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International Journal of Pharmaceutics 233 (2002) 111–122

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

The influence of core materials and film coating on the drug release from coated pellets

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Received 29 May 2001; received in revised form 11 October 2001; accepted 18 October 2001

Abstract

The objective of this study was to analyse the influence of the composition of the core of the pellets on the in vitro drug release profile. The different materials (drugs and fillers) were chosen according to their relative solubility. Pellets were prepared by a standardised process of extrusion/spheronisation. A selected fraction size (1–1.4 mm diameter) of pellets of each preparation was coated with Surelease (an aqueous dispersion of ethyl cellulose) to give 5% weight gain. The dissolution studies were performed and data analysed in terms of the Area under the Curve (AUC) of the % dissolved as function of time and Mean Dissolution Time (MDT). ANOVA was applied in order to identify the influence factors and the relationship of cross effects. Canonical analysis and multiple regression were employed to quantify these relationships. The film coat was found to be the major factor controlling the drug release. The results however, show that both drug and filler solubility influenced the drug release profile. Some of the unusual results could only be explained if consideration was given to the physical characteristics of both powder and pellets. In particular, the specific surface area of calcium phosphate compared with other fillers played an important role on the release profile of the model drug.

Keywords: Drug release; Extrusion/spheronisation; Film coating; Pellets; Pellet structure

1. Introduction

The release pattern of drugs from pellets is clearly influenced by their own physical properties such as solubility and particle size. As pointed out by Ragnarsson (1992) all the three phases of drug release profiles—lag time, constant release phase and declining rate phase—are strongly influenced by the drug solubility. On the other hand since the use of different fillers influences the drug release, their choice depends on the characteristics required for the system. If an insoluble drug is present one way to accelerate the dissolution rate from pellets is the incorporation of water-soluble excipients, surfactants or disintegrants (Kleinebudde, 1994). The use of dicalcium phosphate de-

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0378-5173/02/$ - see front matter
PII: S0378-5173(01)00921-8

hydrate, a commonly used water insoluble pharmaceutical excipient has been found to be useful in controlled release of highly water-soluble drugs by forming either a matrix system (Mulye and Turco, 1994) or a compact structure (Lin et al., 1995). The option to include fillers, such as glucose, which promotes a high osmotic pressure, could also increase the dissolution rate. Hence, the present work studies the influence of type of drug and filler on the release of drug coated with a film coat of constant composition and thickness.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride, (P) (Lusochimica, Milano, Italy), ephedrine (E) (S&D Chemicals Ltd., Harrow, UK), paracetamol (Pa) (Rhone Poulenc, Roussillon, France), ibuprofen (I) (Boots Pharmaceutical, UK) and sodium salicylate (S), (BDH Lab Supplies, Poole UK), microcrystalline cellulose (A) (Avicel PH 101) (FMC Ltd., Cork, Ireland), α-lactose monohydrate (L) (Sheffield Products, Norwich, USA), glucose anhydrous (G) (BDH Lab Supplies, Poole, UK), mannitol (M)(D-) (BDH Lab Supplies, Poole, UK), calcium phosphate (C) (Fisons Sci. Equip., Loughborough, UK) and barium sulphate (B) (BDH Lab Supplies, Poole, UK) were of E.P. quality and were used as received. Details of the particle size and the solubility of the drugs and fillers were reported previously (Sousa et al., in press). Water freshly demineralised, was used as a liquid binder and dissolution medium. An aqueous dispersion of ethyl cellulose (Surelease-E-7-7050 white, Colorcon Ltd., Dartford, UK) was used as the coating system.

2.2. Experimental design

Ternary mixtures were obtained using a model drug, filler and microcrystalline cellulose. The work plan was divided in four parts: group 1 where the model drug was changed according to its solubility; group 2: different ratio of drug/filler; group 3: lower level of filler (30%); group 4: high level (45%) of filler. Formulations are identified by the initials of each component and their relative proportions, expressed on a weight basis. The reference formulation is preparation PLA 2:3:5.

2.3. Extrusion/spheronisation process

The formulations and their method of preparation are described fully by Sousa et al. (in press).

