DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(8), 1323-1339 (1994)

EVALUATION OF HOT-MELT EXTRUSION AS A NEW TECHNIQUE FOR THE PRODUCTION OF POLYMER-BASED PELLETS FOR SUSTAINED RELEASE CAPSULES CONTAINING HIGH LOADINGS OF FREELY SOLUBLE DRUGS

Nicolas Follonier [1], Eric Doelker [1] and Ewart T. Cole [2]

[1] Laboratoire de Pharmacie galénique, Université de Genève, CH-1211 Genève 4, Switzerland.

[2] Capsugel Division, Warner-Lambert Company, CH-4144 Arlesheim, Switzerland.

ABSTRACT

Hot-melt screw extrusion was presented as an alternative method for producing polymer-based sustained release pellets. Special care was paid to the case of highly dosed freely soluble drugs which often pose technological problems with the usual manufacturing processes. In a preformulation study, polymers, plasticizers and drugs were selected according to various criteria including thermal stability. During these preliminary tests, the optimum extrusion conditions were defined. Four polymers were considered for extrusion trials, namely ethylcellulose, cellulose acetate butyrate, poly(ethylene-co-vinyl acetate) and a polymethacrylate derivative (Eudragit® RSPM). Pellets were produced with diltiazem hydrochloride as model drug. The surface appearance of various formulations was examined and the porosity assessed by means of mercury porosimetry. A distinct structure was found for the EVAC-based pellets. The overall porosity was less than 10 %. Lastly, *in vitro* release of the drug showed a biphasic profile with a slow diffusion-controlled phase following a much faster release. The release rate of diltiazem hydrochloride from EVAC-based hot-melt extruded pellets of size 2 x 2 mm was very low. It is the opinion of the authors that this type of dosage form offers many potentialities because of its ease of

processing and the wide possibility of modulating the release through the addition of hydrophilic excipients.

INTRODUCTION

The recent growth in the development of multiple-unit sustained release dosage forms is claimed by their proponents to stem from various advantages they could offer over non-divided forms, among which more predictable gastric emptying, less dependence on the state of nutrition, high degree of dispersion in the digestive tract, less risk of dose dumping and less inter- and intra-subject variability. A literature survey demonstrated that differences in the behavior of divided and non-divided dosage forms are not that obvious [1]. Nevertheless, the easier control of the drug release profile and the possibility of subdividing the dose are enough to explain the popularity of spheroids.

The most widely used pelletization processes in the pharmaceutical industry are solution/suspension layering and powder layering or extrusion/spheronization. Other techniques with limited application include globulation (spray drying and congealing), balling and compression [2,3]. The cores obtained may be used as such when they include a sustained release agent, but they are usually film coated. All these techniques are complex and, as they involve multiple steps, time-consuming.

The goal of the present study is to investigate the possibility of producing sustained-release pellets by hot-melt screw extrusion. This method is simple, continuous and allows the finished product to be obtained in a single stage. Another advantage is the possibility of including a high dose of freely soluble drugs into the pellets without loosing their sustained release properties, which is sometimes difficult to achieve with the other processing methods. However, hot-melt extrusion suffers from several limitations mostly related to mixing and thermal degradation problems.

Hot-melt extrusion has not yet received great attention in the pharmaceutical field. Among the few works reported in the literature, El-Egakey et al. [4] and Bechmann [5] studied both the extrudability of epoxy resins and poly(vinyl acetate-*co*-methacrylic acid) to prepare matrix systems by injection molding. This method was also used by Hüttenrauch and Schmeiss [6] and Snipes [7,8] for polyethylene and polyethyleneglycol based matrices, respectively. Pellets composed of cellulose acetate phthalate were prepared with a rudimentary ram

extruder [9] and more recently, laboratory scale production of matrices based on polyethylene [10] and polycaprolactone [11] was investigated. Other papers report the extrusion of various thermoplastic polymers to obtain sustained release pellets [12,13].

In this work, we first selected polymers suitable for oral administration which were processable at low temperature. A home-made ram extruder designed for very small batches (few grams) was used for preliminary trials. A freely soluble model drug, diltiazem hydrochloride, was then choosen for the extrusion trials with a single screw extruder. Various batches of pellets were produced and characterized.

