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RESEARCH PAPER

Evaluation of Some Protective Agents on Stability and Controlled Release of Oral Pharmaceutical Forms by Fluid Bed Technique

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ABSTRACT

A number of coating agents recommended for protection against humidity were evaluated on granules containing josamycin and paracetamol. The coating films were composed of Eudragit L30D, Eudragit RS30D, Sepifilm LP010, and Compritol 888 Ato and the granules were coated in a fluidized bed. Coated granules were stored in a desiccator with a saturated humidity, and the amount of moisture uptake was determined as a function of the storage time. The low hygroscopicity of drugs and granules allowed us to classify these agents according to their water vapor permeability. The results obtained showed significant differences, depending on the nature of the protective agents and the drugs. Thermal analysis study was realized to investigate the physico-chemical interactions between drugs, excipients, and the coating agents. Finally, the tablet dissolution curves obtained from coated granules showed that release differed with the nature of the coating agents.

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INTRODUCTION

Water adsorption on the surface of solids is of utmost importance in pharmaceutical studies. For most powders, the residual humidity modifies their mechanical and rheological properties. For these reasons, different agents have been used in order to protect oral pharmaceutical forms (1). One of the application methods of such protective agents is fluidized bed coating. The aim of this study was to investigate some protective agents which are widely used in pharmaceutical industries like derivatives of acrylic resins, celluloses, and glycerides.

Two drugs were providing by a pharmaceutical laboratory for a specific industrial technology (2): paracetamol, a water soluble crystalline compound, and josamycin, which is very slightly soluble.

This study consisted of testing the stability of the drugs alone, the drugs in granules, and the coated granules.

In order to investigate the physico-chemical interactions, we performed differential thermal analysis study on the drugs, the excipients, and the coating agents (3).

After evaluating the products according to protection against humidity, we studied the influence of these agents on in vitro release after tableting.

MATERIALS AND METHODS

The two drugs were josamycin and paracetamol. Lactose HMS (fine powder lactose) and Klucel MF (hydroxypropylcellulose) were used respectively as diluent and binder excipients.

The coating agents were:

- cellulose: Sepifilm LP010 (hydroxypropylmethylcellulose) from Seppic, France, available as dry powder, suitable for dispersion in water before coating.
- acrylic resins, ready for use, supplied as latex formulations with solid content of 30% w/w (Eudragit L30D and Eudragit RS30D from SPCI, France).
- a glyceride derivative: Compritol 888 Ato (glycerol behenate from Gattefosse, France) atomized powder usable after dissolving in an organic solvent before coating.

The remainder consisted of a plasticizer, Eudraflex (triethylcitrate) from SPCI, and an anti-sticking agent, Syloïd AL-1 (silica), which are included in Eudragit-based formulations.

Preparation of Granules

The formula retained for the granules was: Drug 80%–Lactose 20%. The granules were manufactured by wet granulation method in a Lödige M20 mixer according to the following protocol:

- mixing of active substance and lactose during 5 min.
- granulation with a binding solution with a 2% hydroxypropylcellulose gel.
- calibration of the granule with a Glatt TR80 sieving machine (1 mm screen).
- drying in an oven at 50°C for 5 hr.

Coating Formulations and Process

The composition of the coating formulations is chosen as industrial standard conditions and is given in Table 1.

After drying, the different batches were coated in a fluidized bed granulator (GLATT WSG-3E) with a top spray system. Josamycin and paracetamol granules were coated to reach theoretical weight gains of 10% w/w.

A preliminary study has optimized the most important operatory parameters for granules coating. Table 2 reports the different parameters used in the fluidized bed coating which remained unchanged during all the process.

Spray rates were 10 g/min. for aqueous dispersions and 20 g/min. for the organic solution.

The aqueous dispersions of coating agents were stirred continuously to prevent sedimentation of some insoluble particles which may be present or added in these dispersions.

