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RESEARCH PAPER

Evaluation of an In Vitro Dissolution and Permeation Apparatus for Oral Solid Pharmaceutical Dosage Forms

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ABSTRACT

An apparatus based in the USP dissolution test, the F-C-SL apparatus (Ferreira–Costa–Sousa Lobo), was developed that allowed the simultaneous evaluation of the in vitro release and permeation of oral solid pharmaceutical dosage forms. The release rate in both dissolution devices (USP and F-C-SL apparatus) was evaluated with acetaminophen tablets. Different test conditions (stirring rate and solvent volume ratio) were investigated and no significant differences in acetaminophen release rate were found between these apparatuses. In the F-C-SL apparatus, the in vitro permeation kinetics of acetaminophen were evaluated using synthetic membranes and followed a zero-order kinetic.

INTRODUCTION

The main purpose of an oral solid pharmaceutical dosage form is to make available to the human body a certain and defined amount of the active substance, through the gastrointestinal system (1). The pharmaceutical industry and the regulatory agencies focus on the evaluation of the drug release kinetics from dosage forms, and this study is generally performed on official or nonofficial dissolution devices (2,3). However, most of the apparatuses used to study solid dosage form disintegration and dissolution are only able to evaluate the release of the active substance from the pharmaceutical form (4–7).

An apparatus was developed that could evaluate, simultaneously, the in vitro dissolution and permeation kinetics of drugs contained in solid dosage forms. This apparatus is based on the USP device, coupled with a synthetic membrane that enables the evaluation of the permeation kinetics.

The objective of this investigation was to compare the two dissolution devices (the USP apparatus and the proposed one) as far as some important factors that affect dissolution and permeation are concerned. The effect of

the chosen method (paddle or basket), of the stirring rate (either in the donor or in the receiver compartments), and of the solvent volume ratio were studied.

In this study, acetaminophen was chosen, because it is a very common drug, generally readily absorbed from gastrointestinal tract, very soluble, and very stable in aqueous solution (8,9). Acetaminophen tablets were prepared in Laboratório de Tecnologia Farmacêutica.

MATERIALS

Acetaminophen was obtained from Sigma, Germany. Synthetic membranes type SM 15702 were obtained from Sartorius, Germany. All chemicals used were reagent grade.

EXPERIMENTAL

Tablet Characteristics

The average tablet weight (n = 20) was determined in a Metller AE 200 balance. All the tested tablets (n = 20) conformed to the USP Uniformity of Dosage Units (10). The tablet hardness was determined (n = 10) in a Erweka TBH 28 tester. The friability (Erweka Type TAP) was determined (n = 20) for 100 revolutions at 25 rpm, for 4 min (Table 1).

Drug Content Study

Drug content of the solid dosage form was evaluated by crushing 8 tablets and dissolving the amount of powder corresponding to 1 tablet, in about 100 ml of the dissolution fluid. This solution was quantitatively transferred to volumetric flasks and appropriate dilutions were made with the same liquid. The resulting solutions were filtered and analyzed by high-performance liquid chromatography (HPLC).

Table 1

Tablet Characteristics

	Average	Standard Deviation
Weight	588.9 mg	4.7
Hardness	9.5 kPa	1.1
Friability	0.17%	—

Apparatus Description

The assembly consists of the two covered vessels made of transparent inert material, a motor, a metallic drive shaft, and a cylindrical basket or a paddle (Fig. 1).

The smaller vessel is immersed in the outer vessel and the whole system is partially immersed in a water bath that maintains the temperature constant in both vessels during the test.

The inner vessel is cylindrical (10 cm wide × 16 cm high), and has a nominal capacity of 1000 ml and a cylindrical basket or a paddle that keeps the fluid in constant smooth motion, as in the USP dissolution apparatus. In its bottom there is a hole (6 cm diameter) where the membrane is fixed. The outer vessel is also cylindrical (16 cm wide × 18 cm high), and has a nominal capacity of 2000 ml and a magnetic stirrer that keeps the fluid in constant, smooth motion.

Release Study

The in vitro release kinetics of acetaminophen were evaluated using both the USP apparatus (n = 6) and the F-C-SL apparatus (n = 3).