EXPERIMENTAL

Materials

Diltiazem hydrochloride (DTZ) and desacetyldiltiazem hydrochloride (DAD) were supplied by Gödecke (Berlin, Germany). Other drugs included oxprenolol hydrochloride (Luso Chimica, Milan, Italy) and disopyramide phosphate (Prographarm, Châteauneuf-en-Thymerais, France). The polymers tested were ethylcellulose (EC N-10, Hercules, Wilmington, USA), cellulose acetate butyrate (CAB 381-0.5, Eastman, Zug, Switzerland), hydroxypropylmethylcellulose (Methocel® K4M, Dow, Zürich, Switzerland), poly(vinyl chloride) (Pevikon® PE737P, Seppic, Paris, France), poly(vinyl chloride-*co*-vinyl acetate) (Vinylite® VYHH, Union Carbide, Versoix, Switzerland), poly (ethylene-*co*-vinyl acetate) (Elvax® 40W, Du Pont, Geneva, Switzerland) and a polymethacrylate derivative (Eudragit® RSPM, Röhm Pharma, Darmstadt, Germany). Plasticizers added to lower the extrusion temperature included triacetin (Siegfried, Zofingen, Switzerland) and diethyl phthalate (Fluka, Buchs, Switzerland). Diazepam (Labatec, Geneva, Switzerland) was used as an internal standard in HPLC experiments.

Methods

1. Thermal transitions of the polymers

Since it was necessary to avoid degradation of both the polymers and drugs, we had to take into account the thermal transitions of the polymeric materials.

These values were also indicative of their extrusion temperatures. When possible, glass transition temperatures and melting points were measured using a differential scanning calorimeter (DSC-4, Perkin-Elmer, Küsnacht, Switzerland). Depending on the material, the heating rate varied from 5 to 40 °C/min. The glass transition temperature of semi-cristalline polymers was recorded on a second scan.

2. Stability testing of the polymers

Three types of methods were considered : thermogravimetry, preliminary extrusion tests and high performance liquid chromatography. With the first one, weight loss against temperature profiles were recorded, using a thermobalance (TGS-2, Perkin-Elmer). The weight loss at 200 °C and a possible discoloration of the material were checked. For one particular polymer (ethylene and vinyl acetate copolymer), the percent weight loss corresponding to the loss of acetate groups was used to determine the vinyl acetate content after various treatments, according to :

$$\% \text{ vinyl acetate} = \% \text{ weight loss} \cdot \frac{MW_{CH_2CHCOOCH_3}}{MW_{CH_3COOH}} \quad (Eq.\ 1)$$

Preliminary extrusion trials were undertaken with the home-made laboratory ram extruder shown in *figure 1*. The main features of this apparatus were: 10 mm diameter ram, 10:1 length/diameter ratio, heating device Hot Tronic 1800 (Electrolux, Aarau, Switzerland), pneumatic extruder drive, single rod die with an opening of 2 mm diameter. Polymer/plasticizer blends were prepared in a mortar, after drying the raw materials. Elvax® 40W, which is supplied as pellets, was ground under liquid nitrogen cooling. The mixture was then introduced into the cylinder and the temperature raised. After a period of time necessary for the plasticization of the material (plasticization time), pressure was applied on the ram and the extrusion process initiated. During this step, processability of the various polymers was evaluated.

The polymethacrylate derivative (Eudragit® RSPM), whose degradation occurs only by chain depolymerization, was studied regarding to its thermal stability by determination of the monomer content of the extrudates using the HPLC assay described in the NF XVII monograph. The apparatus was a Waters 600E pump equiped with a μ-Bondapak C-18 column (Waters, Milford, USA). The detector

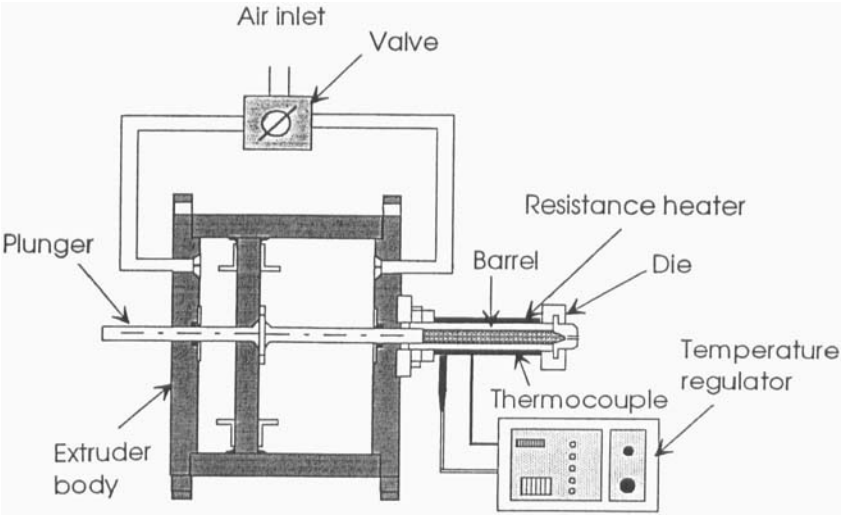

FIGURE 1 *- Scheme of the laboratory ram extruder.*

was a Waters Lambda-Max 481 UV-spectrophotometer set at 202 nm. Data were analyzed with the Maxima 820 software (Waters). The mobile phase was composed of phosphoric acid:methanol 85:15, at a flow rate of 1.7 ml/min.

