together with 150 ml of water was administered either after an overnight fast or 15 min after a breakfast. A light meal was served at 4 hours and an evening meal at 8 hours after dosing. Blood samples were taken from a cubital vein before and 30, 60, 90 and 120 min and 3, 4, 6, 8, 12, 14 and 30 hours after dosing. Serum was separated from the coagulated blood and frozen at -20° until assayed. The concentration of theophylline was determined by high pressure liquid chromatography.[16] The samples were analyzed in duplicate. The absorption was characterized by the method of Wagner-Nelson.[17]

RESULTS AND DISCUSSION

Figure 1 shows the release rate profiles of theophylline from Theograd^{R}-250 mg tablets determined in the USP paddle dissolution apparatus at different rotational speeds of the paddle. Hydrochloric acid 0.1 N was used as dissolution medium. At all rotational speeds of the paddle, from 3 hours

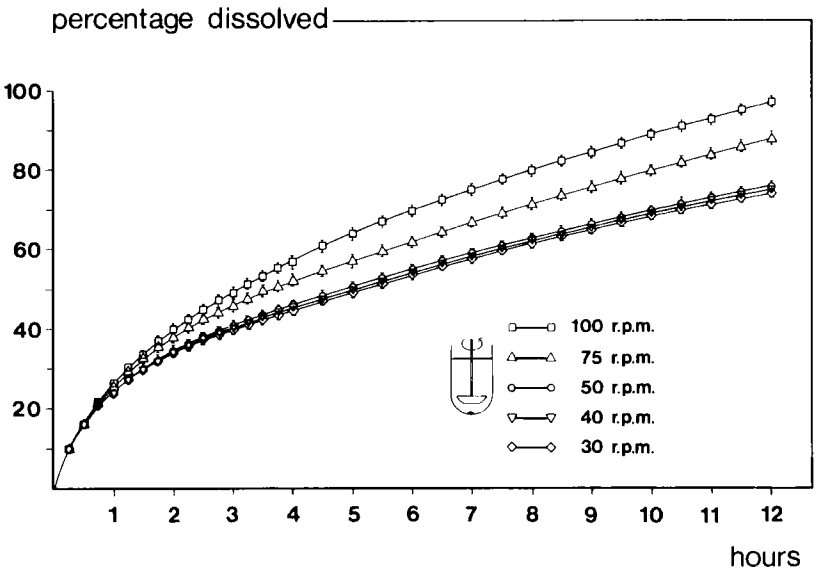

FIGURE 1
In-vitro release profiles of the theophylline sustained release tablet in 0.1 N HCl, determined in the paddle dissolution apparatus at different rotational speeds of the paddle. Bars represent standard deviation.

a rather constant release was observed. At a rotational speed of 100 r.p.m., after 12 hours the release was almost complete. When the rotational speed of the paddle was reduced, until 50 r.p.m. the release rate proportionally decreased. However a further reduction of the rotational speed to 30 r.p.m. did not result in a significantly further decrease of the release rate. Visual observation of the sustained release tablet showed that after the tablet was placed in the dissolution medium, it immediately sank to the bottom of the vessel. During the release process at 100 r.p.m. the dosage form slightly deformed, which was accompanied by dislodging of small pieces of the empty matrix. At reduced rotational speeds of the paddle this phenomenon became less pronounced.

To study the release characteristics of the theophylline sustained release tablet in more detail, the USP rotating basket apparatus and the modified disintegration apparatus were used. Although it is not to be expected that for sustained release tablets these models will provide a useful in vitro-in vivo

correlation[18] with the aid of these models a secondary parameter, that is erosion of the dosage unit, may be introduced in the release process.[19]