2.4. Coating

Pellets were coated with an aqueous dispersion of ethyl cellulose (Surelease E-7050), previously diluted with water to 15% total solids, to give 5% weight gain in a fluid bed coater (Strea 1, Aeromatic Inc., Tadley, UK). The coated pellets were cured in a hot air oven (Gallenkamp Hotbox, Gallenkamp Ltd., London, UK), at 60 °C for 1 h.

2.5. Dissolution tests

Dissolution tests, according to the USP paddle method (TPWS 2C Pharma Test, Hamburg, Germany), were carried out on uncoated and coated pellets in 900 ml of deionised water with an automated analysis system to quantify the drug content of the dissolution fluid. To identify a possible mechanism responsible for the drug release, the dissolution profiles were analysed by the area under the dissolution curve (AUC), mean dissolution time (MDT) and the variation associated with the MDT (VDT). Also the relative dispersion coefficient (RD) was determined as described by Pinto et al. (1997). The relative dispersion coefficient (RD) was used as a discriminator between the different models and the release rate as a function of time was analysed according to the release kinetic models (Voegele et al., 1988) or, where none fitted the data, the general equation proposed by Korsemeyer et al. (1983) was applied.

Statistical analysis has been undertaken to compare the different formulations with the performance of the formulation PLA 2:3:5, which was chosen as the reference formulation.

2.6. Specific surface area

The specific area of all the materials was determined using the adsorption isotherm derived by the Brunauer, Emmet and Teller (BET) method, using krypton as analytical gas, with the exception of calcium phosphate where nitrogen was used. Krypton was used because of the very low specific area of all the other materials (less than 10 $m^2\ g^{-1}$).

The experimental process involved degassing the powder and/or pellet samples with vacuum, followed by physical adsorption of krypton (or nitrogen for calcium phosphate) at the temperature of the liquid nitrogen ($T \approx 77$ K). For this purpose the carrier sample was initially immersed in a liquid nitrogen bath, then the adsorption process was commenced simultaneously with registering of the volume of gas adsorbed as a function of its relative pressure. Five experimental points (BET multipoint) or only one point (BET singlepoint) within a range of relative pressures (≈ 0.05–0.30) was used. The correlation factor and the BET constant obtained were, for all the cases, satisfactory.

3. Results and discussion

The values of the median diameter of powders and the centiles 90 and 10 are shown in Table 1, as are the specific surface area values.

Fig. 1 shows for propranolol hydrochloride, how the solubility of the fillers influences the amount of water required for extrusion and the specific area of the resultant pellets. As the only change in the formulations above is the type of filler used, it is reasonable to accept that there is a relationship between their solubility, or in other words, the amount of water required to successful perform the extrusion process and the specific surface area determined.

For the same drug (propranolol hydrochloride) and filler used at different ratios, it is also interesting to observe the way in which the specific area values vary, and both the mechanical strength and the porosity changes with drug content (Fig. 2). While specific surface area and mechanical strength change in a corresponding manner, porosity hardly changes with change in drug content.

3.1. Dissolution results

The drugs studied were selected according to their solubility in order to analyse the influence of this physical characteristic on the release kinetics and to find out if this influenced the possible mechanisms of the transport of the drug through the polymeric film.

As can be seen in Table 2, the values of AUC, MDT, RD and VDT obtained for different drugs when incorporated in pellets coated with the same amount of Surelease E-7-7050 are quite different.

Table 1
Median diameter and distribution at 10 and 90 percentiles (μm) of the starting materials ($n = 3$)

Materials	Median diameter (μm)			Surface area	
	Mean	10%<	90%>	Single point ($m^2\ g^{-1}$)	Multipoint ($m^2\ g^{-1}$)
Propranolol·HCl[a]	80.64	33.78	110.17	0.16	0.21
Avicel PH101[a]	51.47	18.80	100.20	0.76	1.01
Glucose anhydrous[b]	137.92	63.35	203.97	0.41	0.49
Mannitol (D-)[a]	20.09	6.86	42.85	0.46	0.57
Lactose hydrous[a]	33.20	5.85	74.17	0.34	0.43
Calcium phosphate[a]	8.06	3.19	13.60	19.8	20.2
Barium sulphate[a]	8.74	4.83	12.71	0.31	0.38

[a] Suspending medium water.
[b] Suspending medium ethanol.

