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Investigation of the Biopharmaceutical Behavior of Theophylline Hydrophilic Matrix Tablets Using USP Methods and an Artificial Digestive System

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ABSTRACT This work aimed to investigate the biopharmaceutical behavior of hydrophilic matrix tablets of theophylline using different in vitro methods: USP II, USP IV, and a novel in vitro system simulating the gastrointestinal tract in man called the artificial digestive system (ADS). The potentiality of each method was evaluated by establishing in vitro/in vivo correlation. Using USP methods, the drug release was pH-independent and dependent on agitation intensity. Level A IVIVCs could be established using the different in vitro methods but one to one correlation was established only when the ADS method was used. For the prediction of in vivo drug dosage form behavior based on in vitro methods, the ADS showed a high predictability when compared to USP in vitro methods.

KEYWORDS Artificial digestive system, Hydrophilic matrix tablets, Level A IVIVC, Predictability

INTRODUCTION

In vitro dissolution testing is one of the techniques most widely used in the characterization of drugs and in the evaluation of drug dosage forms (Ford & Rajabi-Siahboomi, 2002). It plays an important role both in the development process of a new formulation and as a means of quality control (Zahirul & Khan, 1996). The dissolution test is of high importance during the development of drugs and the validation of their formulation to identify the biopharmaceutical properties of the dosage forms. It becomes mandatory for the controlled-release dosage forms, for which a specific release of the drug from the dosage form is desired, because in vitro tests allow identifying the different parameters that could influence the drug release and the mechanism of release.

The validation of the final product can be accomplished only by in vivo testing, ultimately in human subjects, but in vivo tests could be reduced

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using reliable in vitro methods. From the technical perspectives of bioavailability studies, it is necessary to establish an in vitro test method that can predict the progress of drug release and eventually its absorption in vivo. In vitro methods become more reliable when they are as far as possible close to in vivo conditions. Therefore, the current in vitro methods try to reflect either one or a combination of the following factors: pH, ionic strength of gastrointestinal (GI) fluid and agitation intensity (motility) of the GI tract.

The limiting factor for absorption in vivo for the drugs that fall in class I and II in the biopharmaceutical classification system (BCS), and which are formulated in controlled-released forms, is the release and the dissolution of the drug from the dosage forms, therefore the establishment of an in vitro/in vivo correlation is of considerable importance.

As a class I drug, theophylline is highly soluble and readily permeates the intestine (Moller, 1983; Avdeef et al., 2000), the limiting factor for drug release is the dosage form. It is available in form of sustained release as tablets or pellets using different techniques.

The current study focuses on the hydrophilic matrix tablets (Christensen & Dale, 1962; Melia, 1991) that are widely used as controlled delivery system. The release from this dosage form depends essentially on two main factors: swelling and erosion (Abrahamsson et al., 1998). Therefore, a reliable in vitro method should maintain all conditions in vivo which can influence the swelling and erosion because the two factors determine the fate of the dosage form in vivo.

The main objective of the current study was to investigate the behavior of theophylline hydrophilic matrix tablets using USP in vitro methods in different conditions and using a new in vitro model called the artificial digestive system (ADS). The conditions of the study for each in vitro method were maintained to be as close as possible to in vivo conditions in the fasted state. The behavior of the same tablets was studied in vivo in human volunteers to investigate the potentiality of the different in vitro methods used in the study to show in vivo performance. The efficacy of each in vitro method was evaluated by establishing in vitro/in vivo correlation and comparing the statistical properties of the curves established using the different method.

MATERIAL AND METHODS

Drug Dosage Form

Theostat® containing 300 mg of theophylline (Theostat® 300 mg, Laboratoires Sinbio, Pierre-Fabre Medicament, Boulogne, France, Batch No.: G00773) is available on the French market since more than 20 years (French National Drug Compendium "VIDAL", 80th edition, 2004). The main polymer used in the formation of the hydrophilic matrix is a mixture of hypromellose of high and low viscosity. It is a well known antiasthmatic drug manufactured in the form of hydrophilic matrix tablets. This sustained release (SR) form is widely used in medical practice to provide a convenient and safe twice daily administration and it is used as model in the current study.