The release profiles from the theophylline sustained release dosage form determined in the rotating basket apparatus at 50 and 100 r.p.m. are shown in figure 2. Although studies with non-disintegrating theophylline tablets showed that the solvent agitation in the rotating basket at 50 r.p.m. was significantly lower than that in the centre of the bottom of the vessel in the paddle apparatus at 100 r.p.m., the release of theophylline from Theograd^{R} tablets however was much faster in the rotating basket apparatus at 50 r.p.m. than in the paddle model at 100 r.p.m. Visual observation of the sustained release tablet showed that unlike the situation in the paddle apparatus the tablets gradually eroded during the dissolution rate determination. After 12 hours the tablet had completely dispersed. A suspension of very small particles of the insoluble matrix was visible at the end of the experiment. An increase of the rotational speed of the basket from 50 to 100 r.p.m. resulted in an enhancement of the release rate as well as in an acceleration of the erosion process.

When a tablet is placed in the basket and rotation commences, at a rotational speed of the basket of 100 r.p.m. the tablet will normally position itself on the base of the basket adjacent to the basket wall. However, at reduced rotational speed (e.g. 50 r.p.m.), due to the reduced centrifugal force, it is also possible that the tablet remains at the centre of the basket base. As shown in figure 3 different positions of the tablet in the basket produced dramatic differences in release rate profiles of the drug. This is caused by different solvent agitation existing in different regions of the basket.[15] The solvent agitation at the basket periphery was found to be significantly higher than in the centre of the basket. Consequently release rates from tablets positioned against the basket wall will be significantly higher than those from tablets placed in the centre of the basket.

To establish whether the tablets erode as the result of mechanical abrasion caused by abrasion of the tablets by the gause, or whether only the leached matrix does not withstand these forces, experiments were carried out in which the weight losses of the tablets were monitored as a function of the time. Determinations were carried out in the rotating basket apparatus using satu-

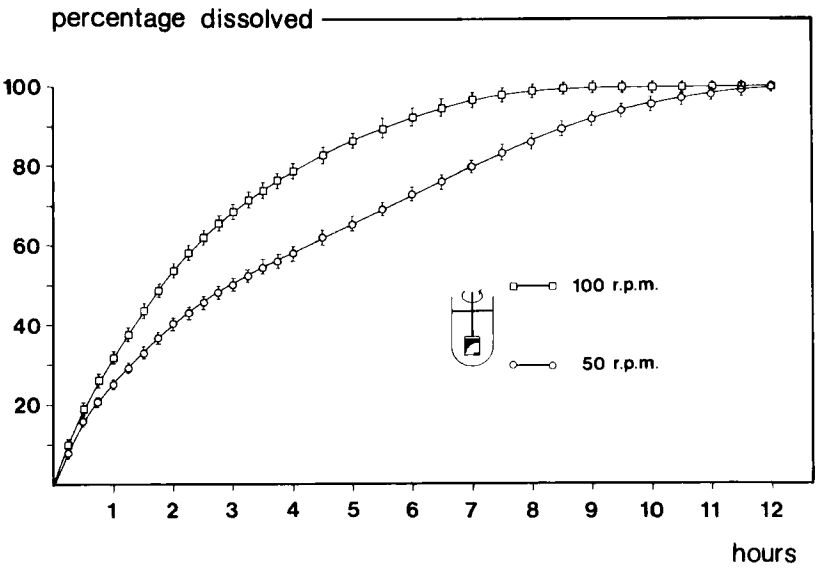

FIGURE 2
In-vitro release profile of the theophylline sustained release tablet in 0.1 N HCl, determined in the rotating basket dissolution apparatus at different rotational speeds of the basket. Bars represent standard deviation.

