DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(16), 2021-2041 (1993)

d-INDOBUFEN EXTENDED-RELEASE PELLETS PREPARED BY COATING WITH AQUEOUS POLYMER DISPERSIONS

R.Bianchini*, G.Bruni**, A.Gazzaniga*** and C.Vecchio*

* Farmitalia Carlo Erba,R.& D.Pharmaceutical Development, Milan, Italy.

** University of Pavia, Chemical Pharmaceutical Dpt., Pavia, Italy.

*** University of Milan, Chemical Pharmaceutical Institute,Italy.

SUMMARY

A multiple units dosage form has been prepared in order to control the release of d-Indobufen, a carboxylic acid used as an inhibitor of platelet aggregation.

The system consists of cores containing the active substance coated with a diffusive film and represents a classic "reservoir" system.

Correspondence to: VECCHIO Carlo, Farmitalia Carlo Erba srl, R & D Pharmaceutical Development Dept., Via Giovanni XXIII,23, 20014 Nerviano (MI), Italy.

Extrusion-spheronization was used in order to prepare the active cores. The drug release control was obtained by modifying both the core composition and the film composition characteristics.
Acid and basic compounds were incorporated in the core to influence the inside microenvironment pH.
Polymers chosen for the film formulation were: ethylcellulose (Aquacoat) and copolymers of acrylic esters with differing permeability characteristics (Eudragit RL/RS 30D).
Technological and physical characteristics of coated pellets proved the production feasibility of an extended release multiple unit dosage form of d-Indobufen.
Preliminary data of accelerated stability indicated the important role played by the thermal treatment of polymer membrane after the coating process.

INTRODUCTION

Microencapsulation is a technological process widely employed over the last few years for the production of modified release dosage forms, when small particles such as crystals, granules or pellets in the size range of 1-2000 µm, are encapsulated in a film of polymer material(1).
Microencapsulation of cores having a size higher than 300 µm is done by pan coating or air suspension coating.
Film coating of these cores is generally justified by the necessity to modify drug release rate(delayed, prolonged or pulsing).

Every single dosage form consists of a multiplicity of coated subunits that all together release drug with rates depending on composition and amount of coating applied.

The subunits filled into hard gelatin capsules represent a dosage form that can be defined as a multiple units dosage form.

Thanks to a better pattern of gastric emptying, it ensures both an improved reproducibility of the gastrointestinal transit time and the distribution of subunits over a large surface area minimizing the risk of local damage to the intestinal mucosa(2).

The manufacturing of modified release multiple-units dosage forms is highly complex and it is influenced by at least four parameters: a) the active substance, b) the core properties, c) the coating process and equipment, d) the membrane material and formulation (3).

The film coating process requires an uniform application of the film and a carefully controlled drying of the coating solvent or vehicle.

In order to create suitable conditions for the encapsulation process it is absolutely necessary to use highly specialized equipment (coating pans and fluidized beds) and to optimize process parameters.

The membrane is the release controlling element and constitutes the essential part of the microencapsulated system.

Factors affecting the membrane properties in addition to thickness are the type of polymer used, the additives as plasticizers and pigments, the solvents or vehicles, which have an important effect on the morphological structure of the membrane.

In order to overcome environmental, toxicological and safety problems, aqueous polymer dispersions constituted of acrylic resins and cellulose derivatives have been recently introduced to coat pharmaceutical dosage forms(4-5).

Film formation from polymer aqueous dispersions is more complex than from organic solvent solutions and takes place through contact, penetration and coalescence of particles as water gradually evaporates.

In order to obtain good results an accurate choice of operative temperatures and the use of plasticizers are essential. When operative conditions are optimal, films obtained from latex are virtually without pores.

The aim of the work was the preparation of a multiple units dosage form for extended-release of d-Indobufen, inhibitor of ADP induced platelet aggregation, chosen as a model drug owing to its pharmacokinetic characteristics.

The prolonged release system consists of cores containing the active principle coated with a diffusive polymer film representing a classic reservoir system.

Extrusion-spheronization process was used in order to prepare active cores containing a high drug dosage(6).

The drug release control was obtained modifying both the core composition and the film characteristics.

Acid and basic compound were incorporated in the core to modify the inside microenvironment pH .

The aqueous polymer dispersions, chosen for this film formulation, consisted of ethylcellulose (Aquacoat ECD-30) or copolymers mixture of acrylic esters with different permeability characteristics (Eudragit RS and RL 30D).

In particular the aims of this study were:

- to investigate the controlling release parameters of d-Indobufen from pellets coated with aqueous polymer dispersions, and
- to prolong the "in vitro" release of 150 mg dose up to 24 hours, established on the basis of the preliminary "in vivo" experiments (unpublished data).

MATERIALS AND METHODS

The pellets making up the core of the extended-release form were prepared by extrusion-spheronization technology using d-Indobufen,microcrystalline cellulose and lactose or fumaric acid. Pellet composition and the manufacturing process are described in a previous work(7).

For the film coating of d-Indobufen cores the materials used were:

- copolymers of methacrylic esters (Eudragit RL/RS 30D, Rohm Pharma Germany);
- Ethylcellulose (Aquacoat, FMC, USA);
- Triethyl citrate (Citroflex 2, PFIZER, USA);
- Talc (Talco e Grafite, Milan);
- Polietylenglycol (PEG 6000, HOECHST, Germany).

Coating method

Pellets were coated in air suspension equipment (STREA-Wurster Aeromatic) by applying the polymer coating dispersion under the following process conditions:

pellets load	850 g
air inlet temperature	55 °C

air outlet temperature	30 °C
pumping rate	9 rpm
drying time	60 min
drying temperature	55 °C

The granules were taken out when pellets weight increased by 3, 6, 9 % w/w (up to 12 % w/w for ethylcellulosic coating).