USP Apparatus II Method

A paddle apparatus (AT7 SOTAX) was used to study the dissolution characteristics of the tablets based on a method described in the USP (XXVI edition). The experiment was performed in a phosphate buffer medium at pH = 7.2. To simulate the fasted state in vivo, FASSIF medium was used as the dissolution medium (Galia et al., 1995; Dressman et al., 1998). Each experiment was performed using six tablets which were placed into stainless steel sinker baskets to prevent floating and sticking to the beaker wall. The sinkers were settled in the bottom of the beakers. The dimensions of the sinkers were as described in the USP. The dissolution media were prepared according to the USP. The dissolution medium was 1000 mL in volume, maintained at a temperature of 37.0 ± 0.5°C. Rotation speeds of 60 and 120 rpm were used to investigate the impact of agitation intensity on the dissolution rate. Eleven 3 mL samples were withdrawn from the dissolution medium at appropriate time intervals and filtered through a membrane filter (pore size 0.45 μm). The samples were appropriately diluted in a fresh quantity of the dissolution medium and the absorbance was measured by a spectrophotometer (SHIMADZU UV-160A) at 271 nm.

USP Apparatus IV Method

To investigate the influence of pH and agitation intensity on the dissolution rate, the behavior of the drug dosage form was studied in the through flow cell

(CY7 SOTAX) with the closed system using a cell of 22.6 mm in diameter. The dissolution medium was 1000 mL in volume, maintained at a temperature of 37.0 ± 0.5°C. The dissolution media were prepared according to the USP. Each experiment was performed using six tablets in three different values of pH by substitution of the medium during the experiment (1 hr at pH = 1.3, 2 hr at pH = 5.4, and 5 hr at pH = 7.2). To investigate the impact of agitation intensity on drug dissolution, two flow rates were used: 20mL/min and 50 mL/min. Eleven 3 mL samples were withdrawn from the dissolution medium at appropriate time intervals and filtered through a membrane filter (pore size 0.45 μm). The samples were appropriately diluted in a fresh quantity of the dissolution medium and the absorbance was measured by a spectrophotometer (SHIMADZU UV-160A) at 271 nm.

ADS Method

The AD system consists of four serial compartments simulating the stomach and the three segments of the small intestine: the duodenum, jejunum, and ileum (Havenaar & Minekus, 1994; Minekus et al., 1995; Blanquet et al., 2004a,b). Each compartment is filled with water pumped from a water bath into the glass jackets around the flexible walls to control the temperature inside the units (37°C) and the pressure on the flexible walls. Changes in the water pressure enable mixing of the chyme by alternate compression and relaxation of the flexible walls. To control the transit of the chyme, a power formula ($f = 1–2^{-(t/t1/2)\beta}$ where f represents the fraction of chyme delivered, t the duration time of delivery, $t1/2$ the half-time of delivery and β a coefficient describing the shape of the curve) is used for gastric and ileal delivery. Chyme transit is then regulated by opening or closing the peristaltic valves that connect the compartments. The volume in each compartment is monitored by a pressure sensor connected to the computer. The pH is computer-monitored and continuously controlled by secreting either water or 0.5 M HCL (0.25 mL/min) into the stomach and either electrolytes or 0.5 M NaHCO3 (0.25 mL/min) into the small intestine. Simulated gastric (0.5 mL/min), biliary (0.5 mL/min) and pancreatic (0.25 mL/min) secretions, i.e., pepsin, lipase, pancreatic and bile salts, are introduced into the corresponding compartments by computer-controlled pumps. All parameters of the system are adjusted to simulate the conditions found in the GI tract of a healthy adult in the fasted state (Chung et al., 1979; Bernier & Adrian, 1988; Beckers et al., 1992; Murray et al., 1993), the parameters are summarized in Table 1. The model is equipped with hollow fiber membranes (HG 600, HOSPAL COBE, France) connected to the two compartments representing the jejunum and the ileum, respectively. Water and small molecules including the drug studied are removed from the lumen of the compartments by pumping dialysis fluid (10 mL/min) through the hollow fibers. After each experiment, the system is washed with detergent and rinsed with water.

If the ADS has been widely used in nutrition studies, few examples of drug dosage forms have been studied (Blanquet et al., 2004a,b; Souliman et al., 2006).