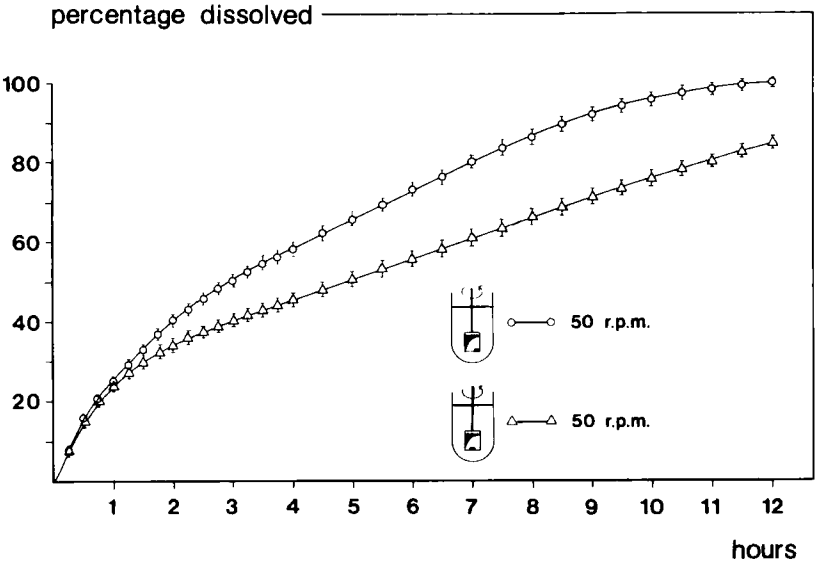

FIGURE 3
In-vitro release profiles of the theophylline sustained release tablet in 0.1 N HCl, determined in the rotating basket dissolution apparatus, as a function of the position of the tablet in the basket. Bars represent standard deviation.

rated solutions of theophylline monohydrate as dissolution medium. The rotational speed of the basket was 100 r.p.m.

It is reported that below the polymorphic transition temperature of 73° anhydrous theophylline is metastable in the presence of water. This implies that when crystals of anhydrous theophylline are suspended in water or a saturated solution of the monohydrate, at temperatures below the transition temperature smaller particles of the monohydrate may crystallize at the surface of the anhydrous crystals. Recently a much lower transition temperature of 64°, found for a polymorph of theophylline is reported.[21] We therefore determined the transition temperature of the theophylline polymorph present in Theograd® tablets. The transition temperature, which was calculated from a Van 't Hoff plot constructed from the solubility data at different temperatures for anhydrous theophylline and the hydrate respectively, was found to be 65°.

Figure 4 shows the results of the experiments in which the weight loss of Theograd® as a function of the time was determined, using the rotating basket apparatus at 100 r.p.m. Saturated solutions of theophylline monohydrate were employed as media. As seen from this figure, at temperatures below the transition temperature a significant weight loss of the tablets was observed. The weight loss increased with increasing temperature, from 2.5% observed at 25° to about 24% found at 50°. According to the metastable character of the anhydrous form, the weight loss took place during the first few hours of the experiment. Crystallization of the monohydrate at the surface of the solid particles then prevented further dissolution of the drug. Interesting results were obtained when the experiments were carried out at a temperature of 65° (the transition temperature). As described previously, at the transition temperature the solubilities of the anhydrous form and the monohydrate are the same. Consequently the anhydrous form will not dissolve in a saturated solution of the hydrate. The observed small weight loss is due to the dissolution of soluble excipients, present in the outermost layer of the tablets. From the experiments it is obvious that the part of the Theograd® tablets, from which the drug has not yet dissolved, will not erode.

Another method, which creates even more rigorous conditions than those existing in the rotating basket apparatus, is the modified disintegration model. By means of intrinsic dissolution rate determinations with non-disintegrating

