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Development and evaluation of prolonged release pellets obtained by the melt pelletization process

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Abstract

This study was performed in order to evaluate the possibility of obtaining prolonged release matrix pellets by a melt pelletization process in a laboratory high shear mixer (Mi-Pro, Pro-C-epT). Phenylephrine hydrochloride pellet formulations based on lactose 450 mesh and a mixture of Compritol® 888 and Precirol® ATO 5 as melting binders were evaluated. The fatty binder content of pellets was substantially increased (from 18 to 80% w/w). The effects of jacket temperature, massing time (MT) and impeller speed (IS) on the pellet characteristics were investigated. It was shown that pellets of narrow size distribution can be produced by using an IS of 800 rpm, a chopper speed of 4000 rpm and a MT of 8 min. On the other hand, the applicability of this technique for the production of sustained-release pellets using ciprofloxacin hydrochloride, ketoprofen and theophylline as less water soluble model drugs than phenylephrine hydrochloride was also studied. This study demonstrated that formulations based on an appropriate mixture of Precirol and Compritol can be used to produce in a short time prolonged release pellets for very hydrosoluble drugs like phenylephrine hydrochloride as well as for the other drugs tested.

Keywords: Melt pelletization; High shear mixer; Controlled-release; Pellets; Lipophilic binders

1. Introduction

It is generally admitted that multiple-unit controlled-release dosage forms such as pellets present some biopharmaceutical advantages, particularly regarding the duration and the individual reproducibility of the gastric emptying, in comparison with larger single-unit dosage forms. Melt granulation is a solvent free process in which granulation is obtained through the addition of a binder, melting or softening at a relatively low temperature. After melting, the binder acts like a binding liquid. Polyethylene glycols (Schaefer et al., 1990; Voinovich et al., 1999), waxes (Mc Taggart et al., 1984; Zhou et al., 1996), stearic acid (Voinovich et al., 2000), fats, fatty acids, fatty alcohols and glycerides (Thies and Kleinebudde, 1999) are typical examples of meltable binders (MBs). By selecting a melting binder, which is insoluble in water, melt granulation might be a way of producing sustained release granules or pellets. When the

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final agglomerates are spherical and of a narrow size distribution in the size range of 0.5–2.0 mm, the process is named melt pelletization (Schaefer, 1996).

The melt pelletization might be a favourable alternative to conventional pelletization by extrusion-spheronization as a very short and a one-step single-pot production process. Since the drying phase is eliminated, the process is less consuming in terms of time and energy. Further, prolonged release properties are generally obtained without performing a final coating process. For water-sensitive materials, melt pelletization is an alternative to the use of organic solvents, which is desirable for both environmental and economic reasons.

The limiting factors of the melt pelletization are known to be a higher risk of chemical degradation of thermolabile substances and a wider size distribution of pellets compared with those obtained by extrusion (Kleinebudde and Nymo, 1995). Moreover, the melt pelletization in high shear mixers can be affected by the physico-chemical and thermal characteristics of the starting materials (particle size and shape, binder viscosity, melting range), and by the different process variables, such as mixer load, impeller speed (IS), chopper speed and moving time (MT) (Thomsen et al., 1993).

In this work, phenylephrine hydrochloride controlled-release pellets were prepared by melt pelletization in a laboratory scale high shear mixer (Mi-Pro, Pro-C-epT), using lactose 450 mesh and lipidic binders, consisting of different Precirol®ATO and Compritol® 888 ATO blends. The effects of jacket temperature, MT and IS on the pellet characteristics were investigated.

Several works have shown that the MB content of pellet formulations obtained by melt pelletization is generally limited to about 20% w/w (Schaefer, 1996; Thies and Kleinebudde, 2000). However, the drug release from the matrix pellets is generally very fast, especially for highly water-soluble drugs like phenylephrine hydrochloride, when the fatty binder content is lower than 20% (Hamdani et al., 2000a). In this purpose, new pellet formulations based on the mixtures of two fatty binders, presenting well distinct melting properties (Precirol and Compritol used, respectively, as low and high melting range lipophilic binders), were evaluated. The fatty binder contents of pellets were substantially increased (up to 80% w/w), by carefully controlling the product temperature in the high shear mixer, in order to avoid the melting of the whole binding material. In this way, effective prolonged-release formulations containing increasing amounts of fatty binders were obtained. The influence of lipidic binder content in the formulations on the release of phenylephrine hydrochloride was investigated.