3. Selection of a model drug

We based this selection on various criteria, among which high water solubility, low pharmacological potency and thus highly dosed, relatively short biological half-life and good thermal stability. The thermal stability of diltiazem hydrochloride was evaluated by heating the drug at 150 °C for 10 minutes, a duration in excess of the residence time of DTZ in the extruder. This sample was further analysed by UV and IR spectrophotometry as well as thin layer chromatography (mobile phase n-propanol:toluene:n-butylamine 80:17:13). The extent of degradation of the drug after extrusion was measured by HPLC, using the apparatus already described. The method applied derived from that proposed by Lacroix et al. [14]. The pellets were ground in a hammer mill (Culatti, Zürich, Switzerland) or in the case of EVAC cut into small pieces. Methanol (100 ml) was added to an accurate weight of about 100 mg and the flask was placed in an ultrasonic bath for 1 h (Sonorex RK 106S, Bandelin, Berlin, D). The clear supernatant liquid was diluted to give a concentration of about 0.05 mg/ml,

diazepam added as internal standard at a concentration of 0.02 mg/ml and the solution injected into the system. Different standard solutions were also injected for the calibration of both DTZ and DAD. This last compound was determined over the range 0.5 to 10 % with respect to DTZ. The mobile phase consisted of pH 6.2 acetate buffer:methanol:acetonitrile 48:22:30 at a flow rate of 2.2 ml/min, the column used was a μ-Bondapak C-18 (Waters) and the UV detector was set at 240 nm.

4. Extrusion trials

The powders were dried, blended and extruded through a Betol Jockey single screw extruder (Betol, Luton, U.K.) equiped with a 18 mm diameter screw having a 20:1 length/diameter ratio. The fitted die was a 2 mm single rod type. The extrudates were cut with a laboratory blade pelletizer (Betol) (except EVAC which was operated manually because of its toughness) to obtain pellets of size 2 x 2 mm. The extrusion conditions (temperature and screw speed) were optimized for each blend.

5. Characterization of the pellets

The pellets were assayed for DTZ by HPLC, with the apparatus described in point 3, under the conditions defined in the USP XXII monograph.

Surface and cross sections of the pellets were examined on scanning electron micrographs (JSM 6400, JEOL, Japan).

Porosity measurements were performed by mercury porosimetry (Carlo Erba macropore unit 120 and porosimeter 2000, Carlo Erba, Milan, Italy). Samples were outgazed 30 minutes before testing. The dilatometer volume was 17.2 cm^3. Pore size distributions were calculated with a surface tension of 480 mN/m and a contact angle of 141° for mercury.

6. *In vitro* drug release

Dissolution studies were performed using a Sotax AT6 apparatus (Sotax, Basel, Switzerland) with baskets rotating at 100 rpm. The medium was 1000 ml of pH 7.0 phosphate buffer at 37 °C. Samples were assayed for DTZ by means of UV spectrophotometry between 230 and 250 nm using an automated dissolution system (Hewlett-Packard, Waldbronn, Germany), comprising a diode array spectrophotometer (HP 8452A) and a dissolution software.

TABLE 1 - Thermal transition of the polymers.

Polymer	ISO Symbol	Trade name	T_g (°C)	T_m (°C)	Heating rate (°C)
Ethylcellulose	EC	EC-N10	130	-	40
Cellulose acetate butyrate	CAB	CAB 381-0.5	125	157	5
Hydroxypropyl methylcellulose	HPMC	Methocel K4M	184	-	-
Poly(vinyl chloride)	PVC	Pevikon PE737P	78	-	10
Poly(vinyl chloride-*co*-vinyl acetate)	VC/VAC	Vinylite VYHH	75	-	10
Poly(ethylene-*co*-vinyl acetate)	EVAC	Elvax 40W	-36	45	5
Poly(ethyl acrylate/methyl methacrylate/trimethyl ammonio ethyl methacrylate chloride)	-	Eudragit RSPM	52 *	-	-

☞ * reference [15].

RESULTS AND DISCUSSION

The transition temperatures of the various polymers tested are listed in *table 1*. When no thermal transition was apparent on the scan, literature data have been considered.

The ethylene and vinylacetate copolymer and Eudragit® RSPM are the only polymers that possess glass transition temperatures below 100 °C. The first is even rubbery at ambient temperature.

Thermogravimetric testing revealed that vinylic polymers with chlorinated groups are very heat sensitive; this is also true, but to a lesser degree, for the hydrophilic cellulosic derivative. Other polymers appeared to have satisfactory thermal stability (*table 2*).