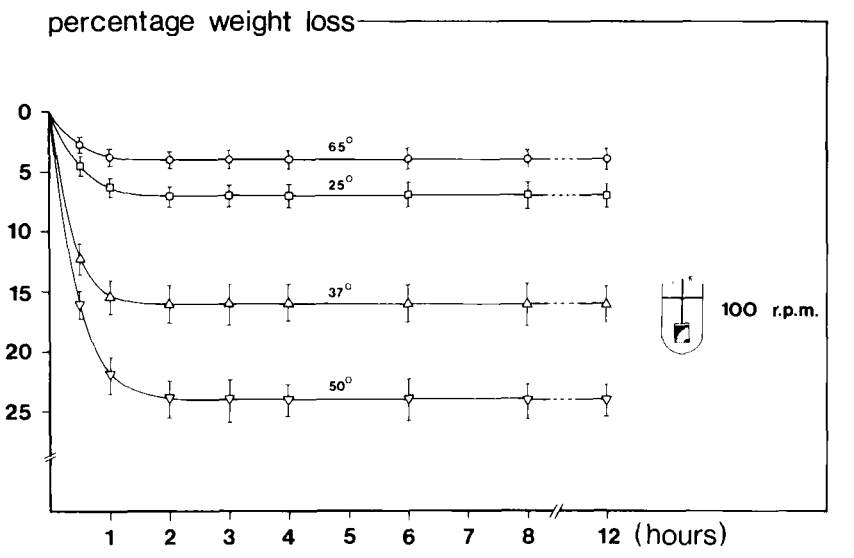

FIGURE 4
Weight loss of the theophylline sustained release tablet as a function of the time, determined in the rotating basket apparatus at different temperatures. The rotational speed of the basket was 100 r.p.m. Saturated solutions of theophylline hydrate were used as media. Bars represent standard deviation.

theophylline tablets it was found that the solvent agitation in the disintegration apparatus is about 35% higher than that observed in the rotating basket at 100 r.p.m.[15] The results of the dissolution rate determinations are shown in figure 5. Hydrochloric acid 0.1 N and phosphate buffer pH 6.8 were used as media. As shown in the acid as well as in the phosphate buffer the release rates were extremely fast; within 5 hours after the start of the experiment the release was completed. Although the release rate in the phosphate buffer was slightly higher than that in the acid medium, the differences were not significant. Visual observation of the tablet showed that in this model also the tablets gradually eroded during the release process.

To study the influence of the surface tension of the medium on the release rate of the drug, the experiments were repeated in the presence of Polysorbate 20. At a concentration of 0.01% this surfactant lowers the surface tension of the dissolution medium to 37 dyne.cm^{-1}. The experimentally observed dissolution profiles coincided exactly with those obtained in the

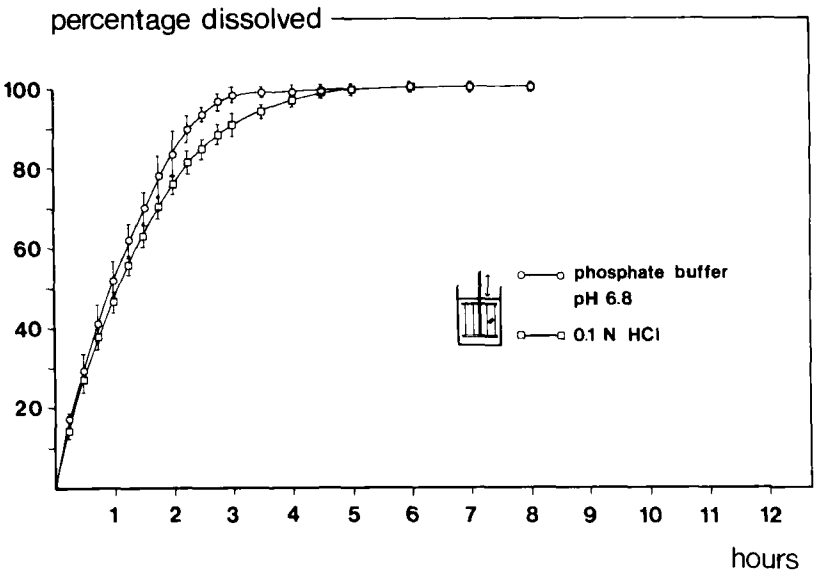

FIGURE 5
In-vitro release profiles of the sustained release tablet in 0.1 N HCl and in phosphate buffer pH 6.8, determined in the modified disintegration apparatus. Bars represent standard deviation.

absence of Polysorbate 20, which means that the release rate of theophylline from Theograd^{R} tablets is independent of the surface tension of the dissolution medium.