The formulation of polymer dispersions used in the coating process were those suggested by the manufacturers and were:

- for acrylic resins:

Eudragit RL 30D	100 parts
Eudragit RS 30D	100 parts
Talc	50 parts
Triethylcitrate	12 parts
Deionized water	338 parts

- for ethylcellulose:

Aquacoat	265.86 parts
Triethylcitrate	19.14 parts
Deionized water	44.67 parts.

In order to make acrylic coating more permeable, the dispersion formulation was modified by adding 6 parts of PEG 6000 or modifying the ratio between Eudragit RL/RS products from 1:1 to 4:1.

Physical tests of pellets

- Moisture content: the weight loss of pellets were determined by thermobalance (Mettler PC 440 with IR Ray oven) at 100 °C to a constant weight.

- "In vitro" dissolution test: It was carried out according to USP XXII method in 900 mL of phosphate buffer solution at pH 7.5, 37 °C, 200 rpm with Apparatus 2 (Dissolutest, PROLABO).
  The amount of d-Indobufen released was tested by HPLC, using an automatic system (3 MP8 Pump and M 231/401 Autosampler, GILSON).

Pellets filling in capsules

The coated pellets were dosed into size "0", hard gelatin capsules to obtain drug unit dosage of 150 mg, employing a semiautomatic filling machine (Z 150, ZUMA).

Accelerated stability

Capsules packaged in Al/PVC blisters were stored at 45 °C and 35 °C/75 % RH. Drug release in phosphate buffer solution pH 7.5 was tested after 1 month and 3 months.

RESULTS AND DISCUSSION

Acrylic resin coating (Eudragit RL 30D/RS 30D) seems more suitable to reduce d-Indobufen release rate than Aquacoat coatings (Fig.1 and 2).
This is in agreement with what is observed under the electron microscope where the ethylcellulose coating show higher size pores than the acrylic ones (Fig.3 and 4).
The release mechanism from such polymer membranes is not specifically a permeation phenomenon through the

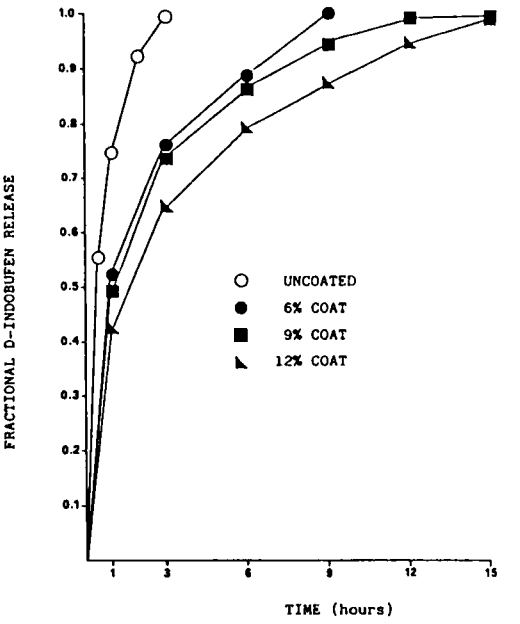

Fig.1 d-Indobufen release rate from pellets coated with aqueous dispersion of Aquacoat ECD 30. Lactose based cores.

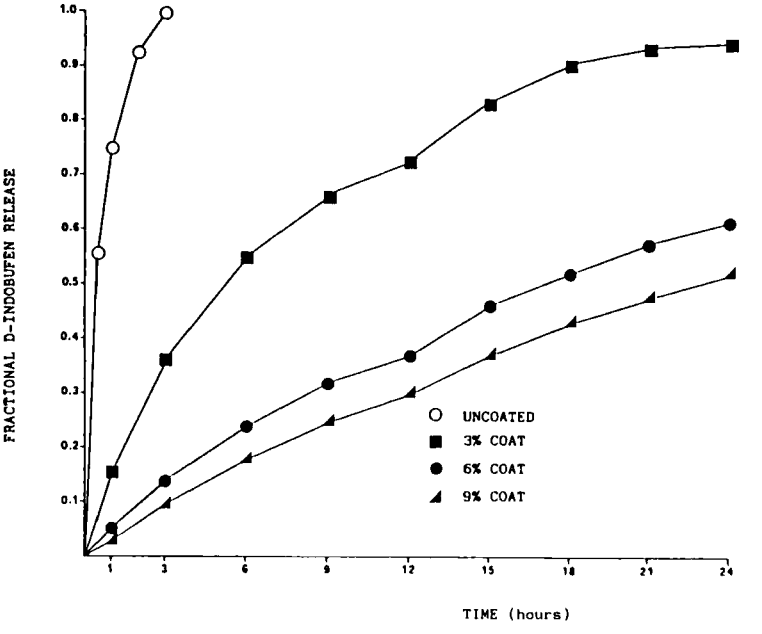

Fig.2 d-Indobufen release rate from pellets coated with aqueous dispersion of Eudragit RL/RS 30D (1:1). Lactose based cores.