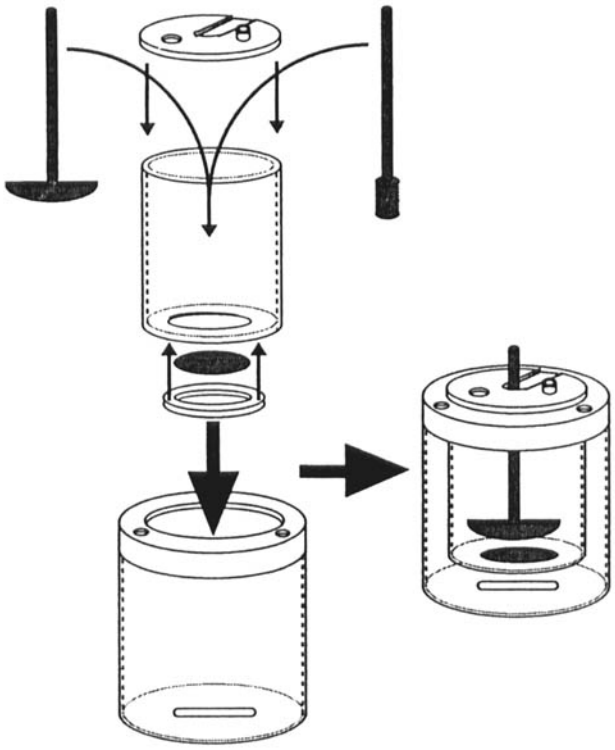

Figure 1. Assembly of the F-C-SL apparatus.

Table 2

USP Apparatus Conditions

Method	Apparatus	Stirring (rpm)
USP 1	Paddle	50
USP 2	Basket	50
USP 3	Paddle	200

When the USP apparatus was used (Table 2), the release kinetics using both the paddle (USP 1) and the basket methods (USP 2) were studied. In these two assays, 900 ml of dissolution fluid and a stirring rate of 50 rpm were used. The dissolution medium is the one indicated in the USP monograph "Acetaminophen Tablets" (phosphate buffer solution with a pH 5.8 and maintained at 37 ± 0.5°C) (10). With the paddle method, the effect of a stirring rate of 200 rpm was also studied.

When the F-C-SL apparatus was used (Table 3), the conditions described above (F-C-SL 1, 2, and 3) were studied. Using also the paddle method and an inner vessel stirring rate of 50 rpm, the effects of the outer vessel stirring rate fluid volume (F-C-SL 4, 5, and 6) were evaluated.

At predetermined time intervals (5, 10, 20, 30, 45, and 60 min for USP apparatus; and 5, 10, 20, 30, 45, 60, 90, and 120 min for F-C-SL apparatus), a sample of the receptor fluid was removed for analysis and replaced with an equal volume of fresh receptor fluid. The concentration of acetaminophen in the receptor fluid was determined by HPLC.

Permeation Study

The in vitro permeation kinetics of acetaminophen were evaluated using synthetic membranes. The permeation medium was pH 7.0 phosphate buffer solution (USP 23/NF 18) with a volume of 1800 ml and was maintained at 37 ± 0.5°C throughout the study.

The synthetic membrane was made of a porous support and two lipid components, and was prepared according to the manufacturer's instructions. At predetermined time intervals (5, 10, 20, 30, 45, 60, 90, and 120 min), a sample of the permeation medium was removed for analysis and replaced with an equal volume of the same liquid. The concentration of acetaminophen in the permeation medium was also determined by HPLC.

The synthetic membrane flux was determined from Fick's law of diffusion:

$$J_s = \frac{1}{A(dM/dt)}$$

$$P_e = \frac{J_s}{\Delta C}$$

where J_s is the membrane flux ($\mu g \cdot cm^{-2} \cdot h^{-1}$), dM/dt is the amount of acetaminophen permeated per unit time, A is the diffusion area (cm^2), P_e is the effective permeability coefficient ($cm \cdot h^{-1}$), and ΔC is the concentration gradient across the membrane. In this case, ΔC was assumed to be the donor concentration (the drug concentration in the receiver compartment never exceeded 10% of the donor concentration). The steady-state membrane flux was determined from the slope of the linear portion of the cumulative amount–time plot (20–120 min).

The conditions studied are described in Table 2 and Table 3.

HPLC Analysis

The HPLC system consisted of a pump (Varian model 9012), a 20-µl loop (release study) and 200-µl

Table 3

F-C-SL Apparatus Conditions

Method	Apparatus	IV Stirring[a] (rpm)	OV Stirring[a] (rpm)	OV Volume[a] (ml)
F-C-SL 1	Paddle	50	100	1800
F-C-SL 2	Basket	50	100	1800
F-C-SL 3	Paddle	200	100	1800
F-C-SL 4	Paddle	50	No agitation	1800
F-C-SL 5	Paddle	50	200	1800
F-C-SL 6	Paddle	50	100	900

[a]IV, inner vessel; OV, outer vessel.

loop (permeation study), and a variable wavelength detector (Varian model 9050).