On the other hand, sustained-release pellets were also produced by melt pelletization with less water soluble drugs than phenylephrine hydrochloride, like ciprofloxacin hydrochloride, ketoprofen and theophylline, in order to show the applicability of this technique to drugs presenting distinct physico-chemical characteristics.

2. Materials and methods

2.1. Materials

Lactose 450 mesh (DMV International, Netherlands) and Phenylephrine hydrochloride (Fédéra, Belgium) were used as diluent and highly water soluble model drug substance, respectively. Anhydrous theophylline (Ludeco, Belgium), ciprofloxacin hydrochloride (Siris, India) and ketoprofen (Sochibo, France) were used as examples of less hydrosoluble drugs than phenylephrine hydrochloride. Glyceryl palmito-stearate (Precirol® ATO 5) and glyceryl behenate (Compritol® 888), were supplied by Gattefossé (France) and used as lipophilic binders. The binders occur as fine, white free-flowing powders.

2.2. Physico-chemical properties of ingredients

The melting characteristics of drugs and lipophilic binders were determined by differential scanning calorimetry (DSC). A Perkin–Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with an intracooler-2 cooling system (Perkin–Elmer Instruments, CT, USA) was used at a scanning rate of 5 °C/min

(Hamdani et al., 2000b). Samples of about 5 mg were analysed using 50 μl aluminium pans.

The mean particle size, represented by the equivalent volume diameter $D[4, 3]$, was determined using a laser diffraction method, with a dry sampling system (Mastersizer 2000, Malvern Instruments, UK).

The physico-chemical characteristics of the active ingredients and lipidic binders are summarized in Table 1.

2.3. Equipment

The pellets were prepared in a vertical small laboratory scale high-shear mixer, Mi-Pro (Pro-C-epT, Belgium), equipped with a transparent bowl and a heating jacket. The bowl capacity and batch sizes were 1700 ml and 250 g, respectively. The rotational speed of vertically positioned mixing arm (impeller) and chopper, can be varied between 0 and 1800 rpm and 0–4000 rpm, respectively.

During the pelletization process, the product temperature (IR temperature probe), the torque (N m), the rotational speed of the impeller and the chopper arms were measured and monitored as a function of time. Analysis of the torque and the temperature profiles opened the possibility to control the granule formation and pelletization process.

2.4. Pellets manufacture

Phenylephrine hydrochloride pellet formulations containing 2 or 10% (w/w) drug, lactose 450 mesh and increasing amounts (18, 25, 40, 60 and 80%) of fatty binder mixtures (Precirol® and Compritol®) were prepared by melt pelletization (Table 2). The content of the lower melting range fatty binder (Precirol®, mp 54 °C) in the mixtures was fixed to 15%, while increasing the content of the higher melting range fatty binder (Compritol®, mp 72 °C) from 3 to 65% (w/w), in the different formulations. During the whole manufacturing process, the product temperature in the high shear mixer must be carefully controlled and kept below about 50 °C in order to avoid any 'over wetting' phenomenon. Around 50 °C, only Precirol® is sufficiently softened to promote the granule formation (Evrard et al., 1999; Hamdani et al., 2000b), while Compritol® stays in the unmelted form and can only acts as lipophilic diluent. By this way, effective prolonged release phenylephrine hydrochloride pellet formulations, based on the use of high amounts of lipophilic binder were obtained.

The pelletization procedure was standardised on the basis of preliminary trials (Hamdani et al., 2000a). The effects of the IS and MT were investigated by means of a factorial experiment with nine different experimental conditions ($n = 2$).

Table 1
Some physico-chemical characteristics of excipients and drugs used

Material	$D[4, 3]$ (μm)	Solubility (mg/ml)	Melting range (°C)	HLB
Precirol ATO 5	31.3	–	46–54	2
Compritol 888	31.7	–	67–72	2
Lactose 450 Me	21.4	–	–	–
Ciprofloxacin HCl	12.4	4[a]; 9[b]	313	–
Ketoprofen	11.3	300[a]	97	–
Phenylephrine HCl	147.8	>1000[c]	144	–
Theophylline	47.0	11[c]	274	–

[a] Solubility at pH 7.0.
[b] Solubility at pH 1.5.
[c] Water solubility.

Table 2
The composition of the phenylephrine controlled-release formulations investigated

Formulation	Phenylephrine HCl (% w/w)	Compritol (% w/w)	Precirol (% w/w)	Lactose 450 Me (g)
18% fatty binder	2	3	15	Ad 250
25% fatty binder	2	10	15	Ad 250
40% fatty binder	2	25	15	Ad 250
60% fatty binder	2	45	15	Ad 250
80% fatty binder	2	65	15	Ad 250

The phenylephrine hydrochloride pellet formulation, containing 2% (w/w) of drug and 60% (w/w) of fatty binder mixture, was used in order to determine the optimal experimental conditions (Table 2).