Table 1

Composition of Coating Films

	Formulations (g)			
	1	2	3	4
Sepifilm LP 010	33			
Eudragit L 30D		110		
Eudragit RS 30D			110	
Compritol 888 Ato				33
Eudraflex		6.58	6.58	
Syloid AL-1		5	5	
Water	300	150	150	
Methylene chloride				135

Table 2

Parameters Used in the Fluidized Bed Coating

Parameters	Value
Charge (g)	300
Inlet air temperature (°C)	40–50
Outlet air temperature (°C)	30–40
Nozzle port size (mm)	0.8
Atomizing air pressure (bars)	1.5
Spray rate (g/min)	10–20

Experimental Storage Conditions

The coated granules were dried overnight (T = 60°C) in an oven. Samples of about 5 g of each batch were laid on petri dishes and stored in a desiccator at constant temperature (20°C) and relative humidity (99 ± 1%) achieved with saturated salt solution (barium sulfate).

The moisture content of the granules was measured at regular time intervals by weighing samples on a Mettler balance (± 1 mg) during 5 days (4)(5).

After this time, we measured the amount of water present in the granules at the end of each experiment (Hf) by drying samples with a Mettler LP16 infrared desiccator (± 0.1 mg).

Calculation of water sorbed:

$$H(t) = 100\ [1\text{-}Po(1\text{-}Ho)/Pt] \quad (1)$$

where, H(t): residual humidity at t (%)
Ho: initial humidity at to (%)
Pt: weight of the sample at t (g)
Po: weight of the sample at to (g)

Calculation of initial humidity:

$$Ho = 1 - Pf\ (100 - Hf)/100Po \quad (2)$$

where, Ho: initial humidity at to (%)
Hf: residual humidity at the end of the experiment (%)
Pf: weight of the sample at the end of the experiment (g)
Po: weight of the sample at to (g)

Thermal analysis

Samples of approximately 25 mg were weighed and put in flatbottom platinum crucibles. Differential thermal analysis (DTA) profiles were drawn in a Differential Thermal Analysis-Thermogravimetric Analysis (DTA-TG) SETARAM 92 apparatus. The differential thermal analysis profiles were obtained by heating the samples from 20 to 250°C with a constant increase of 2 Kmin-1., under an air circulation of 0.5 l/min. Kaolin was used as the thermically inert reference product.

In Vitro Dissolution Studies

Tablets were prepared from the uncoated granules and the coated granules with an alternative tablet press (Model Frogerais OA) equipped with biconcave punches (D7R9). The in vitro release rate was determined with the French Pharmacopeiae Xth rotating paddles method with a dissolution test apparatus (Dissolutest Prolabo).

The operating parameters were as follows:

- Number of tablets = 6
- Nature of the dissolution medium = buffer solution pH1.2 ± 0.5 (artificial gastric juice)
- Volume of the dissolution medium = 1000 ml
- Rotation speed of the paddle = 100 rpm
- Temperature of the dissolution medium = 37 ± 0.5°C

We performed the dissolution tests under the sink conditions and absorbances were measured by a UV spectrophotometer (model CAM-SPEC M330) at the maximum absorption wavelength of 228 nm for josamycin and 240 nm for paracetamol.

RESULTS AND DISCUSSION

Moisture Sorption Studies

Josamycin and its granulated form presented similar profiles of moisture sorption. For paracetamol, we observed that the moisture sorption of the granules was higher than that of the drug alone. The increase in water sorption was probably due to the partial transformation of lactose from crystalline state to amorphous state during the wet granulation process. The moisture was preferentially taken up in the amorphous region (6).

The low hygroscopicity of the granules allowed us to classify the films according to their water vapor permeability.

The aqueous dispersions formed a film for the two drugs, which will be in contact with the water vapor molecules.

The chemical nature of the film and its uniformity around the granule governed the capture of water vapor according to a three step mechanism:

— the adsorption of water molecules on the surface of the film, which is influenced by the state of the surface of the coated granules.
— the diffusion of the molecules through the plastic membrane.
— the desorption on the film-granule interface (7).

Thus, the speed and the intensity of the diffusion of water molecules are governed by the permeability of the film coating.

In our case, the two granules presented low hygroscopicity. Under high humidity, water vapor migrated through the different coatings, whereas the hydrophobic properties of the granules prevented water vapor migration inside. The water remained in the film coatings which led to an increased moisture content of the coated granules (8, 9). So, variations in water sorption of the films may be related to their permeability (Figure 1 & 2).