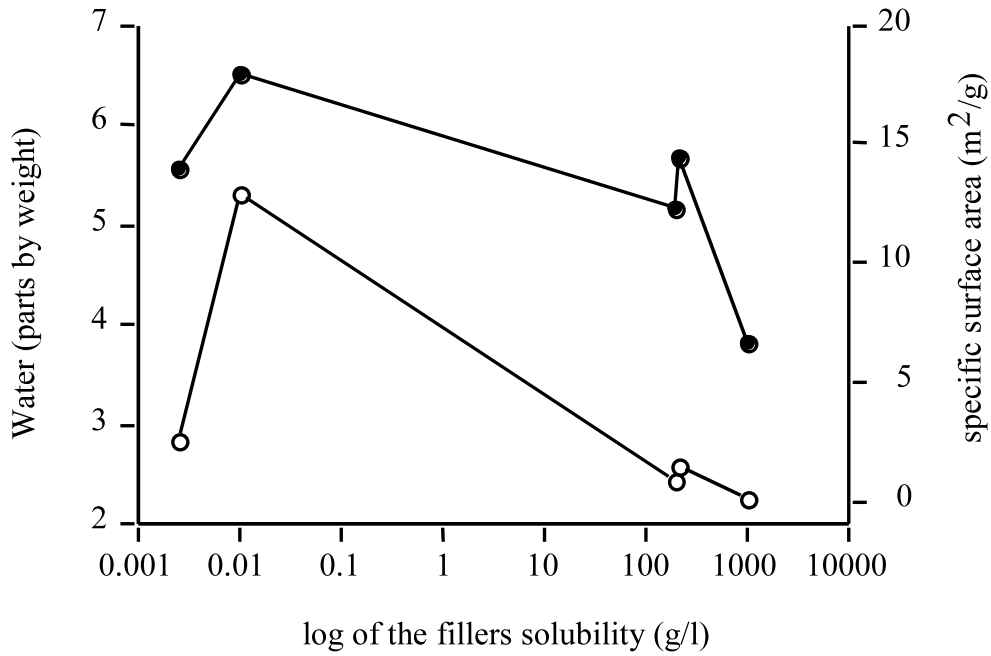

Fig. 1. Influence of the solubility of the fillers on the amount of water (●) used to obtain the wet mass and the specific surface area (○) of the resultant pellets.

The MDT values could be ordered as a function of the solubility of the drug. However, if comparisons were made only taking into account the relative drug solubility, the result obtained with the preparation PaLA 2:3:5 appears as an odd result in this sequence. It is therefore important to look for other physical characteristics of the pellets in order to explain the behaviour of the dissolution test.

Comparing the values for RD for the various formulations it may be observed that, the release of ibuprofen fits the kinetic model proposed by Hixson–Crowell while propranolol hydrochloride provides a first order release. The release profile of the other drugs apparently did not follow any particular model, the release occurring as a diffusion process termed as non-Fickian.

An explanation can be given based on the porosity values of the pellets. Although the small absolute value was registered with the paracetamol and propranalol hydrochloride pellets, the porosity calculated for pellets obtained for the former (0.051) is double the porosity of the latter (0.026).

A lower drug solubility has already been related to higher MDT and AUC values (Blanqué et al., 1995) but for uncoated matrix type pellets. It was considered that, if a well-formed release controlling membrane was achieved, the drug solubility would be less important. It has been suggested that the release rate will be highly dependent on the pore diameter and tortuosity if insolubility of

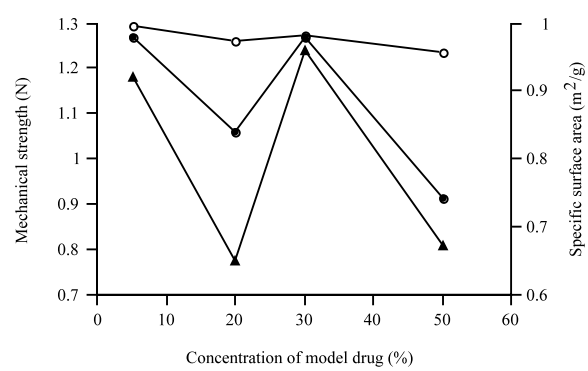

Fig. 2. Analysis of the specific surface area (▲), mechanical strength (●) and porosity (○) of pellets obtained with the same drug and filler at different combinations.