To study the availability of theophylline for absorption, one tablet was introduced into the gastric compartment simultaneously with 200 g of water to simulate the fasted state in an adult. During digestion, dialysis fluids were collected at half hourly intervals up to 4 hr. The volumes were measured and samples were

TABLE 1 **Parameters of In Vitro GI Conditions in Fasted State in an Adult**

Parameter of in vitro GI conditions	Fasted state
Gastric conditions	
Time (min)/pH	0/4.5
	10/3.2
	20/2.4
	40/1.8
	60/1.6
	90/1.5
Secretion	0.25 mL/min of pepsin
	0.25 mL/min of lipase
Time of half emptying $t1/2$	20 min
Duodenal compartment	
pH	Maintained at 6.4
Secretion	0.5 mL/min of bile solution
	0.25 mL/min of pancreatic solution
	0.25 mL/min of intestinalelectrolyte solution
Jejunal compartment	
pH	Maintained at 6.9
Dialysis	10 mL/min of jejunal fluid solution
Ileal compartment	
pH	maintained at 7.2
Dialysis	10 mL/min of ileal fluid solution

taken for each period; the samples were diluted in physiological water and the absorbance was measured using a spectrophotometer (SHIMADZU UV-160A) at 271 nm. The experiment was repeated three times.

It is important to note that the amount of drug that crosses the hollow fibers will be termed "potential absorption in the ADS". It does not represent real absorption in vivo because the model cannot mimic the permeability but represents the quantity available for absorption by passive diffusion in vivo. Therefore, for class I and II drugs, which have a high intestinal permeability, absorption in the ADS may represent the real permeation in vivo.

In Vivo Method

Six male volunteers (age: 24–28 years, weight: 68–82 kg) gave their written consent to take part in the study, which was approved by the Ethics Committee of the Medical Center.

All subjects were healthy with normal hepatic and renal functions and normal haemotological profiles. None was taking any drug, alcohol, or methylxanthine products during the study.

Each subject swallowed one tablet after overnight fasting with 200 mL of water. Blood samples were taken at appropriate time intervals, and kept frozen (–20°C) until analysis. The samples were centrifuged for 5 min at 5000 rpm and the supernatants were collected. The concentration was measured by a validated reversed high-performance liquid chromatography method with UV detection at 271 nm. The mobile phase was composed of 9% acetonitrile in a sodium acetate buffer at pH = 4, column (LICROSPTER RP18), 50 µL was injected at flow rate of 2 mL/min.

The pharmacokinetic parameters were calculated by a noncompartmental approach and the absorption parameters were calculated by the Wagner-Nelson modified method using Kinetica® 2000 software.

RESULTS

USP Apparatus II Method

Fig. 1 shows the percentage of theophylline dissolved in the paddle apparatus at 60 rpm and 120 rpm in a phosphate buffer medium at pH = 7.2 and using FASSIF as dissolution medium. It demonstrates that

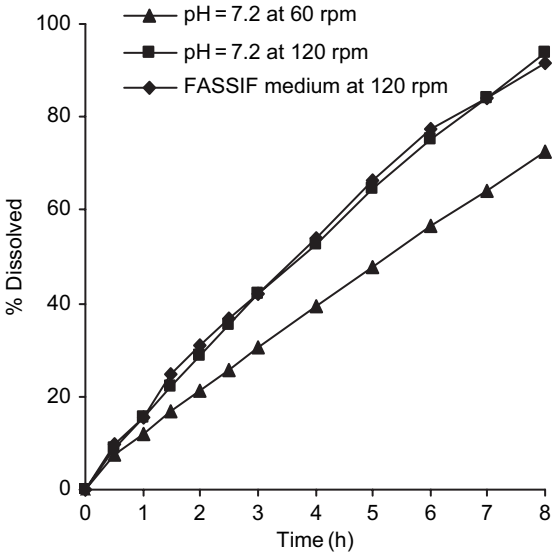

FIGURE 1 **Cumulative Percentage (Mean ± SD) of Theophylline Dissolved From SR Tablets in Different Conditions Using Paddle Apparatus (*n* = 6): (▲) 60 rpm at pH = 7.2 (■) 120 rpm at pH = 7.2 (◆) 120 rpm in FASSIF Medium.**

rotation speed has an important effect on the dissolution rate. At 8 hr, the percentage of theophylline dissolved increased from 73% at 60 rpm to 93% at 120 rpm, but in both cases the dissolution profiles were almost of zero-order.

The FASSIF medium did not change the dissolution profiles. These results indicate that the drug dissolution rate is not affected by dissolution medium constituents, only agitation intensity modifies the dissolution rate.