The vinyl acetate content of EVAC is fairly constant whatever the treatment (grinding, extrusion, storage). This tends to prove that EVAC is heat stable over the conditions of production of the extruded pellets (*table 3*).

The determination of free monomers in Eudragit® RSPM gave values listed in *table 4*. The amount of ethyl acrylate is greater than the other monomer and

TABLE 2 - *Thermogravimetric analysis of the polymers.*

Polymer (ISO Symbol)	Onset dec. temp.*(°C)	% Weight loss at 200 °C	Discoloration
EC	190	2.1	browning from 205 °C
HPMC	185	3.0	yellowing from 190 °C
CAB	230	-	browning from 230 °C
PVC	210	-	browning from 170 °C
VC/VAC	220	-	browning from 160 °C
EVAC	300	-	yellowing from 300 °C
Eudragit	185	0.7	yellowing from 200 °C

☞ * decomposition temperature.

TABLE 3 - *Vinyl acetate content of Elvax® 40W after various sample treatments obtained from thermogravimetric weight loss curves, using Eq. 1.*

Treatment			% Weight loss	% Vinyl acetate
Grinding	Extrusion	2 year storage		
-	-	-	27.9	39.6
+	-	-	28.4	40.6
+	+	-	27.9	39.9
+	+	+	27.5	39.3

TABLE 4 - *Assay for monomers in Eudragit® RSPM.*

Residual monomers *	% MMA	% EA	% Total
Before extrusion	0.001	0.007	0.008
After extrusion	0.001	0.010	0.011

☞ MMA = methyl methacrylate, EA = ethyl acrylate.

TABLE 5 *- Extrusion parameters of the polymers with the ram extruder.*

Polymer (ISO Symbol)	Plasticizer	%	Initial drying	Extrusion temp. (°C)	Plasticization time (min)
EC	Diethyl phthalate	5	2 h at 80 °C	120	10
CAB	Triacetin	5	2 h at 80 °C	160	5
HPMC	PEG 400	3-10	12 h at 80 °C	140-180	5-15
PVC	Dioctyl phthalate	10	2 h at 80 °C	150	5
VC/VAC	Diethyl phthalate	10	2 h at 80 °C	110-120	5
EVAC	-	-	-	80	10
Eudragit	Triacetin	5	2 h at 80 °C	110	5

confers to the polymer its characteristic odor. Anyway, the levels were much smaller than the limits stated by the NF XVII (0.15 % for each monomer). We also noticed that no significant increase in the monomer content resulted from the processing.

Extrusion trials with the ram extruder were performed under the conditions described in *table 5*. We were not able to obtain satisfactory extrudates with PVC, VC/VAC and HPMC, particularly due to some degradation of these polymers during processing. Therefore, four polymers were finally selected for subsequent trials, namely EC, CAB, EVAC and Eudragit® RSPM.

As model drugs, three substances were first examined: oxprenolol hydrochloride, diltiazem hydrochloride and disopyramide phosphate (*table 6*). Oxprenolol had to be eliminated for two main reasons: it was not sufficiently heat stable (high tendancy to form colored and odorous degradation products) and it posed critical technological problems because of its low melting point. The drug melted during the processing step, which led to a very low viscosity of the extrudate resulting in difficult handling conditions. The two other drugs were similar to each other as far as the extrusion conditions and the release are concerned. We decided to investigate further diltiazem hydrochloride.

TABLE 6 - *Potentially interesting drugs for extruded multiple-unit matrices.*

Drug	Dosage (mg) *Regimen*	T_m (°C)	Solubility (mg/ml)	$t_{1/2}$ (h)
Diltiazem·HCl	90,120,180,300 *1-2 t.i.d*	187-188	600	2.1 (α) 9.8 (β)
Disopyramide·PO_4	150 *1-2 t.i.d*	205 (dec)	300	3-11
Oxprenolol·HCl	80,160 *1-4 t.i.d*	107-109	1000	1-3

TABLE 7 - *Extrusion parameters of the blends tested*

Polymer	Plasticizer	%	Extrusion temperatures (°C)				Screw speed
			1	2	3	Die	(rpm)
EC	Diethyl phthalate	3	140	140	140	150	20
CAB	Triacetin	5	150	150	150	160	30
VC/VAC	Diethyl phthalate	10	100	110	110	115	20
EVAC	-	-	50	70	80	85	10
Eudragit	Triacetin	3	130	130	130	140	30

No significant difference between the reference and the heated sample of DTZ was detected either by spectrophotometry or by TLC. The DAD content of both the raw material and the extruded pellets as determined by HPLC was always less than 0.5 % of the DTZ loading (detection threshold of the method). The other possible degradation compounds mentioned by Lacroix et al. [14] were not determined, but no peak was detectable on the chromatograms.