Table 2
Area under the dissolution profile curve (AUC), mean dissolution time (MDT), variance of dissolution time (VDT) and relative dispersion coefficient (RD) of ibuprofen, paracetamol, propranolol hydrochloride, ephedrine hydrochloride and sodium salicylate obtained from pellets of the formulation ILA, PaLA, PLA, ELA and SLA coated with Surelease E-7-7050 at 5% weight gain

Preparation	AUC (mg l^{-1} h)	MDT (h)	VDT (h^2)	RD
ILA 2:3:5	465.33 ± 4.32	4.65 ± 0.04	13.69 ± 0.35	0.63 ± 0.01
PaLA 2:3:5	192.45 ± 7.41	1.94 ± 0.08	5.07 ± 0.52	1.35 ± 0.03
PLA 2:3:5	209.01 ± 13.74	2.34 ± 0.22	7.23 ± 0.72	1.13 ± 0.16
ELA 2:3:5	116.03 ± 4.77	1.16 ± 0.05	1.78 ± 0.22	1.32 ± 0.07
SLA 2:3:5	56.01 ± 1.00	0.56 ± 0.01	0.16 ± 0.03	0.51 ± 0.11

Results are the mean and standard deviation of six replicates.

the solute in the coat material is assumed (Iyer et al., 1990). Applying the Korsemeyer equation to the data obtained with pellets containing drug and lactose, a value for the release constant was obtained. The *K* values obtained were plotted as a function of the drug solubility (Fig. 3) and confirmed the faster release of the drug as it's solubility increases.

The formulations studied in Group II were based on propranolol hydrochloride, lactose and Avicel systems (PLA). The drug load was successively increased as follows: 5, 10, 20, 30, 40 and 50% of the total pellet weight while the amount of lactose was decreased: 45, 40, 30, 20, 10 and 0%, respectively. The amount of Avicel remained constant at 50% of the total pellet weight. The results (Table 3) show that, if the drug release was driven only by a diffusional process, the results would be expected to be similar in terms of the dissolution profiles. However, as seen in Table 3 this was not the case. The MDT value increases from preparation PLA 0.5:4.5:5 to PLA 2:3:5 and then started to decrease.

For the lowest (5 and 10%) and highest (40 and 50%) drug levels, the release was fast but delayed when the drug was present at 20 and 30% level. As the filler present in this group of formulations (lactose) as well as the model drug (propranolol hydrochloride) are a constant feature of the formulation, this behaviour cannot be attributed to changes in the total solubility of the pellets, as both lactose and propanolol have similar solubilities. Presumably, there are structural differences in the pellets. The values of the constant of drug release, *K* calculated applying the Korsemeyer equation showed the same trend, as seen in Fig. 4.

According to the values of RD shown in Table 3, a first order release kinetic can be suggested for the preparations PLA 2:3:5, 3:2:5 and 4:1:5 while the other preparations seem to follow a non-Fickian diffusion. Confirmation of the release mechanism proposed was achieved by calculation of the theoretical release profiles according to the equations for the first order model.

The values of the specific surface area generally decreased as the concentration of propranolol hydrochloride increased, see Fig. 5. Preparations PLA 1:4:5 and 5:0:5 show a different trend which is probably due to the high drug load. Moreover, the behaviour of formulation PLA 5:0:5 is not surprising since this preparation has shown different physical characteristics, such as the aspect ratio and shape factor which could influence the film deposition (Sousa et al., in press). Despite this, the explanation for the dramatic difference between formulation PLA 2:3:5 and the others

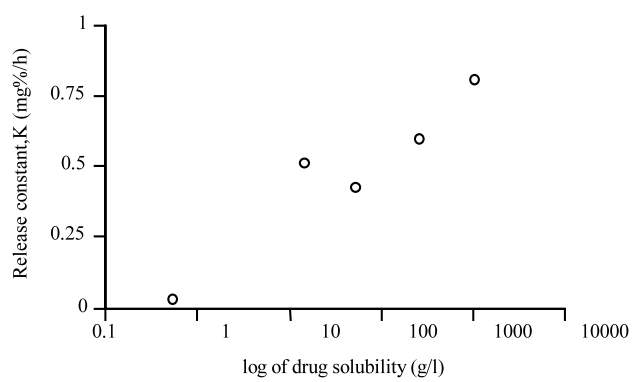

Fig. 3. Drug release constant, K as a function of the drug solubility.