A C18 column (Spherisorb S10 ODS 2 25.0 cm × 4.6 mm) was used. The mobile phase was methanol/water (25/75), at a flow rate of 1.0 ml/min, and the detector was set to 244 nm.

RESULTS AND DISCUSSION

The results of the release and permeation rates of acetaminophen in the USP and F-C-SL apparatus are shown in Tables 4 and 5, and Figs. 2, 3, and 4. The drug release profiles (USP 2) were curve fitted by linear regression to give the following empirical equations:

$$(0 \le t \le 20)\ Q = -10.383 + 21.432t \quad R = 0.996$$

$$(20 \le t \le 30)\ Q = 330.010 + 4.824t \quad R = 1.000$$

where Q is the amount of drug released (mg) and t is the release time.

The drug release profile (F-C-SL 2) was curve fitted by nonlinear regression to give the following empirical equation:

$$Q = -4.175 + 24.232t - 0.405t^2 + 0.002t^3$$

$$R = 0.999$$

The difference for these two basket methods is not significant (11).

The slope (y) of the cumulative amount–time plot (t = 5 min) for the other methods was calculated and the following values were obtained:

$y = 88.088$ (F-C-SL 1) $y = 88.400$ (USP 1)

$y = 97.936$ (F-C-SL 3) $y = 97.209$ (USP 3)

$y = 89.429$ (F-C-SL 4)

$y = 90.673$ (F-C-SL 5)

$y = 78.040$ (F-C-SL 6)

Table 4

Cumulative Amount (%) of Acetaminophen Released

Time (min)	F-C-SL				USP		
	1	2	3	6	1	2	3
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	87.9	22.1	98.2	93.3	88.7	18.7	100.2
10	93.1	39.0	100.0	100.5	95.6	38.3	101.5
20	94.1	71.5	98.5	102.1	96.2	86.4	100.7
30	93.9	87.2	98.3	101.9	96.1	96.2	99.7
45	93.1	96.1	97.2	100.4	95.7	97.1	98.9
60	92.3	97.1	95.9	100.3	95.2	96.9	98.1
90	90.9	96.9	95.0	98.1	—	—	—
120	90.1	96.0	94.0	97.7	—	—	—

Table 5

Cumulative Amount (%) of Acetaminophen Permeated

Time (min)	F-C-SL					
	1	2	3	4	5	6
0	0.0	0.0	0.0	0.0	0.0	0.0
5	0.3	0.1	0.1	0.1	0.5	0.3
10	0.5	0.1	0.2	0.2	0.6	0.5
20	0.7	0.2	0.3	0.4	0.9	0.8
30	0.9	0.3	0.5	0.6	1.0	1.0
45	1.1	0.5	0.8	0.7	1.3	1.2
60	1.4	0.7	1.0	0.9	1.5	1.5
90	1.8	1.1	1.5	1.2	2.0	1.9
120	2.3	1.5	2.0	1.6	2.5	2.6

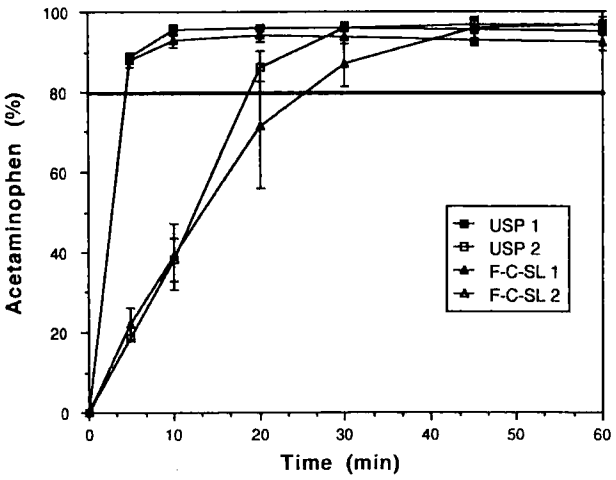

Figure 2. Release of acetaminophen in the USP and the F-C-SL apparatus, using both paddle and basket devices.

The slope is almost identical for each of the methods in both the USP and the F-C-SL apparatus.