Various batches of pellets of diltiazem hydrochloride were then produced with the single screw extruder under the extrusion conditions given in *table 7*.

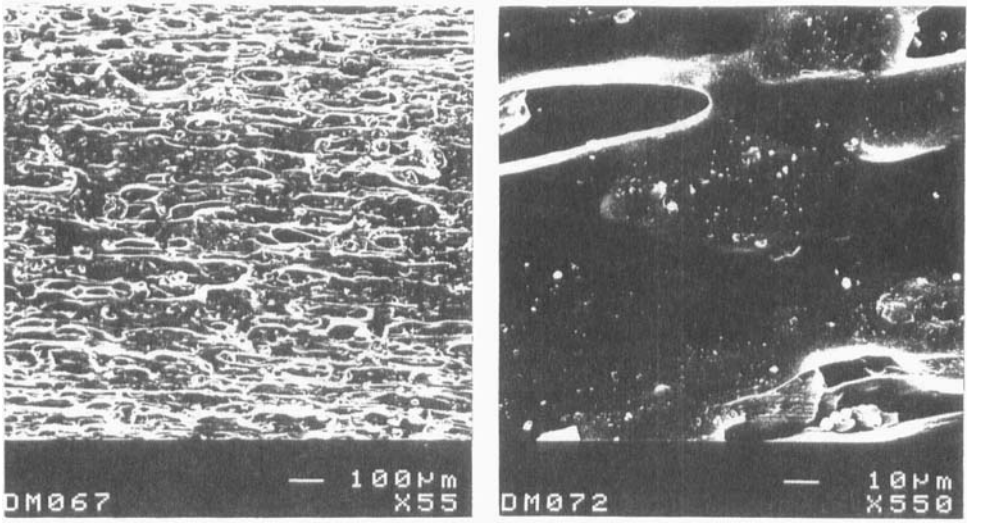

Figure 2 *- SEM micrographs of the external cylindrical surface of Eudragit ® RSPM based pellets, at two magnifications.*

The surface of the pellets observed on SEM micrographs revealed that the drug was very well embedded in the polymer matrix, each particle being enclosed in the molten polymer (*figure 2*).

EVAC based pellets showed a different structure compared to the other formulations. In that particular case, no orientation in the flow direction occured and the packing appeared looser (*figure 3*).

SEM micrographs of pellet slabs before and after release of DTZ pointed out the porosity increase created by the leaching of the drug and the homogeneity of distribution of the drug particles inside the extrudates (*figure 4*).

Pore size distributions of pellets based on Eudragit® RSPM and Elvax® 40W were very different. A bimodal distribution was obtained with Eudragit based pellets (macropores and micropores) (*figure 5a*), whereas the EVAC sample possessed a wide distribution of pore sizes (*figure 5b*). Concerning the absence of any hysteresis in the intrusion-extrusion curves with EVAC pellets in contrast to the other sample, it was expected that the microporosity recorded was an artefact related to the compressibility of this particular material. Mercury porosimetry data indicated that there were larger pores than 1 µm in both cases and that the overall porosity of the pellets was less than 10%.

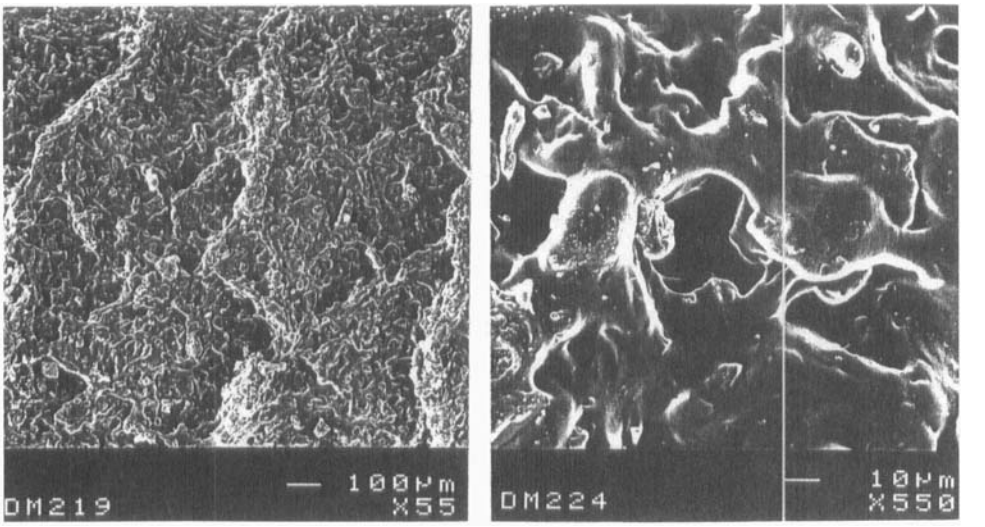

FIGURE 3 - *SEM micrographs of the external cylindrical surface of Elvax ® 40W based pellets, at two magnifications.*