All experiments were started at an IS of 1800 rpm; a chopper speed of 130 rpm while the temperature of the heating jacket was set at 45 °C. When the product temperature reaches sufficiently high values in order to provoke the binder softening, the torque increases sharply resulting from the granule formation.

In order to avoid any further product temperature increase, the IS was reduced after the granule formation step. Moreover, a controlled flow cooling air (2.4–4 m^3/h) was injected, through the bowl lid, in the product during the massing/pelletization step. The IS during the pelletization step was varied at four levels (400, 600, 800 or 1000 rpm), the chopper speed was varied at two levels (130 or 4000 rpm) and the MT was varied at three levels (6, 8 or 15 min). The product temperature was carefully controlled in order to avoid excessive particle size increase and/or agglomeration during the pelletization step. The temperature of the heating jacket was kept at 45 °C. The length of the whole pellet manufacturing process was around 20 min.

At the end of the process, the pellets were cooled at ambient temperature. The adhesion to the bowl was estimated as the difference between the amount of materials placed in the bowl and the amount emptied.

The melt pelletization process was also evaluated for the development of high drug content pellet formulations with ciprofloxacin hydrochloride, theophylline and ketoprofen as model drugs. Pellet formulations were composed of 75% drug and 25% of fatty binder mixture (15% Precirol and 10% Compritol). Experiments were carry out using the optimal experimental conditions (800 and 4000 rpm, respectively, for the impeller and the chopper speed during massing, 8 min MT) as determined for phenylephrine hydrochloride pellets, except for the temperature of the heating jacket which was slightly increased (50 °C for ketoprofen pellets and 55 °C for ciprofloxacin and theophylline pellets) in order to reduce the duration of the granulation step. The differences between the drug particle size characteristics and the drug content of these formulations might explain this adaptation.

2.5. Pellet characterisation

2.5.1. Size distribution

The cooled material was sieved in order to remove lumps and pellets larger than 2 mm. The granule size (geometric-weight mean diameter, d_{gw}) and size distribution (geometric standard deviation, s_{gw}) were estimated by sieve analysis on samples of about 50 g. Sieve analysis was performed with a Rhewum vibrating apparatus, using a set of seven standard sieves in the range of 700–1500 μm.

2.5.2. Scanning electron microscopy

Microphotographs were obtained from pellets coated with a thin gold–palladium layer, using a scanning electron microscope (SEM). Surface structure studies were carried out using a combined mapping X-ray microscopy technique (JSM-6100 Scanning Electron Microscope, EDAX CDU 'LEAP' Detector, JEOL, Japan). Samples were

examined with 5 kV power, at magnifications from 50 to 300 times.

2.5.3. *In vitro dissolution test*

Drug release determinations were carried out at 37 °C using USP 24, number 2 dissolution testing apparatus (paddle), at a rotational speed of 60 rpm. Phosphate buffer solutions (0.05 M), containing 0.05% Polysorbate 20, were used as the dissolution fluid. The volume and the pH of the dissolution fluid were 600 ml and 7.0, respectively. A buffered solution to pH 1.5 was also used for ciprofloxacin, which shows a highly pH-dependent solubility profile.

The drug release from pellets was determined at 275, 276, 272 and 260 nm for phenylephrine hydrochloride, ciprofloxacin hydrochloride, theophylline and ketoprofen, respectively, using an Agilent 8453 UV–visible Dissolution Testing System (Agilent, USA). The percentages of tracing agent released were measured at fixed time intervals and averaged ($n = 5$). Only pellet size fractions in the range of 700–1500 μm were considered for dissolution studies.

The in vitro drug release was also evaluated from phenylephrine hydrochloride pellets after storage in different temperature and humidity conditions: 4±2 °C (fridge), 25±2 °C—60% RH, 30±2 °C—60% RH for 1 year and 40±2 °C—75% RH for 6 months.

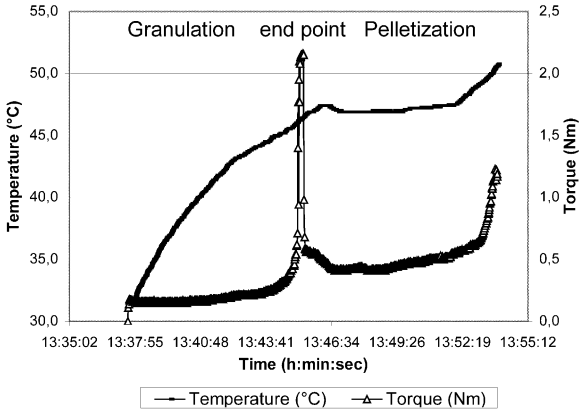

Fig. 1. Measurements of the torque (N m) and the temperature as a function of time.