Water vapor permeability has been shown to be dependent on the relative polarity of the polymer (10). The coefficient of permeability increases with the structural similarity between the polymer and the diffusing molecule (11). So, Sepifilm LP010, cellulosic polymer which contains a certain proportion of hydrophilic substituents (hydroxypropyl groups), would be the most permeable to the water vapor.

Few differences were observed between acrylic resins, whatever the granules. The two polymers had about the same increase in weight.

We also used a glycerol tribehenate in an organic solvent (methylene chloride). For josamycin we observed a significant difference in the amount of water sorbed between the granule coated by Compritol 888 Ato and the uncoated granule. In this case, the coating was performed by dissolving the wax in an organic solvent and the solvent quasi-instantaneously evaporates from the granule surface. This phenomenon prevents the formation of a continuous film, so, the Compritol 888 was certainly deposited in the form of an atomized product distributed on the granule surface and it obstructed the pores responsible for adsorption. This wax, a very hydrophobic compound with long chains of fatty acids (C22), presents lower affinity for water vapor than the film with some hydrophilic groups. Cohesive forces between vapor molecules are stronger than the interactions between Compritol and vapor, leading to a decrease in both adsorption and diffusion of the water molecules (12).

Differential Thermal Analysis Study

DTA profiles were obtained for the different products, and for the coated granules. In most of the cases,

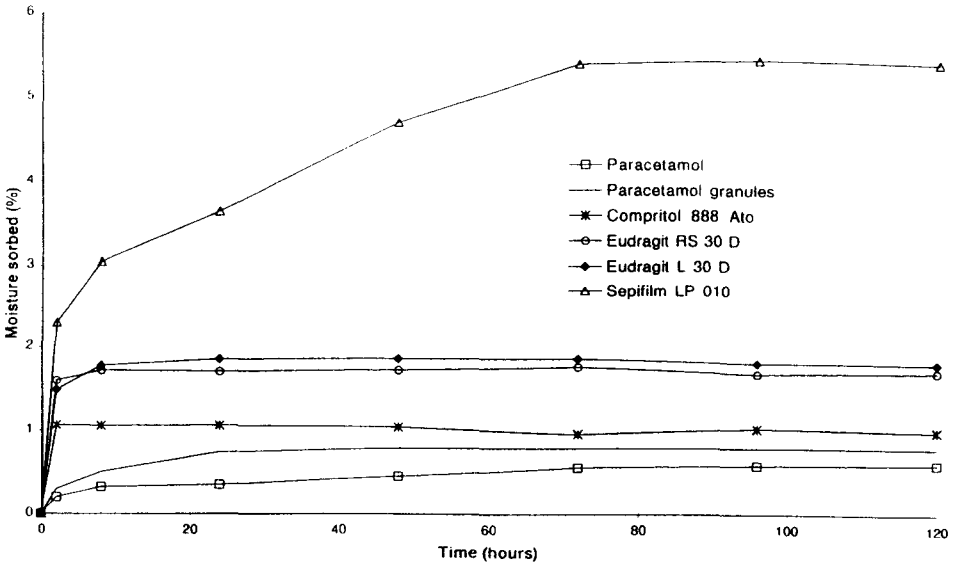


Figure 1. Moisture sorption profiles for different coating films in the case of paracetamol.