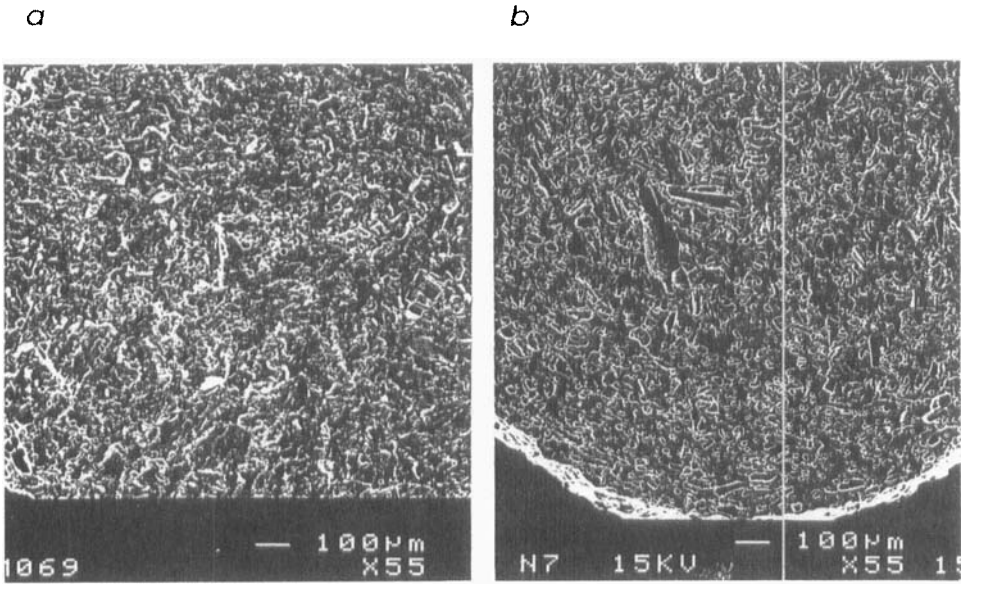

FIGURE 4 - *SEM micrographs of slabs of Eudragit ® RSPM based pellets, before (a) and after (b) release of diltiazem hydrochloride.*

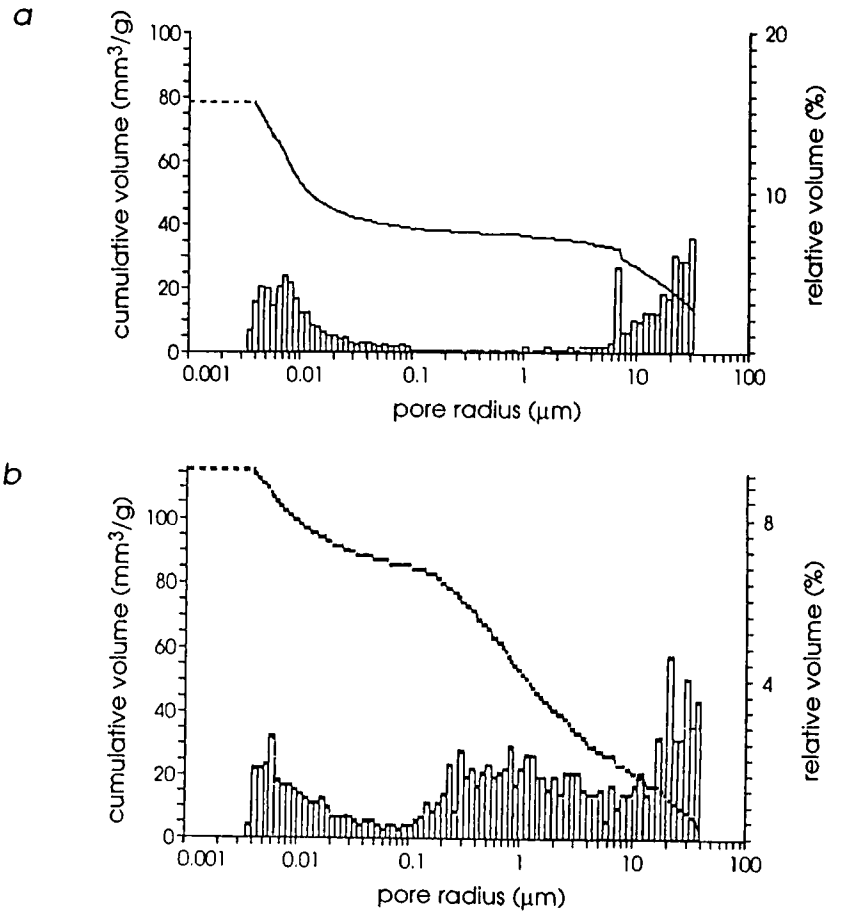

FIGURE 5 *- Mercury intrusion curves and pore size distributions of Eudragit ® RSPM (a) and Elvax ® 40W (b) based pellets containing diltiazem hydrochloride.*