3. Results and discussion

As we can see in Fig. 1, two stages can be observed during the melt pelletization process in high shear mixers. During the first one, the product temperature increases quickly by the important heat of friction generated by the impeller blades because of the very fast IS set during the granulation step (1800 rpm) and by the heating jacket (45 °C). When the binder is sufficiently soften to be deformed, the torque increases sharply resulting from the granule formation. The granulation end point determination in melt pelletization is critical for pellet formulations with high lipidic binder contents, as any further increase of product temperature, i.e. by keeping the starting experimental parameters, may provoke the formation of an excessive powder agglomeration. Thus, during the pelletization, the IS is decreased from 1800 to 800 rpm and the chopper speed increased from 130 to 4000 rpm (optimal conditions) in order to keep the product temperature as stable as possible. Moreover, the injection of cooling air through the bowl lid allows a better control of the product temperature during the pelletization step (between 45 and 50 °C).

In accordance with the melting and the rheological properties of Precirol (Evrard et al., 1999; Hamdani et al., 2000b) the monitoring of the product temperature and the impeller motor power consumption during the melt granulation process, show that the granule formation is quite effective at product temperatures even below the melting point of the fatty binder, (around 45 °C) i.e. when the binder is sufficiently softened to be deformed under the action of very high shearing forces (Fig. 1).

The evaluation of size characteristics of pellets by sieve analysis (Tables 3–5) and by SEM (Fig. 2), show that the mean size, size distribution and morphology of pellets are highly dependent on the process parameters during the pelletization step, mainly product temperature, MT, IS and chopper speed. Spherical pellets with an important yield in the range of 700–1500 μm (68.8%) were obtained when appropriate experimental conditions (chopper speed of 4000 rpm, IS of 800 rpm and MT of 8 min.) were used during the pelletization step. On

Table 3
Effect of the chopper speed (IS 800 rpm, MT 8 min) for phenylephrine hydrochloride pellets (formulation containing 2% of drug and 60% w/w of MBs)

Chopper speed (rpm)	d_{gw} (μm)	s_{gw}	(%) < 700 μm	(%) 700–1500 μm	(%) > 1500 μm
130	1480	1.59	0.8	44	34.5
4000	1240	1.47	3.4	68.8	19.9

the other hand, the influence of process parameters, during the granulation step, on the pellet characteristics is less critical, as far as the impeller rotation rate is reduced just after the detection of the granulation end point (from 1800 to 800 rpm), in order to avoid any further increase of the product temperature.

The chopper is generally used in order to break down lumps formed during the process. It rotates generally with a higher speed than does the impeller, typically within a range of 1000–4000 rpm (Schaefer, 1996). Although the chopper starting up is not always necessary during melt pelletization process, slightly larger mean granule size and size distribution, with an important increase of the larger particle size fraction (> 1500 μm) were observed when the chopper was removed or when slower rotation rates were selected (130 rpm). Table 3 shows that the pellet size, expressed by the geometric weight mean diameter (d_{gw}) grows from 1240 to 1480 μm when the rotation rate of the chopper is slowed down from 4000 to 130 rpm. Moreover, the larger particle size fraction (> 1500 μm) increases from 19.9 to 34.5% when a slower chopper speed is selected.

The MT can be defined as the time during which the binder is present in a soften or molten state. When the binder is added in a solid state, the melting point can be identified as an inflection point on the product temperature recording curves (Schaefer, 1996). The effects of a higher IS are assumed to be similar to those of a prolonged MT, since both increase the total energy input during the process. During melt agglomeration in high shear mixers, the induced energy is converted into heat in the powder mass. Consequently, a higher IS as well as prolonged MT will induce higher product temperature. As discussed before, the heat generation is counterbalanced in our experiments by reducing the IS and by introducing a controlled flow air stream in the mixing bowl at room temperature.