Table 3
Area under the dissolution profile curve (AUC), mean dissolution time (MDT), variance of dissolution time (VDT) and relative dispersion coefficient (RD) of propranolol hydrochloride from pellets of the formulation PLA (propranolol hydrochloride content: 5, 10, 20, 30, 40 and 50%), coated with Surelease E-7-7050 at 5% weight gain

Preparation	AUC (mg l^{-1} h)	MDT (h)	VDT (h^2)	RD
PLA 0.5:4.5:5	68.32 ± 3.41	0.69 ± 0.03	0.24 ± 0.06	0.492 ± 0.08
PLA 1:4:5	95.08 ± 11.16	0.96 ± 0.12	1.15 ± 0.49	1.28 ± 0.72
PLA 2:3:5	209.01 ± 13.74	2.34 ± 0.22	7.23 ± 0.72	1.13 ± 0.16
PLA 3:2:5	126.27 ± 15.08	1.28 ± 0.15	1.70 ± 0.93	0.98 ± 0.30
PLA 4:1:5	70.43 ± 5.16	0.69 ± 0.04	0.54 ± 0.18	1.12 ± 0.26
PLA 5:0:5	64.83 ± 6.88	0.63 ± 0.04	0.24 ± 0.19	0.57 ± 0.36

Results are the mean and standard deviation of six replicates.

with respect to the MDT value could be associated with the specific surface area measured for these pellets. Using nitrogen as gas adsorbent it was possible to calculate the size and volume of pores as 186 and 0.002487 cm^3 g^{-1}, respectively. Ozturk et al. (1990) have already shown that pellets with a large surface area (0.2184 m^2 g^{-1} and an average pore diameter of 0.627 μm) gave a faster release rate when compared with a smaller area (0.0065 m^2 g^{-1} and an average pore diameter of 0.79 μm).

To evaluate the influence of the filler solubility, the model drug propranolol hydrochloride was combined with different fillers, at a lower level (20%), ranked according to their water solubility (glucose, mannitol, lactose, calcium phosphate and barium sulphate). The pellets of the resultant formulations, identified as PGA 2:3:5, PMA 2:3:5, PLA 2:3:5, PCA 2:3:5 and PBA 2:3:5, were then coated with Surelease E-7-7050 at 5% weight gain. The values of dissolution analysis are shown on Table 4.

As can be seen the MDT value obtained with the preparation PLA 2:3:5 is significantly different compared to the values obtained when the other fillers were used. Replacing the model filler (lactose) by the more soluble (glucose or mannitol) or more insoluble (barium sulphate) results in similar kinetic parameters. The odd result in this sequence was obtained with calcium phosphate which seems not to be related only to the porosity. For instance pellets made with calcium phosphate or barium sulphate despite the high porosity, showed a faster release compared with the model formulation. Actually pellets prepared with calcium phosphate as well as with barium sulphate (however to a lesser extent) repeatedly showed small pieces of the coat membrane floating in the dissolution vessel after 5–6 h. This was initially considered as a production error, and repeated batches were tried with the same result. The explanation for this behaviour can be found in the large specific surface area presented by pellets made with this filler in comparison with the others. The value of 12.9 m^2 g^{-1} measured with krypton adsorption analysis demonstrates the enormous labyrinth formed inside the matrix. This appears to result in a large ingress of dissolution fluid and subsequent break up of the pellets.

To analyse the influence of the filler solubility, present at a higher concentration, on the drug release profile from coated pellets the model drug propranolol hydrochloride was combined with different fillers, at a higher level (45%).