Finally, the extruded pellets were submitted to a dissolution test. The *in vitro* release profiles (represented in *figure 6*) follow approximately a square root of time dependency over the first 60 % of drug released (*figure 7*). Nevertheless, the entire curves were best described by a double exponential decay of the form :

$$M = A_0 (1 - e^{-\alpha \cdot t}) + B_0 (1 - e^{-\beta \cdot t}) \qquad (Eq.2)$$

where M is the amount of drug remaining in the pellets at time t, and A_0 and B_0 are pre-exponential constants.

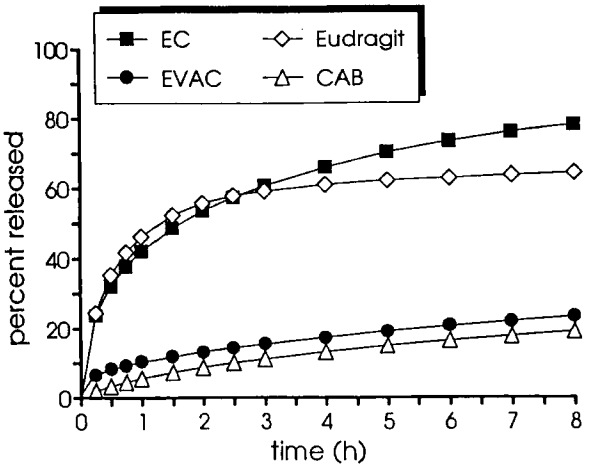

FIGURE 6 *- Release profiles of diltiazem hydrochloride from extruded pellets based on various polymers (polymer/drug ratio 1:1, size 2 x 2 mm).*

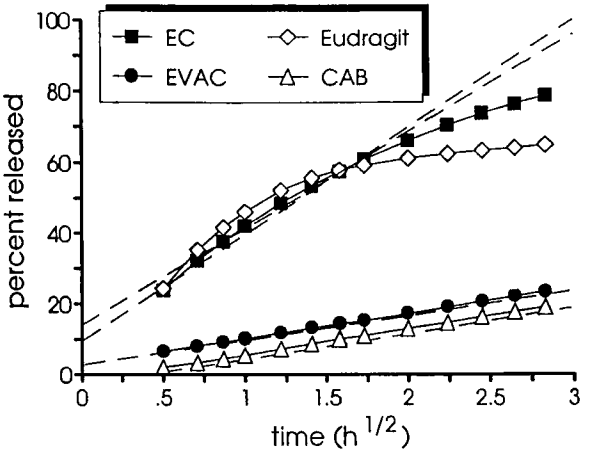

FIGURE 7 *- Diltiazem hydrochloride released (%) as a function of the square-root of time and calculated regression lines (- - -).*

TABLE 8 *- Coefficients of Higuchi's relationship for the release of diltiazem hydrochloride from extruded pellets.*

Polymer	Slope ($\%\cdot h^{-1/2}$)	y intercept (%)	t_{lag} (min)	χ^2_{calc}	υ	$\chi^2_{0.05}$
EC	29,6	11,2	- 8,6	2,00	5	11,07
Eudragit	27,3	15,8	- 20,1	11,03	5	11,07
EVAC	7,2	3,0	- 10,3	0,01	10	18,31
CAB	7,4	-1,8	3,3	0,02	10	18,31

☞ υ = degree of freedom, χ^2_{calc} = calculated value of χ^2 for the fitted curve, $\chi^2_{0.05}$ = theoretical value of χ^2 for a probability of 5 % and the degree of freedom mentioned.

TABLE 9 *- Coefficients of double exponential decay equation for the release of diltiazem hydrochloride from extruded pellets.*

Polymer	A_0 (%)	B_0 (%)	α (h^{-1})	β (h^{-1})	χ^2_{calc}	υ	$\chi^2_{0.05}$
EC	29,82	1,212	55,35	0,121	1,76	8	15,51
Eudragit	45,22	1,391	43,48	0,027	1,36	8	15,51
EVAC	5,86	0,852	89,04	0,019	0,08	8	15,51
CAB	7,64	0,593	91,73	0,016	0,08	8	15,51

The biexponential release behavior of extruded pellets, already observed by Mank et al. [9], could be explained by the rapid release of the drug easily accessible at the surface of the pellets, followed by a slow second phase where diffusion prevails.