Tables 4 and 5 show the effect of the IS and MT on the pellet size characteristics. As it can be observed, relatively low mean particle size (d_{gw} of about 200 μm) and high size distribution (s_{gw}) values are obtained at the lowest ISs (400 and 600 rpm) and MT (6 min). The smaller particle size values observed, result probably from the significantly higher fine particles content, caused by an insufficient energy input and/or an improper movement of the powder mass at the lowest ISs. On the other hand, at the highest IS (1000 rpm), an excessive powder agglomeration caused by an 'overwetting' phenomenon is observed. In these

Table 4
Effect of IS (chopper 4000 rpm, MT 8 min) for phenylephrine hydrochloride pellets (formulation containing 2% of drug and 60% w/w of MBs)

IS (rpm)	D_{gw} (μm)	s_{gw}	(%) < 700 μm	(%) 700–1500 μm	(%) > 1500 μm
400	230	4.67	94.6	3.6	1.6
600	210	4.82	94.6	3.6	1.6
800	1240	1.4	3.4	68.8	19.9
1000[a]	–	–	–	–	–

[a] Overwetting, powder agglomeration.

Table 5
Influence of the MT (IS 800 rpm, chopper 4000 rpm) for phenylephrine hydrochloride pellets (formulation containing 2% of drug and 60% w/w of MBs)

MT (min)	d_{gw} (μm)	s_{gw}	(%) < 700 μm	(%) 700–1500 μm	(%) > 1500 μm
6	210	4.85	97.8	1.8	0.2
8	1240	1.47	3.4	68.8	19.9
15	1370	1.68	4.8	30.5	30.3

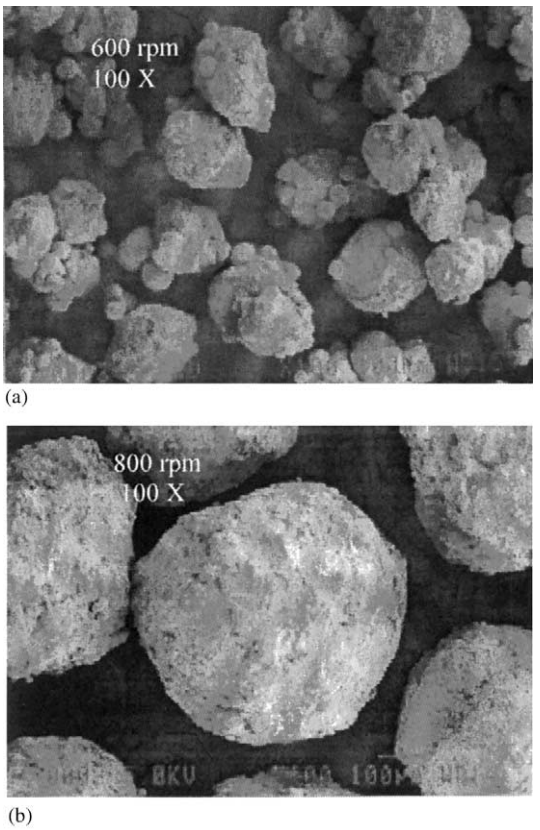

Fig. 2. SEM microphotographs of phenylephrine pellets, effect of IS (600–800 rpm). Magnification 100 ×.

conditions, the process becomes uncontrollable as the excessive heat of friction generated by the impeller blades provokes a further increase of the product temperature above the melting range of Compritol, and thus, the melting of the whole lipophilic binders.

The observed effects of MT, as gradually increasing mean pellet size and gradually narrowing size distribution, are assumed to be a result of increasing particle densification and of the gradual inclusion of fine particles in the pellets (Thomsen et al., 1993). However, when the fatty binder content of the pellet formulations is very high (60% w/w) and as observed for the highest IS, prolonged MT may also provoke an increase of the product temperature an thus, the appearance of an excessive powder agglomeration (see Fig. 1; Table 5).

Scanning electron microphotographs of pellets massed at different ISs (Fig. 2) showed that pellets prepared at an IS of 800 rpm are bigger and more homogeneous than those run at 600 rpm. Pellets prepared at 800 rpm show also a smoother surface texture and are well rounded.

On the other hand, the chemical composition analysis of the surface and the pellet cross section, as determined by scanning electron microscopy combined with X-ray image (distribution of the chemical elements Cl, C and O), indicate a homogeneous distribution of drug in the matrix pellet (Figs. 3 and 4).

It can be concluded that for the phenylephrine controlled-release pellet formulations containing 60% fatty binders mixture, the use of an IS of 800 rpm, a chopper speed of 4000 rpm and a MT of 8 min can be considered as optimal process parameters during the pelletization step. By this way, homogeneous matrix pellets showing desirable size and shape characteristics, with important yield in the 700–1500 μm size fraction (around 70%) were obtained. These optimal process parameters were thus considered for the evaluation of the different pellet formulations.