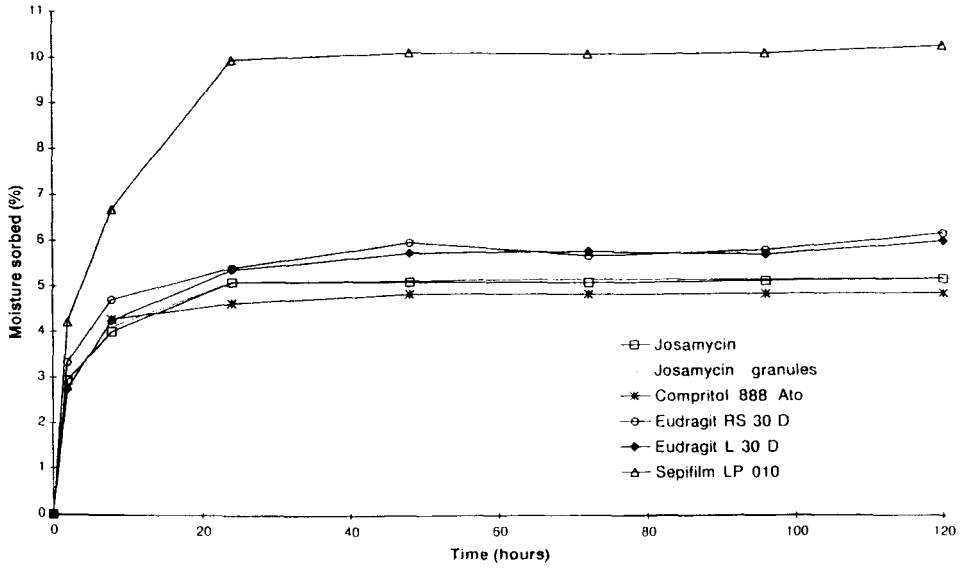


Figure 2. Moisture sorption profiles for different coating films in the case of josamycin.

for the mixture (drug + lactose + coating agents), the DTA peaks specific of each product were superposed. For all coated granules, the composition became: drug 72%, lactose 18%, and coating agent 10%.

The DTA profile of paracetamol (trace b, Figure 3A) showed an endothermic peak at 172°C due to the melting. The DTA profile of lactose (trace a, Figure 3A) showed an endothermic peak at 143°C indicating the elimination of water molecule (theoretical loss in weight: 4,99%; loss in weight measured: 4,87%), and a second peak at 209°C due to the melting. In the case of the granules paracetamol and lactose (trace c, Figure 3A), the endothermic peak due to the melting of paracetamol still exists but the endothermic peak at 209°C due to the melting of lactose disappeared, indicating that probably only lactose crystals became amorphous in the granules.

TGA profiles of lactose (trace b, Figure 3B) showed a decomposition at 214°C but in TGA profiles of granules (trace c, Figure 3B), the decomposition occured before because the presence of paracetamol promoted the decomposition of lactose.

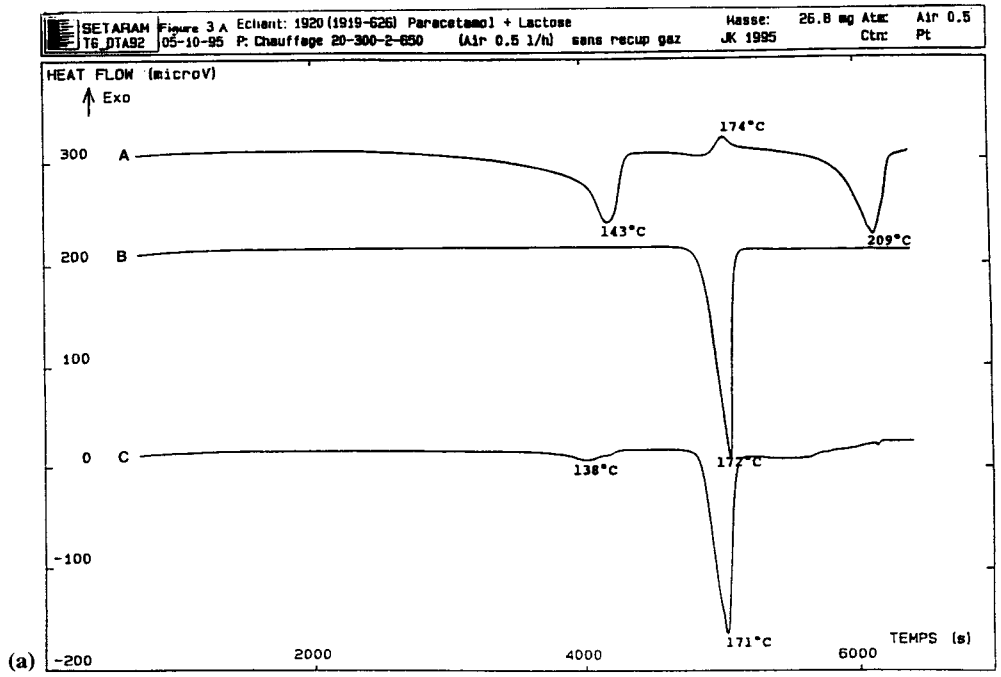
The DTA profile of josamycin (trace a, Figure 4A) showed an endothermic peak at 119°C due to the melting (13). Trace b of Figure 4A is the DTA curve of lactose. For josamycin, we made DTA study of binary and ternary mixtures with a superposition of the DTA peaks specific of each product. It was only in the case of Sepifilm that we observed an oxydation peak at 197°C (trace d, Figure 4A). Trace c of Figure 4A is the DTA profile of Sepifilm LP 010 which showed an endothermic peak at 57°C. This endothermic peak disappeared in trace d because of the departure of volatile compounds during the drying in fluidized bed. Loss in weight of 4% was measured by TGA study (trace c, Figure 4B) and after drying of Sepifilm LP 010 in a Mettler LP16 infrared desiccator.