To study the release rate under non-eroding conditions the stationary basket-rotating paddle model was used. In this model the tablet is placed in the basket, which is situated in a region with non-turbulent circular flow. The experiments were carried out by using 0.1 N hydrochloric acid as medium. From the results depicted in figure 6 it is shown that at rotational speeds of the paddle of 100 as well as 50 r.p.m. from 3 hours a rather constant release was observed. The release rate slightly decreased when the rotational speed of the paddle decreased from 100 to 50 r.p.m. Under 50 r.p.m. the release rate was found to be independent of the rotational speed of the paddle, which is characteristic for a matrix type of dosage form. This is endorsed by the observation that the release profile found at 50 r.p.m. overlapped that observed in the paddle apparatus at the same rotational speed. Visual observation showed

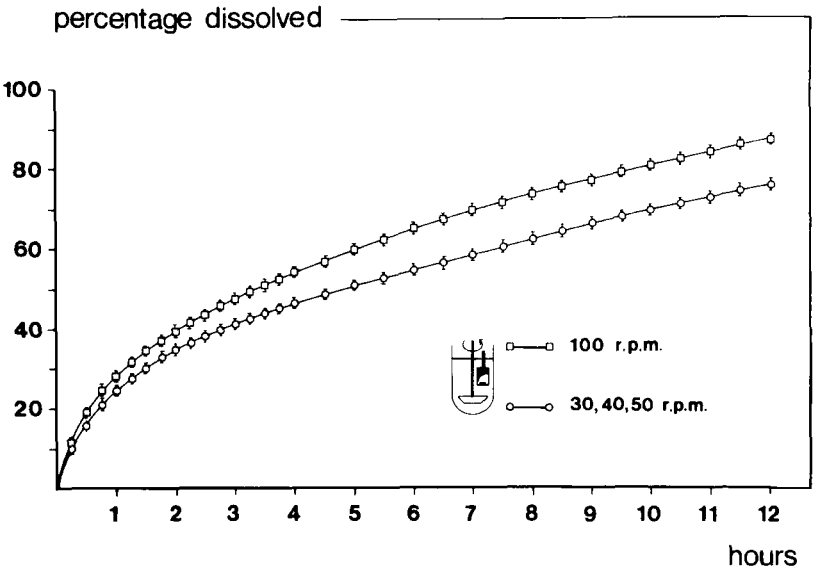

FIGURE 6
In-vitro release profiles of the sustained release tablet in 0.1 N HCl, determined in the stationary basket-rotating paddle apparatus, at different rotational speeds of the paddle. Bars represent standard deviation.

that during the release process the tablet in the stationary basket neither deformed nor eroded and, that no dislodging particles of the leached matrix were suspended in the medium. When a basket with a leached matrix was removed from the medium, the matrix appeared to be structurally very weak. After drying at 105^{o} the weight of the empty matrix was found to be about 15 mg.

Based on the preceding results it was now possible to visualize the processes, which took place during the release (see figure 7). Under rather rigorous conditions, which for the Theograd^{R} tablet exist in the rotating basket and in the disintegration apparatus, the leached matrix of the theophylline sustained release tablet erodes. At gentle solvent agitation, which is existing in the paddle apparatus at low rotational speeds of the paddle and particulary in the stationary basket-rotating paddle apparatus, during the entire release the empty matrix remains unimpaired.

The results of the in-vitro release determinations were evaluated by comparing these with the results obtained from the in-vivo absorption studies.