The in vitro dissolution properties of phenylephrine controlled-release pellets containing increasing amounts of fatty binders mixtures were

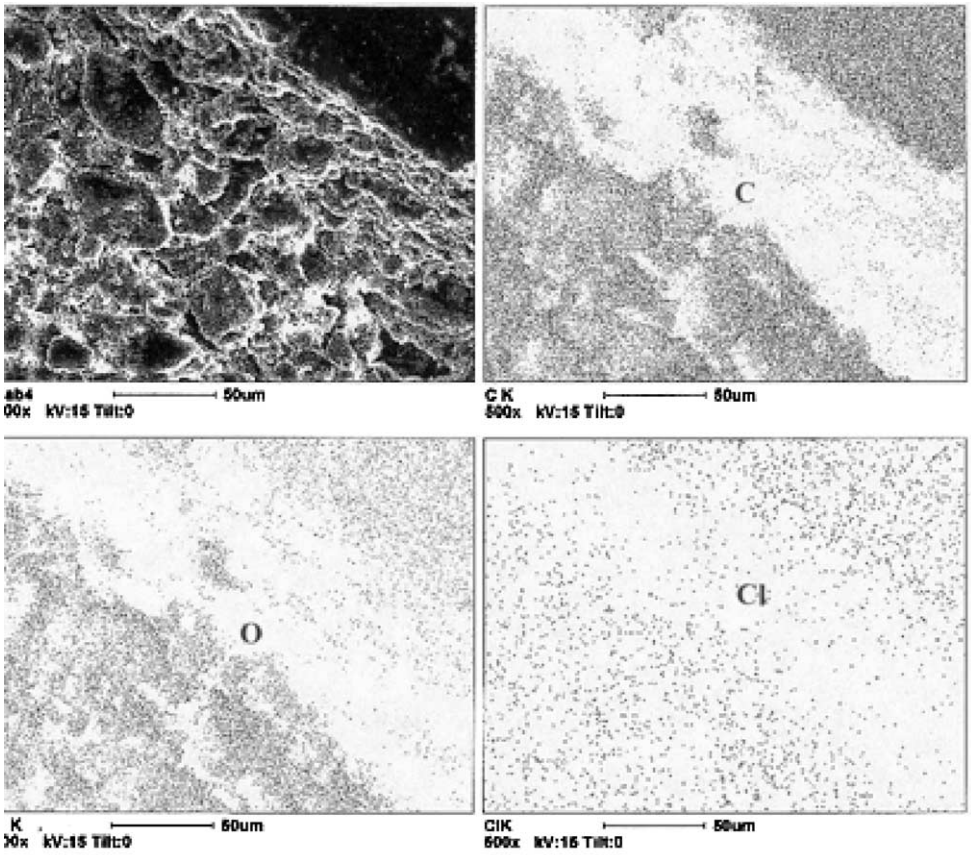

Fig. 3. Chemical composition of the surface structure of a phenylephrine hydrochloride pellet cross section obtained by the mapping X-ray microscopy technique.

determined, in phosphate buffer pH 7.0, on the selected size fractions (700–1500 μm) obtained by sieving in order to reduce the size variation effects on the dissolution properties.

As shown in the Fig. 5, the phenylephrine hydrochloride release is remarkably lowered when the amount of lipidic binder is increased from 18% (almost 94% release after 2 h) to 80% w/w (only 58% drug release after 12 h). An important decrease of the phenylephrine release is already apparent for the formulation containing 25% (95% drug release after 12 h) and even more for that containing 40% (64% drug release after 12 h) fatty binders. A further increase of the fatty binder content of pellet formulations seems not to decrease the drug release rate as similar dissolution profiles are observed for formulations containing 40, 60 and 80% lipidic binders. We can thus assert that, for highly water-soluble drugs like phenylephrine hydrochloride, effective prolonged-release pellets are obtained for formulations containing 25 or 40% of fatty binder mixtures.

The stability of drug release profiles was also evaluated, from phenylephrine hydrochloride pellets, containing 10% drug and 60% fatty binders mixture, after storage in different temperature and humidity conditions.