Tables 8 and *9* list the parameters of Higuchi's relationship [16] and of *equation 2* for the various batches tested, calculated by non-linear regression (Grafit®, Erithacus Software, London, U.K.). The low values of χ^2 corresponding to the double exponential decay equation show the good fit of data carried out by this relationship.

CONCLUSION

This work demonstrated that hot-melt screw extrusion could be a simple method for producing sustained release pellets with a high loading of a freely soluble drug. To optimize the production and reduce the degradation phenomena of both polymers and drugs, we first carried out a preformulation study. Several polymers were selected according to their good processability and thermal stability characteristics. As a model drug, diltiazem hydrochloride was choosen for extrusion trials. The pellets produced exhibited generally smooth surface and low porosity. In that sense, EVAC-based pellets appeared to be somewhat different.

The *in vitro* release of the drug was found to be biphasic. The systems based on CAB and EVAC gaved a very low release rate. This last formulation seems most promising for further studies because of its low extrusion temperature, ease of processing and slow release characteristics. This fact might allow the inclusion of very high loadings of drugs and the possibility to obtain the desired release profile by adding various hydrophilic excipients.

ACKNOWLEDGEMENTS

This work was supported by a grant from Capsugel A.G., Arlesheim, Switzerland. We are grateful to Gödecke (Germany), Ciba-Geigy (Switzerland) and Luso Chimica (Italy), for supplying the samples of drugs.

REFERENCES

[1] FOLLONIER N. and DOELKER E.- Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms.- *STP Pharma Sciences*, **2**, 141-158, 1992.

[2] GHEBRE-SELLASSIE I.- Pellets : a general overview.- *In:* Pharmaceutical pelletization technology.- Ghebre-Sellassie I. ed., Marcel Dekker, New-York, 1989, chap. 1.

[3] VIAL A.C., DOELKER E. and BURI P.- Gélules à libération prolongée : formes divisées et monolithiques.- *STP Pharma*, **4**, 397-409, 1988.

[4] BECHMANN G. - Ueber die verzögerte Wirkstoff-Freigabe aus peroralen, festen Arzneiformen. - Ph.D. Thesis, University of Francfort, 1964.

[5] EL-EGAKEY M.A., SOLIVA M. and SPEISER P. - Hot extruded dosage forms. Part 1 : Technology and dissolution kinetics of polymeric matrices. - *Pharm. Acta Helv.*, **46**, 31-52, 1971.

[6] HÜTTENRAUCH R. and SCHMEISS U. - Spritzgiessverfahren zur Herstellung peroraler Retardpräparate. Teil 2 : Aufbau der Matrix. - *Pharmazie*, **30**, 229-233, 1975.

[7] SNIPES W.C. - US Patent 4,774,074, 1988.

[8] SNIPES W.C. - US Patent 5,004,601, 1991.

[9] RIPPIE E.G. and JOHNSON J.R. - Regulation of dissolution rate by pellet geometry. - *J. Pharm. Sci.*, **58**, 428-431, 1969.

[10] SHIVANAND P., HUSSAIN A.S. and SPROCKEL D.L. - Factors affecting release of KCl from melt extruded polyethylene disks. - *Pharm. Res.*, **8**, S-192, 1991.

[11] PRAPAITRAKUL W., SPROCKEL D.L., SHIVANAND P. and SEN M. - Abstracts of the 4th AAPS Atlanta 1989 : Development of a drug delivery system through melt extrusion. - *Pharm. Res.*, **6**, S98, 1989.

[12] MANK R., KALA H. and RICHTER M. - Darstellung wirkstoffhaltiger Extrusionformlinge auf der Basis von Thermoplasten. Teil 1 : Untersuchungen zur Wirkstoffliberation. - *Pharmazie*, **44**, 773-776, 1989.

[13] MANK R., KALA H. and RICHTER M. - Darstellung wirkstoffhaltiger Extrusionformlinge auf der Basis von Thermoplasten. Teil 2 : Untersuchungen zur Optimierung der Wirkstofffreigabe. - *Pharmazie*, **45**, 592-593, 1990.

[14] LACROIX P.M., BEAULIEU N., CYR T.D. and LOVERING E.G.- HPLC method for assay of diltiazem hydrochloride and its related compounds in bulk drug and finished tablets.- *J. Pharm. Sci.*, **78**, 243-246, 1989.

[15] JENQUIN M.R., LIEBOWITZ S.M., SARABIA R.E. and Mc GINITY J.W.- Physical factors influencing the release of drugs from acrylic resin films.- *J. Pharm. Sci.*, **79**, 811-816,1990.

[16] HIGUCHI T.- Mechanism of sustained action medication.- *J. Pharm. Sci.*, **52**, 1145-1149,1963.