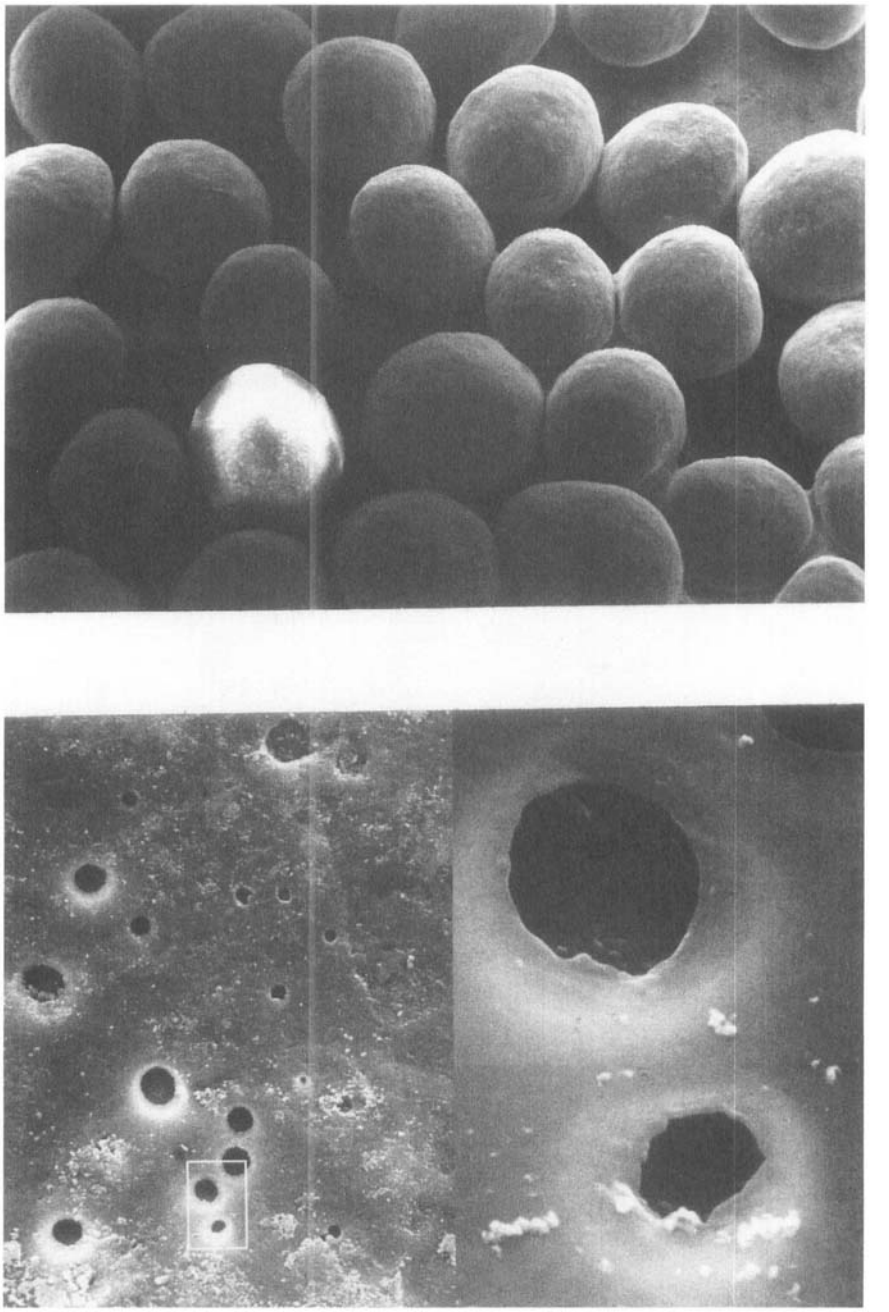

Fig.3 SEM of d-Indobufen pellets coated with ethylcellulose (Aquacoat ECD-30).
Magnification 20x, 1000x, 8000x.