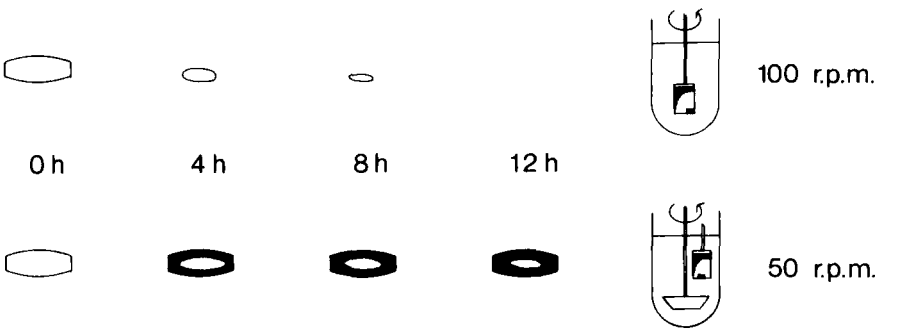

FIGURE 7
The sustained release tablet during the release process: non-matrix controlled release and matrix controlled release, respectively.

By using the method of Wagner and Nelson[17], the percentage absorbed as a function of the time was calculated (see figure 8). As shown rapid absorption was observed when the tablet was taken in the fasting state. However the amount absorbed was found to be 54% after 12 hours and 65% after 30 hours. When the tablet was taken after a meal, the initial absorption rate significantly decreased. This was probably due to the delayed gastric emptying rate, caused by food intake. Then the absorption increased, resulting in a bioavailability of 77% after 12 hours and 90% after 30 hours.

When the mean percent absorbed-time profile, obtained on preprandial administration of Theograd^{R} was compared with the different in-vitro release curves, then the in-vivo absorption always appeared to be slower than the in-vivo release. The best in vivo-in vitro correlation was found for the paddle method and the stationary basket-rotating paddle method, both at rotational speeds of the paddle up to 50 r.p.m. As described, at these low rotational speeds, the leached matrix of the sustained release tablet did not erode. This implies that at these mild agitation conditions, small fluctuations in the solvent flow did not influence the release rate of the drug. Consequenly the slightly smaller in-vivo release rate must be due to physiological factors, such as different ionic strength, viscosity and pH of the gastro-intestinal fluid compared with 0.1 N hydrochloric acid. The effect of the pH on the release rate of theophylline is illustrated in figure 9. Due to the amphoteric character of the drug with pK_a values of 0.2 and 8.8 respectively, the lowest solubi-

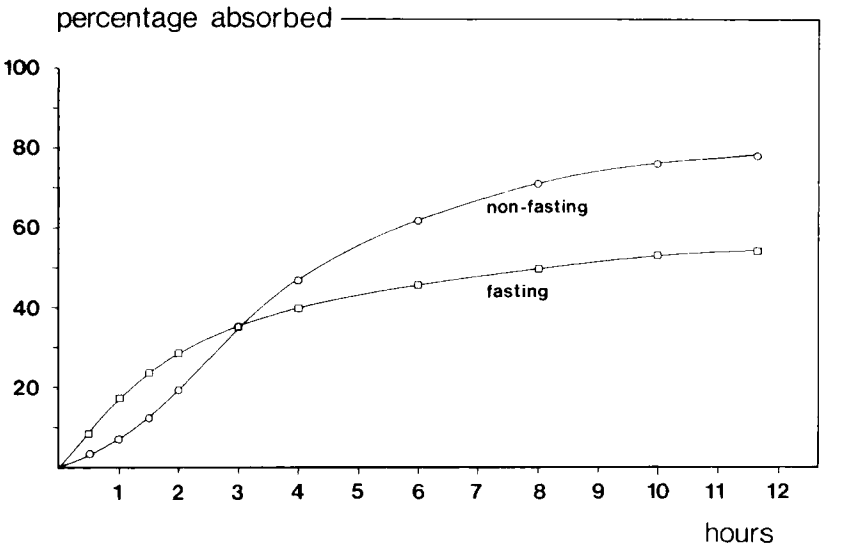

FIGURE 8
In-vivo absorption rate of theophylline from the sustained release tablet, on preprandial and postprandial administration of the tablets.