The drug permeation profiles were curve fitted (in the linear region) to give the following empirical equations:

$$Q = 1.980 + 0.081t \qquad R = 0.999 \text{ (F-C-SL 1)}$$
$$Q = -0.508 + 0.066t \qquad R = 0.997 \text{ (F-C-SL 2)}$$
$$Q = -0.014 + 0.082t \qquad R = 0.999 \text{ (F-C-SL 3)}$$
$$Q = 1.141 + 0.055t \qquad R = 0.997 \text{ (F-C-SL 4)}$$
$$Q = 2.615 + 0.078t \qquad R = 0.998 \text{ (F-C-SL 5)}$$
$$Q = 2.006 + 0.091t \qquad R = 0.991 \text{ (F-C-SL 6)}$$

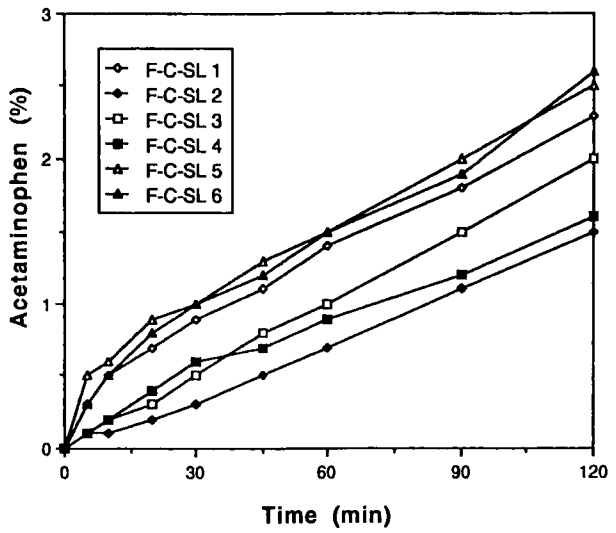

Figure 3. Permeation of acetaminophen in the F-C-SL apparatus.

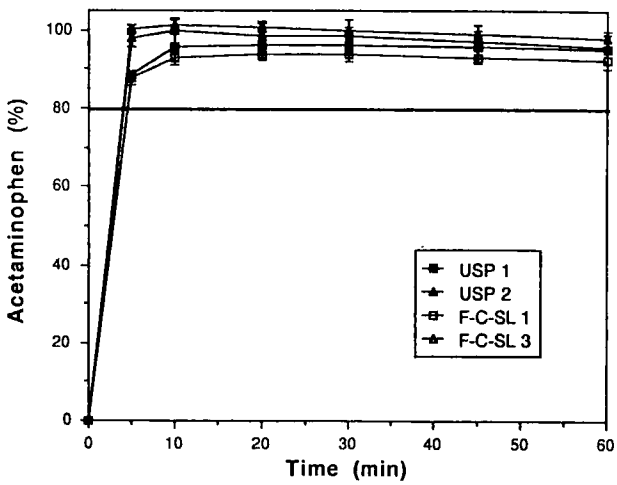

Figure 4. Release of acetaminophen in the USP and F-C-SL apparatus, with different stirring rates.

where Q is the amount of drug permeated (mg) and t is the release time.

The slopes of these curves are very similar (0.78–0.91) except for the F-C-SL 2 curve (basket apparatus) and the F-C-SL 4 curve (no agitation in the outer vessel). These differences are not significant for the F-C-SL 2 method but are significant in the case of the F-C-SL 4 method. Statistical analysis was performed using analysis of variance (one-way ANOVA) (11).

CONCLUSIONS

The acetaminophen release rate from this solid dosage form varies with the dissolution method used (paddle or basket) (Fig. 2). The acetaminophen release rate does not vary significantly with the modification of the inner vessel stirring rate (Fig. 4). The amount of acetaminophen released after 30 min complies to the official monograph (≥80%), for all methods. The paddle apparatus gives more exact results (with lower standard variation) and is the one indicated in the United States, European, and Japanese Pharmacopoeias. In the basket apparatus, once the tablet disintegrates, the granules may either clog the basket or quickly pass through the mesh to settle on the bottom of the dissolution vessel. These factors can explain the high variability of this apparatus. The problems of the basket method are well documented in the literature (12–14). With the same devices, the results in both the USP and the F-C-SL apparatus are very similar (Figs. 2 and 4). The acetaminophen permeation rate across the synthetic membrane (Fig. 3) shows no significant variation with the disso-

lution method used (paddle or basket), nor with different stirring rate in the inner vessel, nor with a smaller volume in the outer vessel (900 ml instead of 1800 ml). The average steady-state membrane flux for all these methods is 168 $\mu g \cdot cm^{-2} \cdot h^{-1}$. The acetaminophen effective permeability coefficient for this membrane is 0.32 $cm \cdot h^{-1}$. Without agitation in the outer vessel, the flux is lower (120 $\mu g \cdot cm^{-2} \cdot h^{-1}$), and this fact can be explained by the formation of a saturated unstirred layer near the outer side of the synthetic membrane.

This research demonstrated the similitude of the dissolution assay in both F-C-SL apparatus and USP apparatus. The F-C-SL apparatus is a good choice for the simultaneous release and permeation study.

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