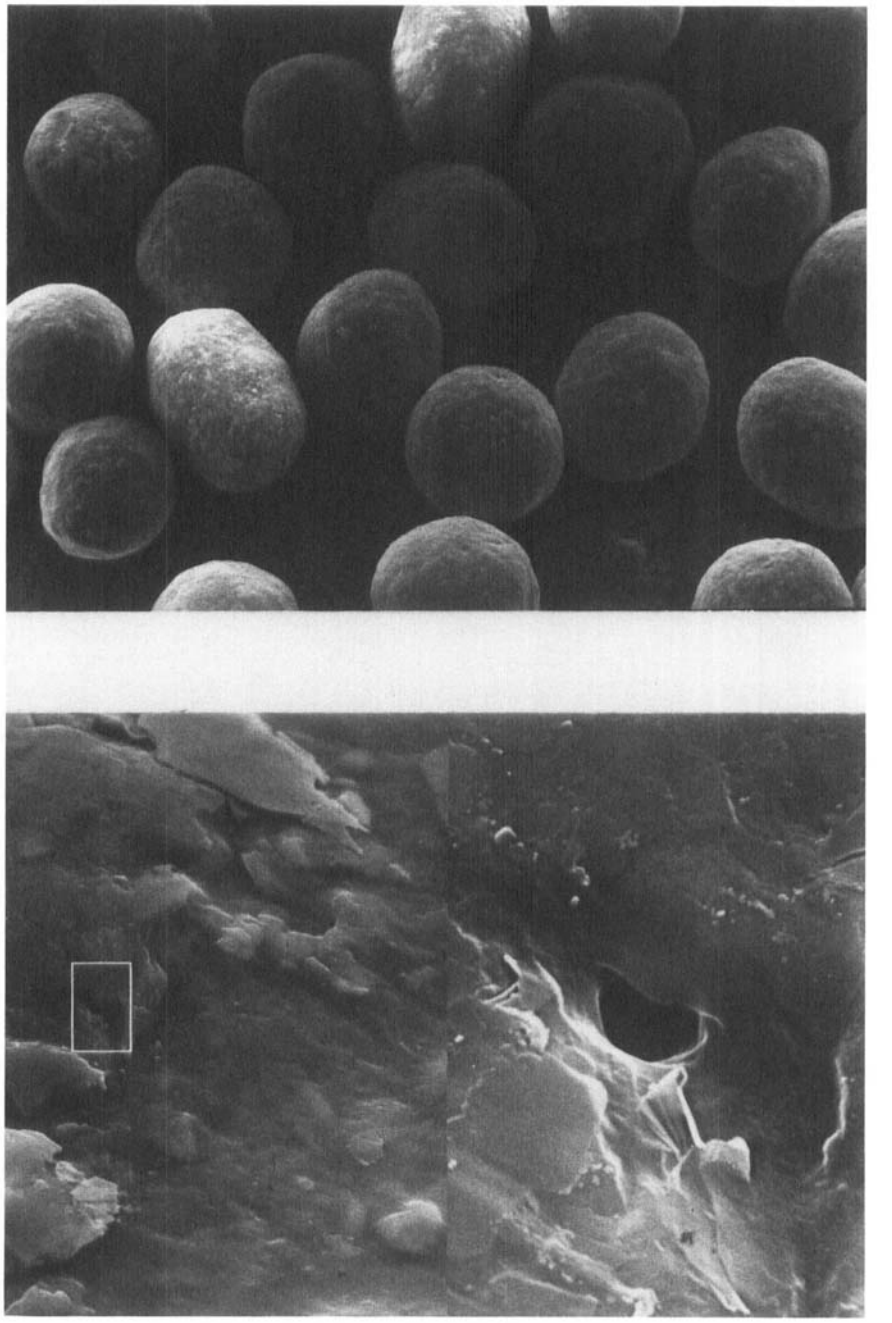

Fig.4 SEM of d-Indobufen pellets coated with acrylic resins (Eudragit RL/RS 30D, 1:1).
Magnification 20x, 1000x, 8000x.

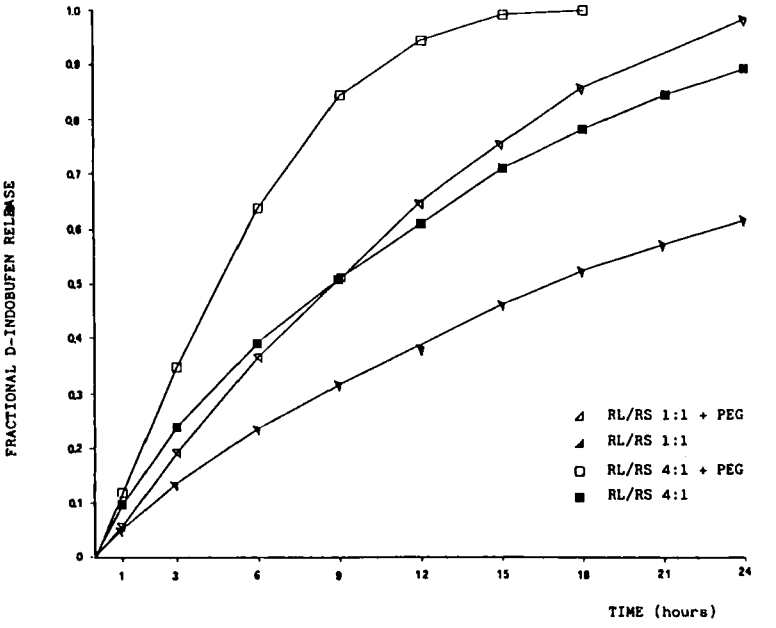

Fig.5 d-Indobufen release rate from pellets coated with aqueous dispersion of Eudragit RL 30D/RS 30D and PEG 6000. Lactose based cores, 6 % coat.

polymer segments, but it can be associated to a mixed system in which also the flow through pores plays an important role. Pore size therefore influences the total diffusion characteristics.

With regards the presence in acrylic films of a soluble substance (PEG 6000) induces a further pore formation, thus making the release faster (Fig.5).

By increasing the amount of more permeable acrylic resins (Eudragit RL 30D), analogous results in terms of release rate improvement are obtained (Fig. 5).

The substitution of lactose in the cores with tartaric or citric acids causes a clear decrease in drug release rate; on the contrary fumaric acid or sodium citrate do not modify substantially the drug release

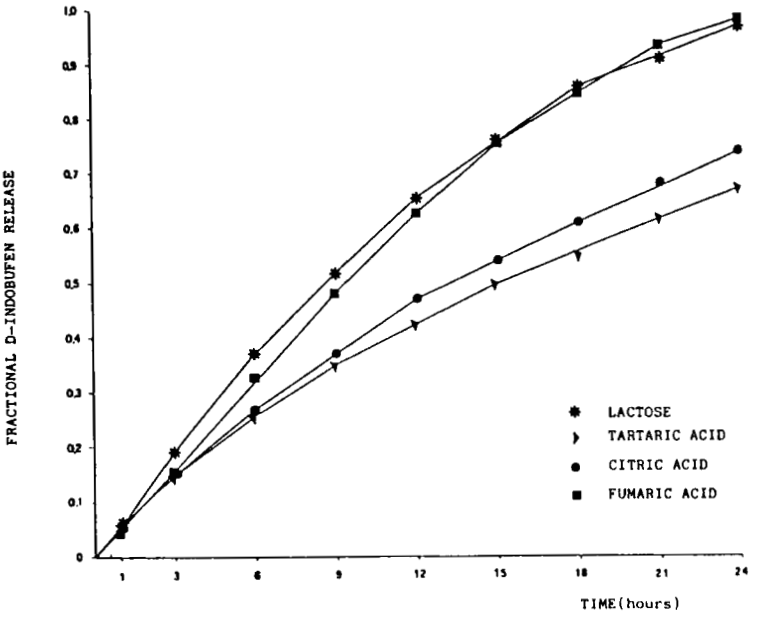

Fig.6 d-Indobufen release rate from pellets coated with aqueous dispersion of Eudragit RL 30D/RS 30D (1:1) and PEG 6000. 6 % coat.

profiles at least at pH of the examined dissolution medium (Fig. 6 and 7).