In vitro dissolution tests (phosphate buffer, pH 7) from pellets show a significant influence of storage parameters on the release of phenylephrine hydrochloride. As we can see in Fig. 6 pellets stored at 40 °C and 75% RH loose their prolonged release properties after 6 weeks. The presence of an oxydable drug (Millard et al.,

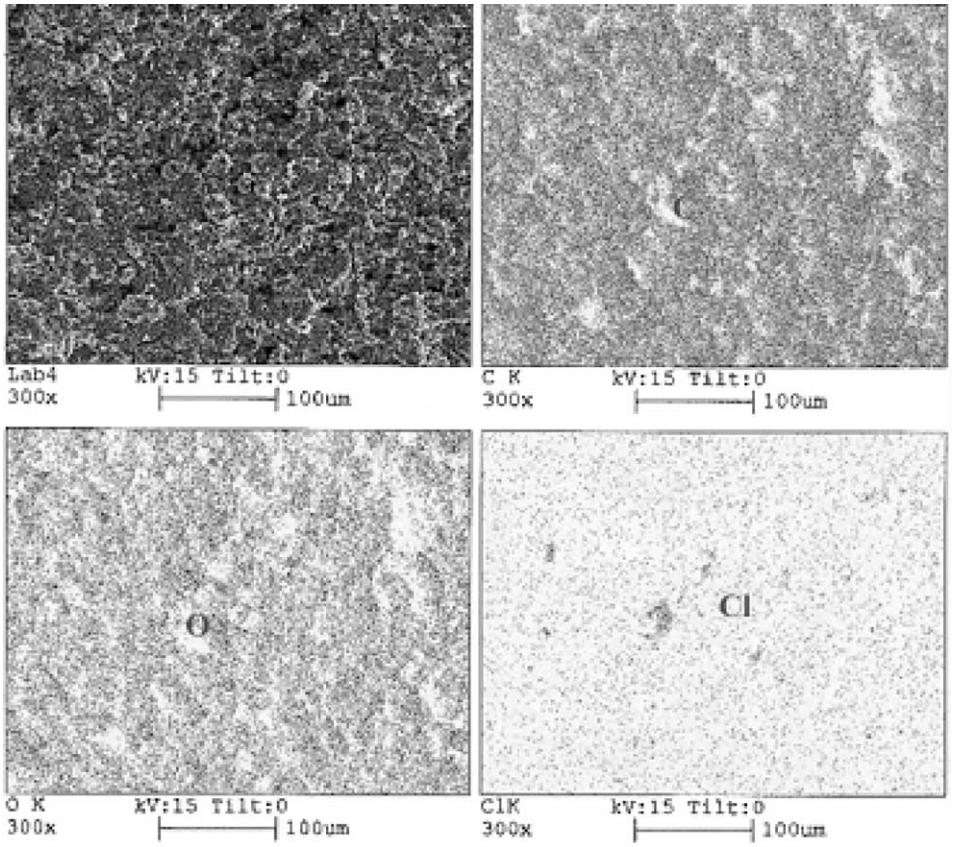

Fig. 4. Chemical composition of the surface structure of a phenylephrine hydrochloride pellet obtained by mapping X-ray microscopy technique.

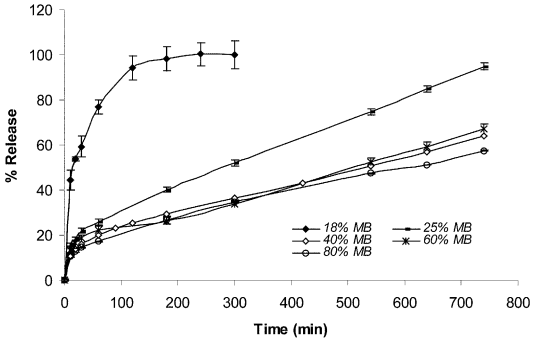

Fig. 5. Drug release (phosphate buffer, pH 7.0) from phenylephrine hydrochloride pellets (2% w/w) containing different MB contents (18–80% w/w).

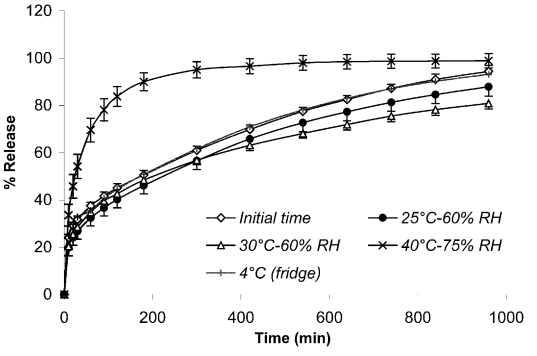

Fig. 6. Drug release (phosphate buffer, pH 7.0) from phenylephrine hydrochloride pellets (10% of drug and 60% (w/w) of fatty binders mixture) stored during 6 weeks in different conditions of temperature and humidity.