USP Apparatus IV Method

For the purpose of investigating the impact of pH on the dissolution profiles, the dissolution characteristics of these tablets were studied in the through flow cell in different values of pH simulating those found in vivo. Fig. 2 shows that the dissolution profiles remained of zero-order after changing the pH value of the dissolution medium and this confirms that the release is pH-independent.

The influence of agitation intensity on the dissolution rate was also confirmed by the through flow system at 8 hr, which showed an increase of the dissolution rate from 45% at 20 mL/min to 58% at 50 mL/min.

ADS Method

Fig. 3 shows the mean cumulative percentage of theophylline potentially absorbed in the jejunum and

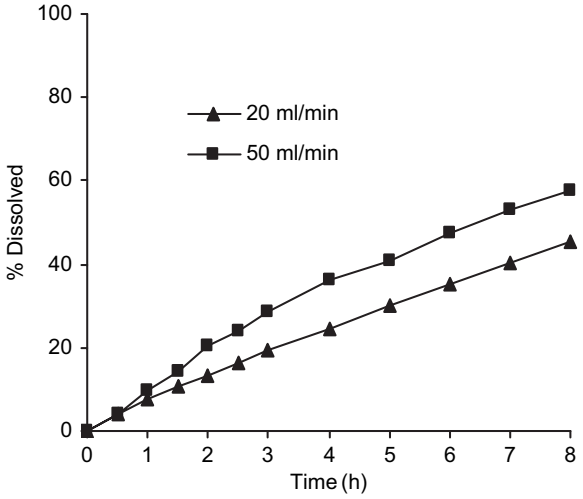

FIGURE 2 **The dissolution profiles remained of zero-order in spite of the change of pH value of the dissolution medium.**

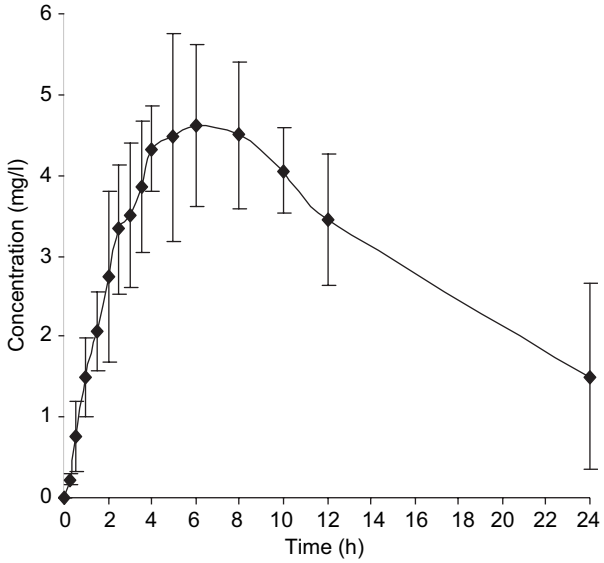

FIGURE 4 **Theophylline Plasma Concentrations (Mean ± SD) in the Fasted State (*n* = 6).**

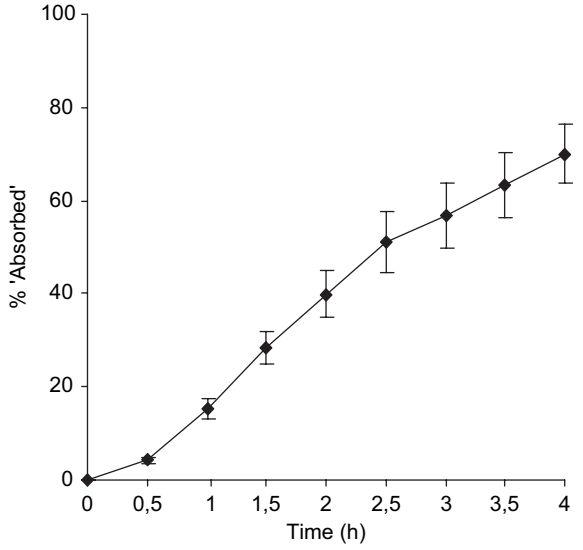

FIGURE 3 **Cumulative Percentage of Theophylline "absorbed" in the ADS (Mean ± SD) in the Fasted State (*n* = 3).**