Influence of Film Coating on in vitro Release (2H)

To investigate the influence of the coating agents on the release of the two active substances, we conducted dissolution tests on tablets. Dissolution controls of paracetamol (Figure 5) and josamycin (Figure 6) tablets obtained from coated granules showed that the release profiles were modified according to the nature of the coating agents.

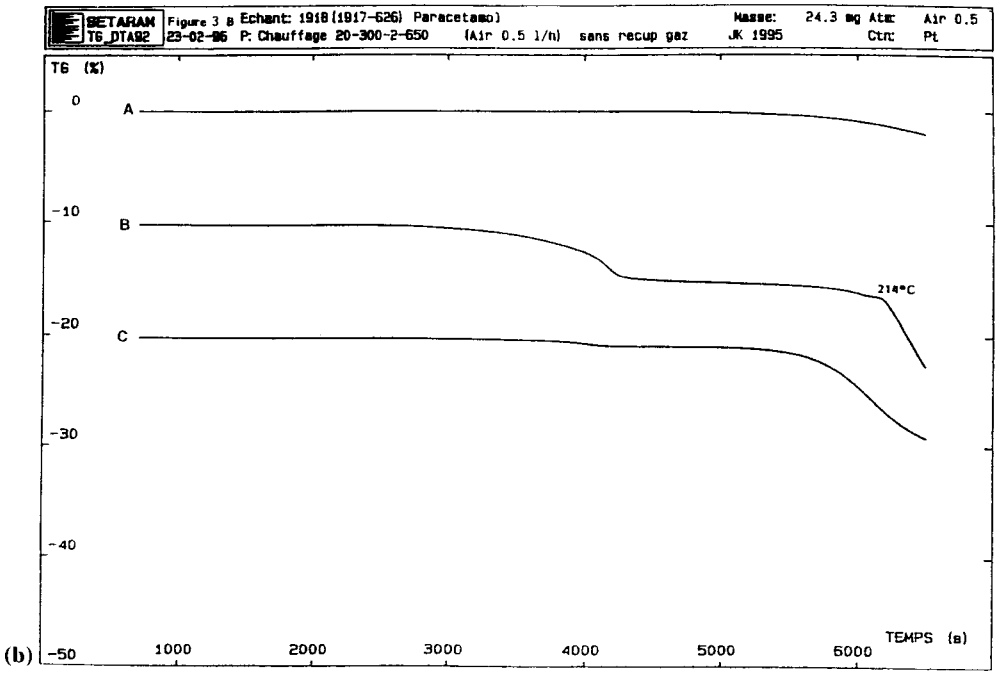
It should be noted that the behavior of the galenic forms during the dissolution test were different except in the case of the tablets made from

Sepifilm coated granules, there was few differences with uncoated-tablet profiles. This increase in release rate was due to formation of swollen hydrated channels



(a)

Figure 3a. DTA profiles of paracetamol (trace b), lactose (trace a), and paracetamol-lactose granules (trace c).



(b)

Figure 3b. TGA profiles of paracetamol (a), lactose (trace b) and paracetamol-lactose granules (trace c).