As mentioned above the ethylcellulose coating is not so effective in the prolongation of the release. The micro- environment created inside the cores by fumaric acid or sodium citrate, does not cause evident changes other than a short lag time for acid system cores (Fig.8).

Release kinetics were analyzed applying the following semiempiric equation $M_t/M_\infty = Kt^n$, where M_t/M_∞ is the release fraction as a function of time t. K and n are constants that describe structural and geometric characteristics of the system; by means of n values it is possible to follow the gradual change of release

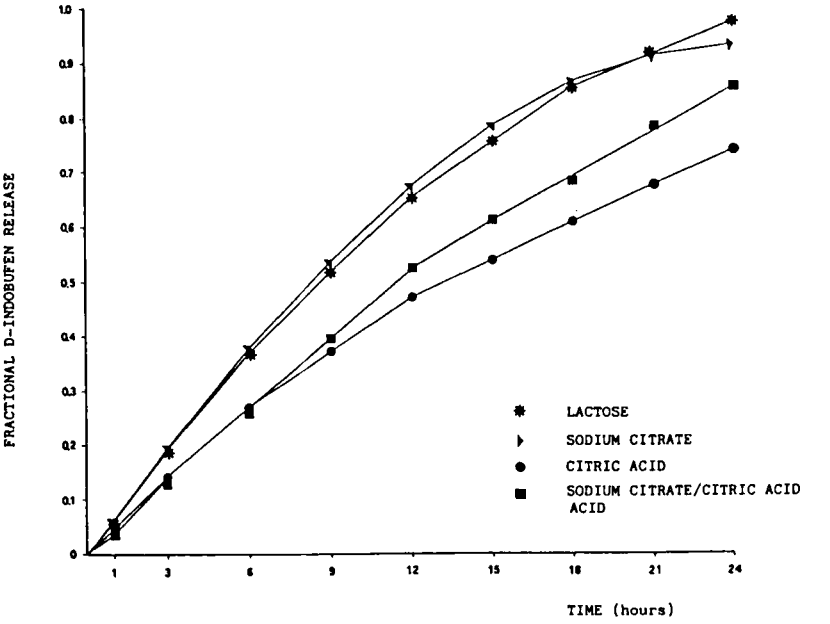

Fig.7 d-Indobufen release rate from pellets coated with aqueous dispersion of Eudragit RL 30D/RS 30D (1:1) and PEG 6000. 6 % coat.

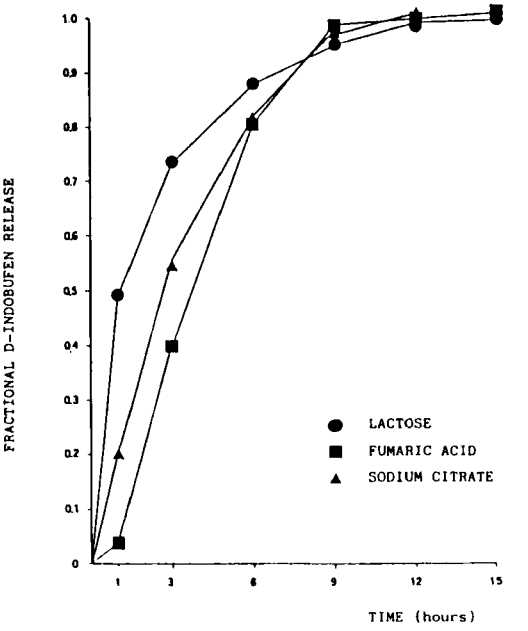

Fig.8 d-Indobufen release rate from pellets coated with aqueous dispersion of Aquacoat ECD-30. 9 % coat.

Table I Parameters obtained from regression analysis from the release rate of d-Indobufen pellets containing d-Indobufen, Avicel, Lactose.

Acrylic resins ratio	Soluble substance addition	%	K	n	r^2	F
Eudragit RL/RS (1/1)	-	3	18.044	0.554	0.973	248.1
		6	5.475	0.782	0.996	506.9
		9	3.451	0.875	0.996	999.9
Eudragit RL/RS (1/1)	PEG 6000	3	18.501	0.585	0.952	138.2
		6	7.208	0.851	0.992	722.4
		9	4.712	0.941	0.998	999.9
Eudragit RL/RS (4/1)	-	3	25.307	0.462	0.994	999.9
		6	10.052	0.683	0.997	999.9
		9	6.597	0.769	0.968	148.9
Eudragit RL/RS (4/1)	PEG 6000	3	31.889	0.462	0.884	38.3
		6	14.031	0.751	0.964	132.9
		9	8.932	0.884	0.991	525.1

where: r^2 is multiple correlation coefficient squared (fraction of total variation) and F is the value used to judge the "significance" of the value r^2.

kinetics toward zero order (n=1). As is well known for this kind of system, the equation does not give information about the transport mechanism, but it is useful only from a descriptive point of view.

For systems coated with Eudragit mixture dispersions (Tab. I, II, III), n assumes values close to 1 (zero order kinetics); this condition occurred for highest levels of coating (6 and 9 % w/w) which guarantees a continuous and uniform application of film over the whole pellet surface (Fig.9 and 10).

However the constant drug release for the desired time (24 hours) was obtained only with pellets containing fumaric acid and coated with 6 % acrylic film (Eudragit RL/RS, ratio 1:1, PEG six parts).