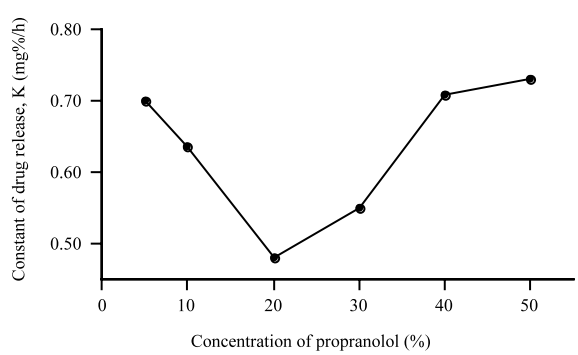

Fig. 4. Release constant of propranolol hydrochloride, K from preparations PLA 0.5:4.5:5.0, 1:4:5, 3:2:5, 4:1:5 and 5:0:5 as a function of the drug concentration (%).

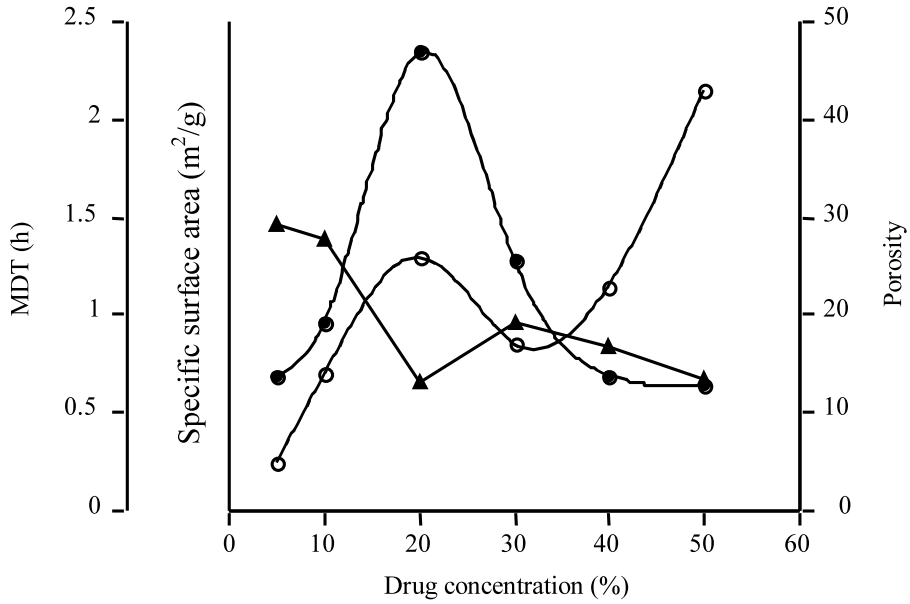

Fig. 5. Analysis of the (●) MDT, (○) porosity and (▲) specific surface area values showed by preparations based on propranolol hydrochloride as a function of its relative concentration (%) in the total pellet weight.

The dissolution profiles of the model drug maintained the same trend (Table 5) as observed when these fillers were used at a lower level except that the formulation with lactose (PLA 0.5:4.5:5.0) showed a drug release closer to the others. However, a faster release was observed with pellets made with both glucose and mannitol, which is not surprising if the potential increase in osmotic pressure is considered. On the other hand, the insoluble fillers showed more effectiveness in terms of sustained release than before.

The explanation of these findings can be related to the osmotic pressure inside the core as reported by Recki et al. (1995). The total osmotic pressure may be due to the core, i.e. from the drug itself and excipients i.e. sugar pellets which in addition to the solubility of the drug, may be a drug release rate regulating factor. This means that the release of the drug not only takes place by a classical diffusion process but can also be modulated by osmotic pressure.

The osmotic pressure is probably responsible for the rupture of the film. Actually, the appearance of the films obtained with 5% coat appears as a far from smooth surface and in some cases the membrane is rather porous when observed by scanning electron microscopy. The exterior appearance of the membrane was identical before and after the dissolution test, for the preparations formulated either with lactose or calcium phosphate. However, when glucose was used, the membrane after the dissolution test clearly contained numerous cracks. This behaviour seems to be related to the type of filler used but not to the shrinking of the cores during the dissolution.

3.2. General discussion

The values of AUC and MDT obtained with the uncoated and coated pellets (5% film load) were analysed by ANOVA, using a simultaneous pair comparison with the reference formulation PLA 2: 3:5 and the results are shown on Tables 6 and 7.