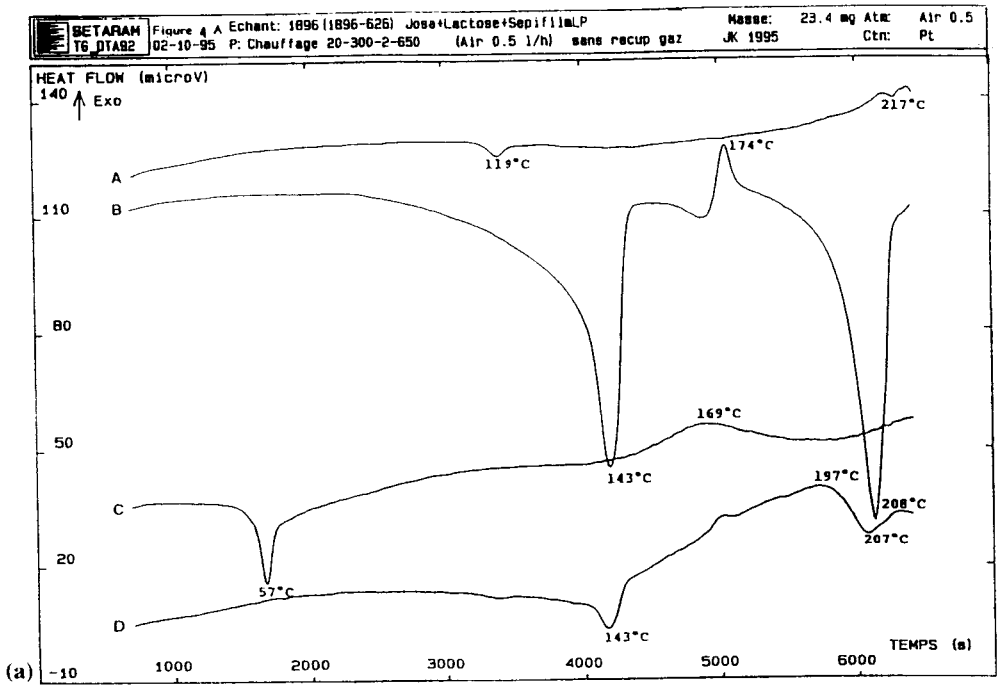


Figure 4a. DTA profiles of josamycin (trace a), lactose (trace b), Sepifilm LP (trace c) and josamycin - lactose - Sepifilm coated granules (trace d).

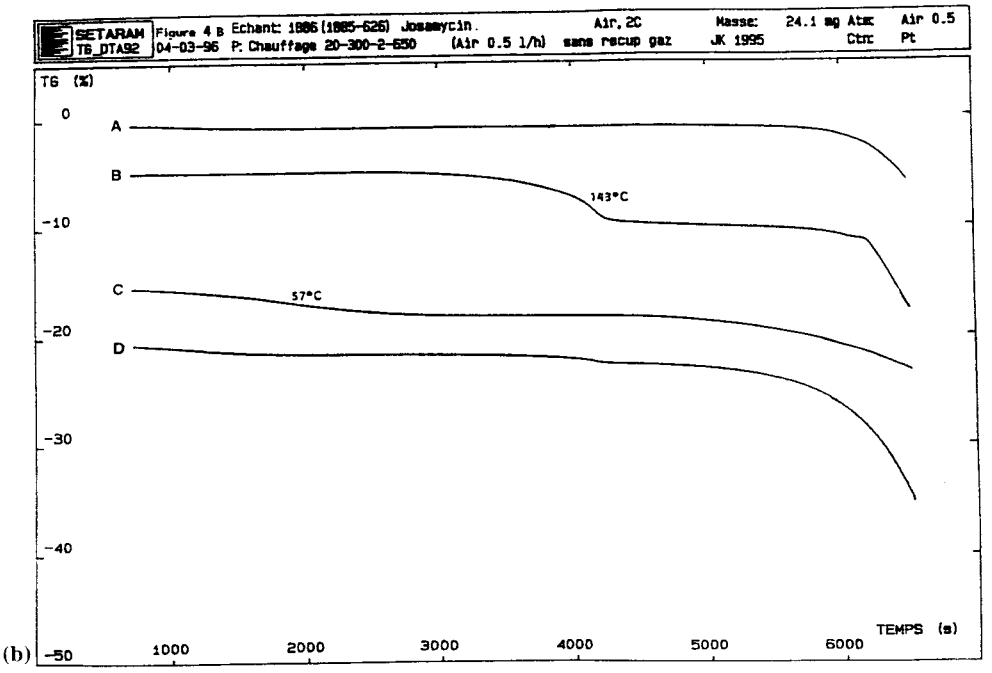


Figure 4b. TGA profiles of josamycin (trace a), lactose (trace b), Sepifilm LP (trace c) and josamycin - lactose - Sepifilm coated granules (trace d).