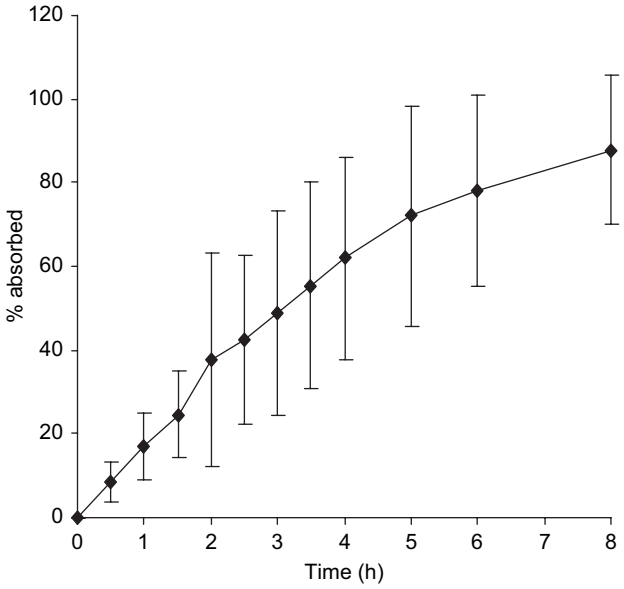

FIGURE 5 **Cumulative Percentage of Theophylline (Mean ± SD) Absorbed in the Fasted State In Vivo (*n* = 6).**

ileum in the ADS in the fasted state. About 70% of the drug is absorbed after 4 hr which corresponds to the transit time of the tablet within the different compartments in the ADS.

In Vivo Method

Fig. 4 shows blood concentrations of theophylline in the fasted state while Fig. 5 shows the amount absorbed. It could be observed that during the first 4 hr, the kinetics of absorption stayed almost of zero-order. The pharmacokinetic parameters are shown in Table 2.

In Vitro/In Vivo Correlation (IVIVC)

The fraction of drug dissolved in vitro is compared to the fraction of drug absorbed in vivo obtained after the deconvolution of plasma concentrations of the drug. Level A IVIVCs were established using the USP methods and the ADS. The relationships established were evaluated by comparing the statistical characteristics including the slope and the correlation coefficient of each IVIVC curve. Table 3 summarizes the statistical properties of IVIVC curves using the different in vitro methods.

TABLE 2 **Pharmacokinetic Parameters in the Fasted State In Vivo (C_{max}: Maximum Plasma Concentration. AUC: Area Under Concentration Curves. T_{max}: Maximum Concentration Time. *t*1/2: Half-Life of Elimination. T10, 50, 90: Time Required for Absorption of 10, 50, 90% of the Drug)**

	Fasted state
Parameter	Mean ± SD
C_{max} (mg/L)	4.85 ± 0.70
$AUC_{0-\infty}$ (mg.hr/L)	66.56 ± 20.06
T_{max} (hr)	5.83 ± 1.21
*t*1/2 (hr)	8.75 ± 9.04
*T*10% (hr)	0.83 ± 0.59
*T*50% (hr)	3.59 ± 1.60
*T*90% (hr)	8.96 ± 3.79

The slope is closer to one using the ADS and paddle apparatus at 120 rpm. Using the paddle apparatus at 60 rpm and the flow through cell at 20 and 50 mL/min, the slope is different from one (Table 3).

DISCUSSION

Dissolution testing is considered as one of the most important tests in the assessment of the drug dosage form behavior. However, in vitro tests are not always reliable in predicting the behavior of a drug dosage form in vivo. This is due to the complexity of the gastrointestinal tract in vivo and to the inability of the conventional in vitro methods to maintain the necessary conditions found in vivo.

For hydrophilic matrix tablets, swelling and erosion are the most critical properties for such drug dosage forms when seeking to obtain the desired target plasma concentration profiles and clinical benefits of SR administration (Abrahamsson et al., 1998). After exposure to aqueous medium, the outer surface of these tablets swells by polymer hydration and chain relaxation, forming a hydrogel coat around the dry central core (Baumgartner et al., 2005). The release takes place by diffusion through the gel layer and/or erosion of the tablet matrix. The extent of polymer swelling, the relative mobilities of the dissolution medium and the drug, and matrix erosion dictate the kinetics as well as mechanism of drug release from the polymeric matrices (Roy & Rohera, 2002). The varying conditions including the peristaltic movements along the GI tract can potentially affect the tablet swelling and erosion and thereby alter the drug release rate.