Table II Parameters obtained from regration analysis from the release rate of d-Indobufen pellets containing pH adjusters. Coats consisted of Eudragit RL30D/ RS30D (1/1) with PEG 6000.

pH adjusters	Coat %	K	n	r^2	F
Fumaric acid	3	14.742	0.671	0.952	132.6
	6	4.812	1.003	0.988	559.4
	9	3.031	1.088	0.993	948.2
Tartaric acid	3	12.409	0.632	0.992	870.3
	6	6.311	0.758	0.997	999.9
	9	3.729	0.917	0.998	999.9
Citric acid	3	13.435	0.652	0.973	248.2
	6	5.332	0.854	0.986	506.9
	9	2.826	1.011	0.996	999.9

where: r^2 is multiple correlation coefficient squared (fraction of total variation) and F is the value used to judge the "significance" of the value r^2.

Table III Parameters obtained from regration analysis from the release rate of d-Indobufen pellets containing pH adjusters. Coats consisted of Eudragit RL30D/RS30D (1/1) with PEG 6000.

pH adjusters	Coat %	K	n	r^2	F
Citric acid and sodium citrate	3	11.053	0.745	0.975	272.8
	6	4.052	0.993	0.994	999.9
	9	2.947	1.021	0.995	948.2
Sodium citrate	3	15.218	0.715	0.968	148.9
	6	7.292	0.859	0.985	470.1
	9	5.131	0.921	0.995	999.9

where: r^2 is multiple correlation coefficient squared (fraction of total variation) and F is the value used to judge the "significance" of the value r^2.

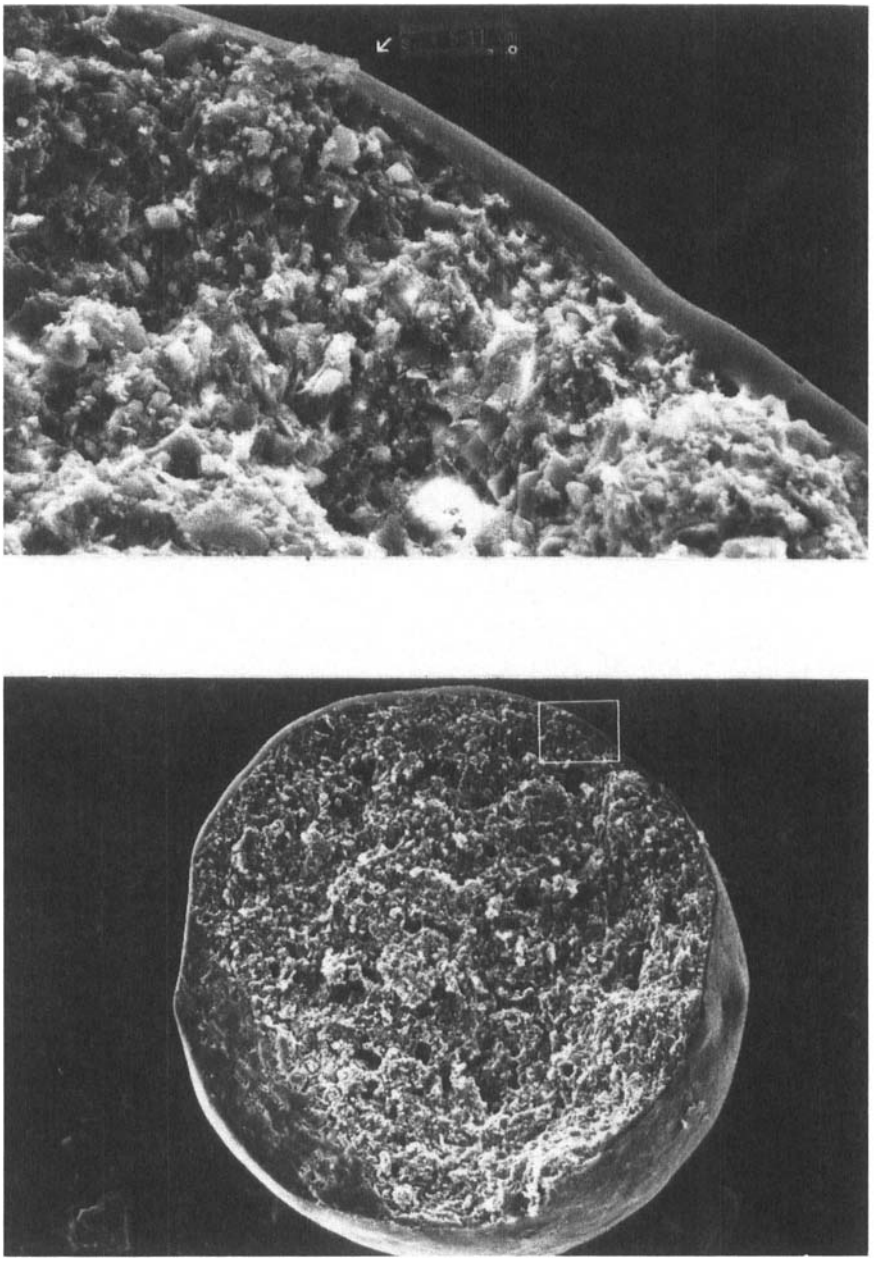

Fig.9 SEM of d-Indobufen pellets coated with ethylcellulose membrane(Aquacoat ECD-30). Cross-section magnification 8x and 500x.