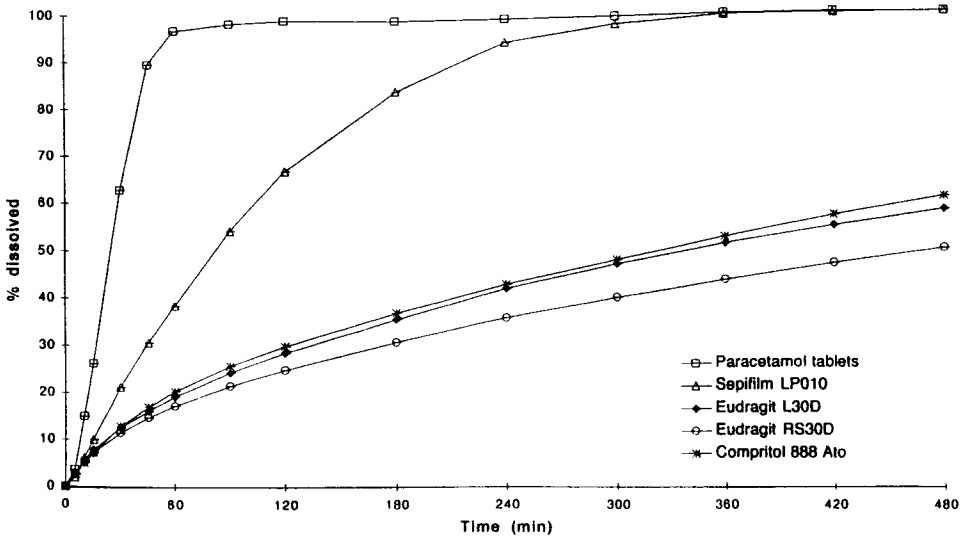


Figure 5. Influence of the coating agents on the release of paracetamol tablets.

by hydroxypropylmethylcellulose through which the dissolution fluid can penetrate into the matrix, dissolve the drug, and diffuse out (14). In the case of acrylic and glyceridic derviatives, the release of the drugs was sustained according to the chemical nature of the different agents.

Profiles showed different dissolution rate for josamycin and paracetamol which was due to the faster solubilization of josamycin tablets in our experimental conditions as evidenced by the dissolution curves of control tablets.

Kinetic Release Models (15,16,17)

To investigate the mechanism of release, each set of dissolution data was fitted to four different kinetic mod-

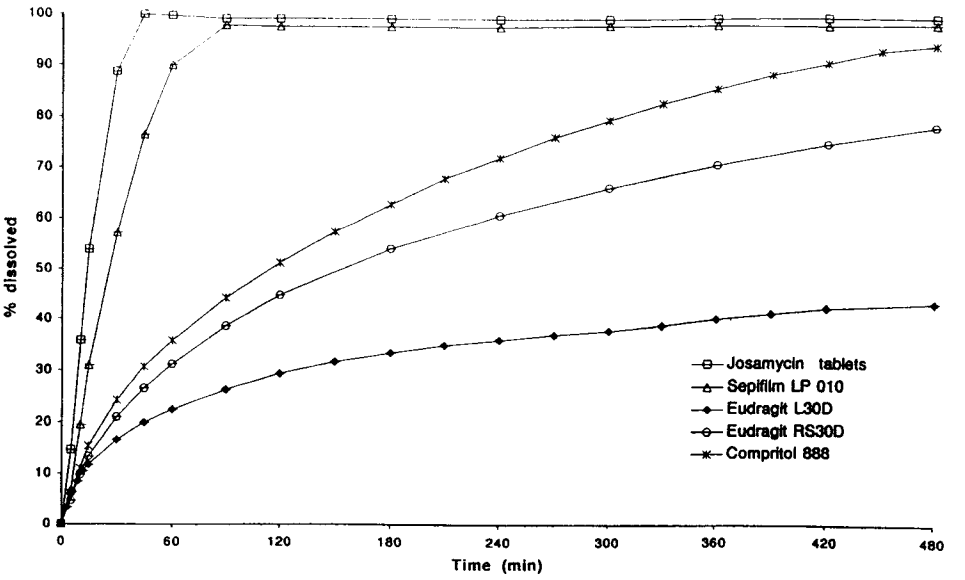


Figure 6. Influence of the coating agents on the release of josamycin tablets.

els proposed for the relationship between the percentage of drug undissolved (W) and time (t) under various assumptions.