An in vivo scintigraphic study (Sournac et al., 1988, 1991) for the drug dosage form used in this study has demonstrated that on an average period of 15 min after intake, the tablets settled in the stomach and after 72 min, the tablets were located in the duodenum and small intestine, the mean gastro-cecal transit time was about 245 min. The tablets do not undergo any breaking, just erosion phenomenon, and they swelled in the GI tract.

During the passage of the tablets in the GI tract, they were undergoing different conditions including the GI movements. Using USP II method, the tablets were in contact with the dissolution media which allowed forming the hydrogel layer around the central core and then the tablets exposed to turbulent movements produced by the paddles. The solid–liquid interface between the dosage form and the dissolution medium was renewed by the turbulent movements of the liquid up and down. Increase of rotation speed of the paddles accelerated the renewal of the solid–liquid surface and also increased the erosion, which led consequently to increase the amount of drug released. This was observed in the study when the rotation speed was changed from 60 to 120 rpm.

With USP IV, the dosage unit is placed in the cell and the dissolution medium is pumped from the reservoir within the cell. The dissolution is maintained by the laminar flow passage of the dissolution medium and by the permanent renewal of the liquid–solid interface. The laminar flow is maintained by the glass beads located in the bottom of the cell. The agitation intensity produced by the passage of the dissolution liquid within the cell is less important than that

TABLE 3 **Statistical Properties of IVIVC Curves Established Using Different Methods**

IVIVC		ADS	USP II120 rpm	USP II60 rpm	USP IV50 mL/min	USP IV20 mL/min
Fasted state	Slope	1.2636	1.2005	1.6115	1.7024	2.6401
	Intercept	0.8973	–0.7396	0.6649	1.2840	–1.4544
	Correlation coefficient (r)	0.9860	0.9965	0.9957	0.9980	0.9952

produced by the paddles in USP II. This can be observed by the amount released of the drug using each method.

In the ADS, the relaxation and contraction of the flexible membrane in each compartment allow simulating the motility patterns in vivo. The tablets undergo during 240 min (corresponding to the same passage time observed in the scintigraphic study) hydrodynamic movements produced in the different compartments. Therefore, the mechanical force exerted on the tablets using the ADS seems to be closer to that exerted in vivo.

To be close to in vivo conditions, in vitro methods should maintain all necessary conditions that can influence the behavior of these tablets. The simulation of the hydrodynamic effects in the GI tract is maintained by the rotation movements of the paddles using the USP II method or by the laminar flow rate of the dissolution medium using USP IV method. Using these two methods, the mechanism of release of the active pharmaceutical ingredient from the tablets could be studied, but the GI effects, particularly the peristaltic movements, cannot be simulated exactly. These effects are the main potential factors that determine the fate of the hydrophilic matrix tablets in vivo. In addition, there is another force exerted on the tablets in vivo, it is the "squeezing force" which resulted from the contraction and relaxation of GI muscles. This force can relatively destroy the gel layer formed around the tablet and then facilitate the release of the drug from the dosage form. This force could be simulated by the ADS but not by USP methods.

Table 3 shows that excellent quantitative correlations of level A were established between in vivo results and those in vitro with the different in vitro methods. But the question raised is related to the predictability of the different in vitro methods, especially during the selection phase of the drug dosage form before any in vivo study.

To evaluate the predictability of each method, one to one (y = x) IVIVCs were established using in vitro results obtained with USP and ADS methods. The mean ratio between in vitro and in vivo data is very close to one when in vitro results are compared to those in vivo using the ADS (Table 4). The mean ratio is 0.61 using USP method II at 60 rpm and 0.88 at 120 rpm and 0.42 using USP method IV at 20 mL/min and 0.58 at 50 mL/min, whereas it is 1.02 using the ADS in the fasted state. It can be observed that the standard deviation (SD) using the ADS is more important than

TABLE 4 **Ratio Between the Percentage Dissolved (or Potentially Absorbed) In Vitro and That Absorbed In Vivo Over the Same Time Using Different Methods**