1973) as well as the high amounts of low melting lipidic binders may explain the sensibility of the dosage form to the higher temperature and humidity conditions. In contrast, no significant differences were detected by the statistical two sample Student's t-test ($P > 0.05$) between drug release profiles obtained from pellets stored for 38 weeks at 4 °C and those obtained from initial ones ($T = 0$).

The evolution of drug release profiles versus the storage time for samples stored at 25 °C–60% RH (Fig. 7), shows a significant decrease of the release of phenylephrine hydrochloride between initial pellets and those stored ($P < 0.05$) for 6 weeks. The same phenomenon was observed between pellets stored for 12, 26 and 38 weeks. But there is no significant difference ($P > 0.05$) between samples stored during 51 weeks at 25 °C–60% RH and those which were stored for 38 weeks in the same conditions.

Finally, in order to demonstrate the huge potential of the melt pelletization process in high shear mixers for the preparation of controlled release dosage forms, the melt pelletization process was also evaluated for the preparation of formulations with high drug content (75% drug and 25% fatty binders mixtures).

Fig. 8 shows the drug release profiles obtained, in phosphate buffer medium at pH 7, from ketoprofen, theophylline and ciprofloxacin hydrochloride controlled-release pellets. Moreover, drug release profiles were also evaluated at pH 1.5, for

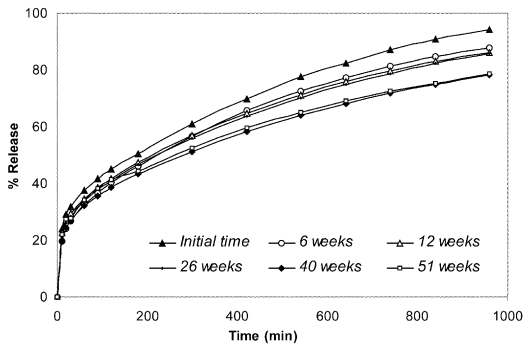

Fig. 7. Drug release profiles from phenylephrine hydrochloride pellets (10% of drug and 60% (w/w) of fatty binders mixture) stored at 25 °C–60% RH.

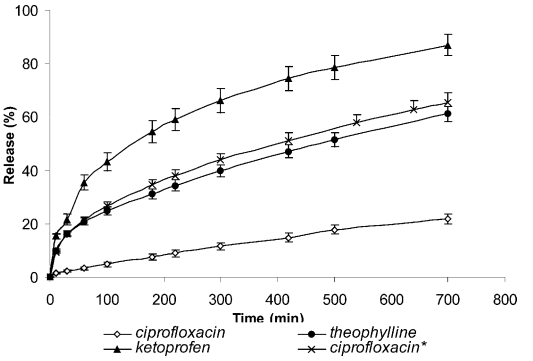

Fig. 8. Drug release (phosphate buffer, pH 7.0) from pellets containing 75% w/w of drug (ciprofloxacin, ketoprofen or theophylline) and 25% of lipidic binders mixture. Ciprofloxacin * release performed in phosphate buffer, pH 1.5.

ciprofloxacin pellets because of the very low water solubility of this drug at pH 7 (Table 1).

As can be seen, drug release results are in accordance with the physico-chemical properties, and more particularly with solubility properties of drugs in aqueous mediums. At pH 7, much faster drug dissolution profiles were obtained from ketoprofen pellets ($s = 300$ mg/ml) than from theophylline ($s = 11$ mg/ml) pellets and finally, from ciprofloxacin pellets ($s = 4$ mg/ml).

The faster drug release profiles observed from ciprofloxacin pellets at pH 1.5 ($s = 9$ mg/ml), can be explained by the pH dependent aqueous solubility of the drug. The poor aqueous solubility of this drug at pH values higher than 5, may explain the bioavailability problems observed for ciprofloxacin sustained-release dosage forms (Louie-Helm et al., 2001).

4. Conclusion

By using appropriate mixtures of lower (Precirol®) and higher (Compritol®) melting range fatty binders, and by carefully controlling the product temperature, the melt pelletization technique in high shear mixers might be an advantageous method to produce effective controlled-release pellets in a very short and one-step single-pot production process.

Depending on the physico-chemical properties of the active ingredient, relatively high amounts of lipophilic binder must be used in order to obtain prolonged-release properties from multi-particulate matrix systems. This production process might be especially useful for the preparation of controlled release dosage forms with highly hydrosoluble drugs like phenylephrine hydrochloride and for drugs used at high dose range.

The storage conditions of pellets must be carefully controlled in order to assure the stability of the dosage form.

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