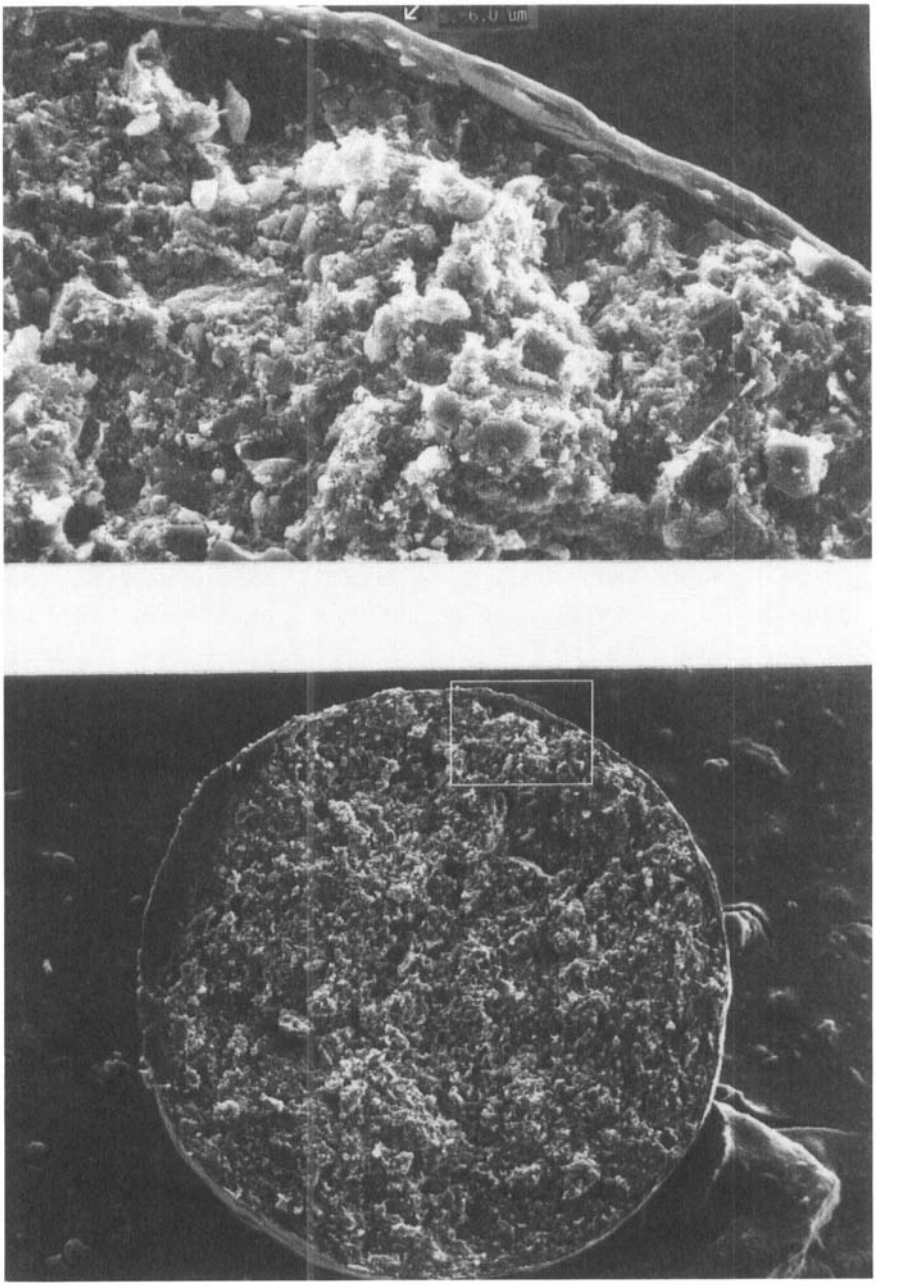

Fig.10 SEM of d-Indobufen pellets coated with acrylic resin membrane (Eudragit RL/RS 30D, 1:1). Cross-section magnification 8x and 500x

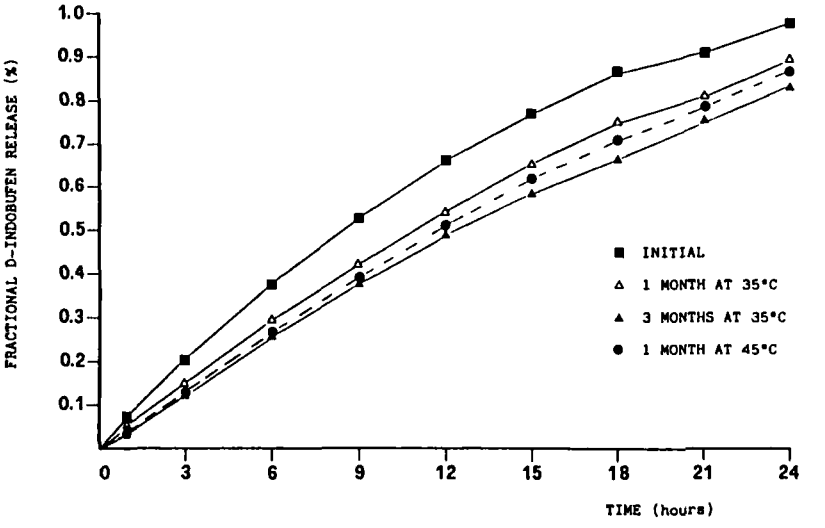

Fig.11 d-Indobufen release rate from 6% coated pellets after 1 month and 3 months storage at 35°C /75% R.U., and 1 month at 45°C in comparison to initial drug release rate. Eudragit RL/RS,1:1 ratio, with PEG. Lactose based cores.

Stability of pharmaceutical form

Preliminary results of accelerated stability on pellets coated with acrylic resins show a modification of overall release patterns.

In particular the tested systems of different formulation present a progressive decrease of drug release rate, as a function of both storage time and temperature (Fig.11, 12 and 13).