	Fasted state				
Time (hr)	II 60	IV 20	ADS	II 120	IV 50
0,5	0.65	0.50	0.49	1.04	1.02
1	0.62	0.46	0.91	0.92	0.63
1,5	0.61	0.43	1.15	0.89	0.45
2	0.54	0.35	1.06	0.76	0.50
2,5	0.59	0.38	1.21	0.83	0.47
3	0.63	0.39	1.17	0.86	0.50
4	0.63	0.39	1.13	0.85	0.51
Mean	**0.61**	**0.42**	**1.02**	**0.88**	**0.58**
SD	**0.03**	**0.05**	**0.23**	**0.08**	**0.19**
CV	**5.38**	**11.08**	**23.04**	**8.95**	**31.91**
t	31.53	33.59	0.18	3.99	5.90
p	<0.001	<0.001	0.86	0.01	<0.001
S/NS	S	S	NS	S	S

those with USP methods and this is due essentially to the first sampling point (0.5 hr). The nonhomogenization of the first sampling point in the ADS in comparison with the rest of sampling points can be explained by the necessary time for the ADS to adjust and stabilize its parameters. Since Theostat is a noncoated hydrophilic matrix, a small burst (probably due to the solubilization of the drug dispersed on the tablet surface) takes place during the hydration phase. The combination of this small burst and the lack of homogenization at time 0.5 hr could probably explain the low value obtained for the ratio (0.49).

To investigate whether in vitro and in vivo results in the different conditions using the various methods are significantly (S) or nonsignificantly (NS) different from one another, the student's *t*-test was applied. Table 4 confirms that in vivo and in vitro results obtained by ADS are nonsignificantly different, whereas they are significantly different using the conventional USP in vitro methods.

These results confirmed that the conventional in vitro methods could be of high importance during quality control procedures, but for an innovative drug dosage forms, as hydrophilic matrix tablet, the need for new in vitro methods that could forecast the progress of the dosage form in vivo is increasingly important.

Before validation of an in vitro method using USP methods, several parameters have to be determined. For the ADS, the default program is used for all the drug dosage forms, whereas the parameters (speed and

the flow rate) for the conventional in vitro methods have to be adjusted for each drug and dosage form. The adjustment of the parameters for USP methods is due to the inability of these methods to simulate the real conditions found in vivo particularly the hydrodynamic effects that potentially affect the behavior of the hydrophilic matrix tablets.

The mechanical force exerted by the different movements of the stomach and the small intestine was able to be simulated well by closing and opening the flexible membranes in each compartment of the ADS. In addition to the simulation of the hydrodynamic effects, the ADS offered other advantages including the sequential use of enzymes in physiological amounts and appropriate pH for the enzymes. All these advantages allowed the ADS to study the behavior of the hydrophilic matrix tablets in conditions simulating those found in vivo.

A level A IVIVC was established by the ADS with a correlation coefficient and a slope close to one which confirmed that this system may be considered as a very useful in vitro method simulating in vivo conditions, particularly during the development of an innovative solid oral dosage form.

This will be of considerable importance for the pharmaceutical industry, particularly during the development of an innovative drug dosage form. It will be helpful in the selection of the drug dosage forms which exhibits the desired release profiles and to optimize the formulation before in vivo study. It might predict the bioavailability of a drug from class I and II instead of using difficult, time-consuming and expensive in vivo bioequivalence studies.

CONCLUSION

Data from this work applied to the hydrophilic matrix tablets suggest that USP in vitro methods could be used in the quality control for the drug dosage forms already available. But in the research field, in vivo prediction from in vitro data requires new reliable in vitro models. This work showed the efficacy of the ADS in predicting in vivo theophylline hydrophilic matrix tablets behavior and enabled a level A IVIVC to be established. When applied to a hydrophilic matrix tablet, a monolithic SR dosage form where the release mechanism is a combination of diffusion and erosion, the ADS mimics well the erosion of the hydrophilic matrix tablet in the GI tract. The ADS could also be a useful method for ranking different formulations from a hydrophilic matrix tablet as they have the same release mechanism and the same biopharmaceutical behavior. This study was applied to the hydrophilic matrix tablets of theophylline, a previous study was applied to the immediate release tablets of Acetaminophen (Souliman et al., 2006). Further works will have to investigate the behavior of other sustained release monolithic and multiparticulates dosage forms with different and specific release mechanism to evaluate the efficacy of the ADS for various pharmaceutical applications. This system can be considered as a very useful complementary tool for in vitro dissolution techniques during the development of an innovative drug dosage form, making more information about drug behavior in various GI conditions available.

ABBREVIATIONS

ADS	artificial digestive system
GI	gastrointestinal
FASSIF	fasted state simulated intestinal fluid
IVIVC	in vitro/in vivo correlation
SR	sustained release

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