1) $100 - W = K1.t$: the zero order model to study the release from hydrophilic matrix.
2) $100 - W = K2.\sqrt{t}$: the model developed by HIGUCHI for drug release controlled by the diffusion of the drug through the pores of the matrix.
3) $\ln W/Wo = K3.t$: an exponential model developed by WAGNER for erodible matrix.
4) $3\sqrt{100} - 3\sqrt{W} = K4.t$: the model developed by HIXSON and CROWELL in which the release rate is controlled by the dissolution rate of the drug particles.

The results obtained are listed in Tables 3 and 4 and the tablets behaved in accordance with 2 models.

In our study, the release of the active substances through the tablets was best fitted to Hixson-Crowell model for Sepifilm LP010 but the tablets prepared from Eudragit and Compritol 888 Ato coated granules followed Higuchi porous penetration model as the dissolution data fitted well to the square-root equation.

Kinetics values obtained from the experimental data which were best fitted to the models are given in Table 5:

CONCLUSION

This comparative study of film coating for the two active substances of different solubility revealed variable

Table 3

R^2 and F Values for Paracetamol Obtained from a Stepwise Multiple Linear Regression Program

		Sepifilm LP010	Compritol 888	Eudragit L30D	Eudragit RS30D
Zero-Order	F	56.8	75.7	72.6	62.7
	R^2	0.826	0.844	0.838	0.818
Higuchi	F	406.6	5563.9	6684.9	10303.7
	R^2	0.978	0.998	0.998	0.999
Wagner	F	707.1	713.5	629.3	446.9
	R^2	0.988	0.982	0.98	0.972
Hixson-Crowell	F	3231.2	425.1	396.4	321.6
	R^2	0.997	0.97	0.968	0.961

R^2 = determination coefficients.
F = snedecor factor.

Table 4

R^2 and F Values for Josamycin Obtained from a Stepwise Multiple Linear Regression Program

		Sepifilm LP010	Compritol 888	Eudragit L30D	Eudragit RS30D
Zero-Order	F	47.6	79.5	19	34.9
	R^2	0.872	0.85	0.475	0.713
Higuchi	F	190.4	9392.7	540.1	1355.6
	R^2	0.974	0.999	0.988	0.993
Wagner	F	349.1	1408.1	179.8	1125.4
	R^2	0.986	0.994	0.928	0.992
Hixson-Crowell	F	897.7	2009	193.3	571.8
	R^2	0.994	0.997	0.942	0.988

Table 5

Models and Kinetics Values of Dissolution for the Two Drugs

	josamycin	paracetamol
Sepifilm LP010	$3\sqrt{100} - 3\sqrt{W} = 39.2 \times 10\text{-}3 .t$	$3\sqrt{100} - 3\sqrt{W} = 10.9 \times 10\text{-}3 .t$
Compritol 888 ATO	$100 - W = 5.46. \sqrt{t}$	$100 - W = 2.91. \sqrt{t}$
Eudragit L30D	$100 - W = 1.41 . \sqrt{t}$	$100 - W = 2.79 . \sqrt{t}$
Eudragit RS30D	$100 - W = 3.47 . \sqrt{t}$	$100 - W = 2.36 . \sqrt{t}$

efficacies in protection against moisture. Efficacies varied with the permeability of the protective agents and their mode of deposition (coating in organic or aqueous solvents).

In our study, the derivative of glycerides applied with an organic phase presented a better efficacy against humidity than the polymers applied with aqueous solvents. This is essentially due to the hydrophobicity of this wax which presents lower affinity for water vapor.

The thermal analysis study showed no physicochemical interactions between drugs, excipients, and the coating agents except for granules of josamycin coated by Sepifilm LP 010 which presented an oxydation peak.

The dissolution profiles of tablets from acrylic and glyceridic coated granules showed that the release of the drugs was sustained and the dissolution curves were best fitted by the HIGUCHI model. Therefore, the main mechanism responsible for drugs release appears to be diffusion through the pores of the acrylic and fatty matrix.

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