The final curing, i.e.the thermal treatment of the coated pellets at 55 °C for 60 minutes, seems not to be sufficient to optimize the progressive coalescence of 1:1 ratio of acrylic resin formulations as well as for the 4:1 ratio formulation,which present a more pronounced release rate decrease.

On the basis of these results it will be essential during the phase of development to investigate the

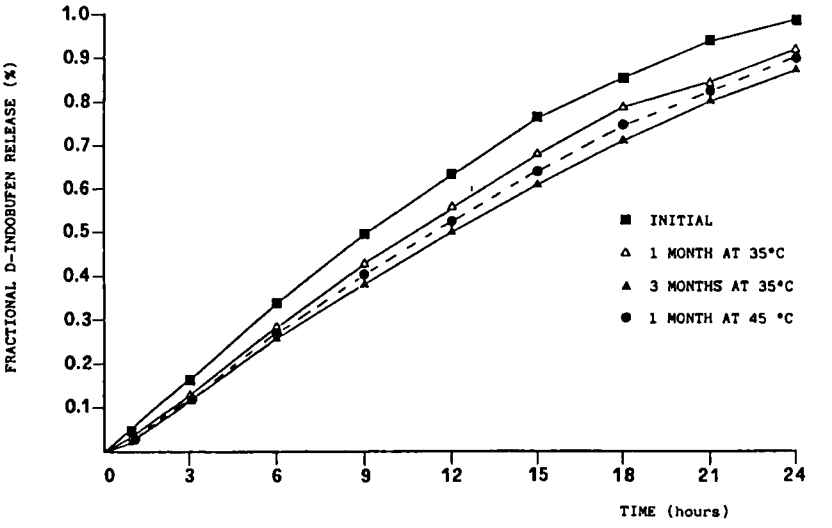

Fig.12 d-Indobufen release rate from 6% coated pellets after 1 month and 3 months storage at 35°C /75% R.U., and 1 month at 45°C in comparison to initial drug release rate. Eudragit RL/RS,1:1 ratio, with PEG. Fumaric acid based cores.

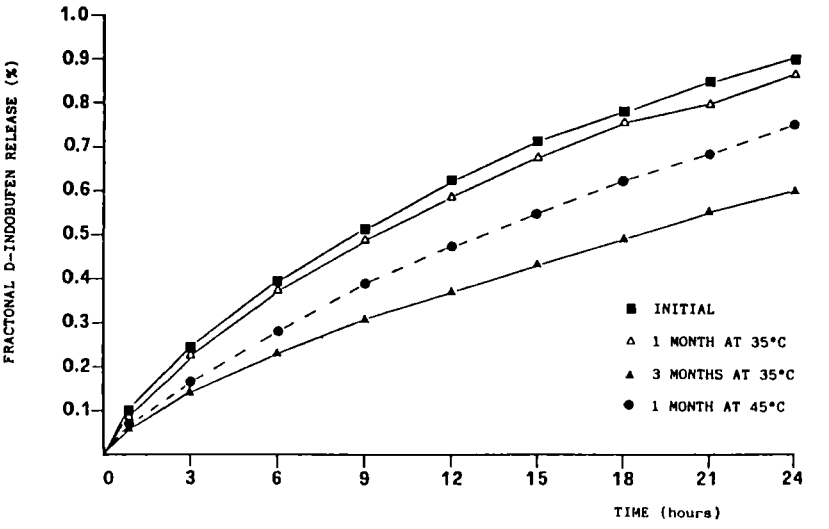

Fig.13 d-Indobufen release rate from 6% coated pellets after 1 month and 3 months storage at 35°C /75% R.U., and 1 month at 45°C in comparison to initial drug release rate. Eudragit RL/RS,4:1 ratio. Lactose based cores.

effect of time/temperature parameters on the stabilization of the polymer membrane.

CONCLUSIONS

This study has proved the applicability of fluidized bed coating technology to the production of multiple units dosage forms for d-Indobufen extended-release.
A modification of the microenvironment inside the cores can lead to suitable control of drug diffusion,thus better defining the release kinetics, which remains however largely dependent on the membrane characteristics .
However a further investigation should be carried out to study the effect of the pH adjusters on drug release by analyzing the dissolution test at different conditions of pH.
Film composition and thickness are reconfirmed as parameters that greatly influence drug release profile.
Preliminary data of accelerated stability seem to indicate that the coated pharmaceutical forms should undergo further thermal treatment after coating to obtain a better membrane stabilization .

ACKNOWLEDGEMENTS

The authors appreciate the collaboration of A. Capoccia, R.DePonti, G. Cristina, F. Fabiani and G.C. Rossi.

Thanks are also due to R. Braglia of Donegani Institute for SEM analysis.

REFERENCES

1) P.B. Deasy "Microencapsulation and related drug process", Drug and Pharm. Sc. (1984)

2) E. Hunter, J.T. Fell e H. Sharma, Drug Ind. Pharm. 8 (5) 751-757, (1982)

3) R. Bianchini e C. Vecchio, Il Farmaco, 44 (6), 645-654, (1989)

4) S.I. Hsich, Controlled Release Systems, Fabrication Technology, Vol. I, chapt II, pg 17, C.R.C. Press, (1988)

5) J.W. Mc Ginity, Aqueous polymer Coating for Pharmaceutical Dosage Forms, Vol. 36

6) I. Ghebre-Sellassie, Pharmaceutical Pellettization Technology, Vol. 37, M. Dekker, N.Y. (1982)

7) R. Bianchini, G. Bruni, A. Gazzaniga, C. Vecchio, Drug Dev.Ind.Pharm. 18(14) 1485-1503 (1992)