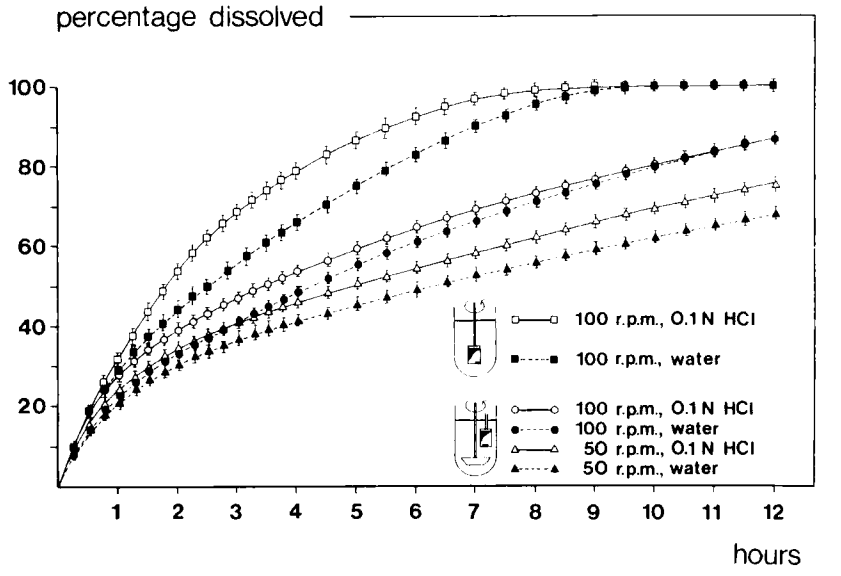

FIGURE 9
In-vitro release profiles of the sustained release tablet in 0.1 N HCl and in water respectively, determined in different dissolution apparatus. Bars represent standard deviation.

ty will be found at a pH value of about 4.5, exhibited by a solution of the drug in water.

As described the in-vitro release appeared to relate well with the in-vivo absorption. However from 4 to 5 hours after administration of the tablets the absorption slightly lagged behind the in-vitro release. Although it is demonstrated that after ingestion of a solution of the drug the absorption is completed within 1 hour[12], it is postulated that the absorption of the dissolved drug from the more distal part of the gastro-intestinal tract may be delayed. This is endorsed by similar observations for indomethacin from osmotically controlled oral delivery systems[22].

When the Theograd[R] tablet was taken after a meal, due to the delayed gastric emptying rate caused by food intake, the initial absorption rate was found to be slow. However after 1 hour, the absorption rate increased and became of the same order of magnitude as the initial rate observed on preprandial administration of the drug. It is conspicuous that in the former case the steep segment of the absorption rate profile was found to be twice as long as that of the preprandial curve. So it is likely that the food induced increase in the gastro-intestinal motility produced erosion of the leached matrix. This is endorsed by feacal examination by the volunteers: only on preprandial administration of the sustained release tablet a small remainder of the tablet was found occasionally in the feaces. After 5 to 6 hours the curve flattened. This together with the observation that after 5 hours 55% of the drug was released, indicated that further release was matrix controlled.

In conclusion, on preprandial administration of a matrix type of sustained release theophylline tablet (Theograd[R]) it is likely that the release of the drug is matrix controlled. After 12 hours 54% and after 30 hours 65% of the drug had been absorbed. The in-vivo release could succesfully be simulated by means of the paddle method and the stationary basket-rotating paddle method, both at rotational speeds of the paddle up to 50 r.p.m.

When the Theograd[R] was taken after a meal, the bioavailability of the drug was found to be greatly enhanced: after 12 hours 77% and after 30 hours 90% of the drug was absorbed. In vitro release studies demonstrated that the empty matrix was structurally very weak. It is plausible that the food induced increase of the gastro-intestinal motility caused partial erosion of only the empty matrix, resulting in a significant increase in the bioavailability of the drug. Because

only the empty matrix was found to erode and not that part of the tablet from which the drug has not yet been dissolved, it is very unlikely that the erosion will lead to dose-dumping.

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