Although, the release of the different drugs from uncoated pellets, with the exception of preparation ILA 2:3:5, was almost instantaneous, the shapes of the dissolution profile curves were significantly different compared with the reference formulation. Only preparation PBA 2:3:5 showed

a similar release profile. Pellets coated with Surelease E-7-7050 at 5% weight gain showed similar behaviour dissolution patterns. The exception was preparation PaLA 2:3:5.

From the results in Tables 6 and 7, it can be concluded that the drug type, filler type and level as well as the coating amount behave as interacting factors with respect to the mean dissolution time of the drug. To analyse the influence of the drug and the filler type, studies within each set were carried out (uncoated pellets and coated at 5% weight gain). The objective was to exclude the influence of the variable film coating. The results of the analysis of variance performed are shown in Table 8 (uncoated pellets) and Table 9 (5% coated pellets). Analysing the data present in these tables it can be concluded that none of the factors can be considered as though it acts on its own because in all the three cases the interaction is significant and so, the preceding individual results, though statistically significant, cannot be used in a comparative study.

It is possible therefore, to conclude that the type of filler used in the production of pellets has a strong influence on the mean dissolution time of propranolol hydrochloride pellets. This observation means that the level of this filler is important when uncoated or coated pellets (with a low level of coat) are considered. On the other hand, the more soluble fillers maintained their relative position, in terms of solubility, showing a gradual increase in the MDT values, which does not suggest a clear influence of their amount. On the contrary, the presence of the more insoluble fillers seems to be identical for uncoated pellets while for 5% coated pellets only barium sulphate followed the 'solubility rule'. The anomalous behaviour of calcium phosphate has already been discussed.

3.3. Canonical analysis

The ANOVA already showed that the independent variables drug level and solubility, filler level and solubility and level of film coat can have an influence on the dependent variables AUC and MDT. To identify the possible relationship and predict the behaviour of the dependent variables related to the dissolution pattern of the model drug (propranolol hydrochloride), a canonical analysis was performed.

3.3.1. Canonical analysis for drug release

The coating levels studied (0 and 5%) and the result in the dissolution performance of propranolol hydrochloride were analysed. The Wilks test confirms a significant interdependence between the independent (X) and dependent (Y) variables ($\Lambda = 0.342$; F approximately $= 6.67$ ($f_1 = 10$; $f_1 = 94$); $P < 0.001$).

3.3.2. Measures of redundance g

These values can explain which part of the whole variance of one range can be explained by the canonical variables of the other range of variables.

$g^2_{Y/U}$:12.47%; $g^2_{X/V}$:63.9%

With the values obtained only a part of the results (63.9%) can be explained by the canonical

Table 4
Area under the dissolution profile curve (AUC), mean dissolution time (MDT), variance of dissolution time (VDT) and relative dispersion coefficient (RD) of propranolol hydrochloride from pellets produced with the lower level of filler (glucose, mannitol, lactose, calcium phosphate and barium sulphate) and coated with Surelease E-7-7050 at 5% weight gain

Preparation	AUC (mg l^{-1} h)	MDT (h)	VDT (h^2)	RD
PGA 2:3:5	81.18 ± 5.61	0.81 ± 0.06	1.97 ± 0.57	2.97 ± 0.55
PMA 2:3:5	81.00 ± 8.95	0.80 ± 0.09	1.69 ± 0.82	2.45 ± 0.71
PLA 2:3:5	209.01 ± 13.74	2.34 ± 0.22	7.23 ± 0.72	1.13 ± 0.16
PCA 2:3:5	66.07 ± 9.65	0.64 ± 0.10	0.54 ± 0.35	1.21 ± 0.54
PBA 2:3:5	93.16 ± 11.12	0.93 ± 0.11	1.54 ± 0.65	1.86 ± 0.49

Results are the mean and standard deviation of six replicates.

Table 5
Area under the dissolution profile curve (AUC), mean dissolution time (MDT), variance of dissolution time (VDT) and relative dispersion coefficient (RD) of propranolol hydrochloride from pellets produced with the higher level of filler (glucose, mannitol, lactose, calcium phosphate and barium sulphate) and coated with Surelease E-7-7050 at 5% weight gain

Preparation	AUC (mg l^{-1} h)	MDT (h)	VDT (h^2)	RDC
PGA 0.5:4.5:5	54.22 ± 0.82	0.54 ± 0.01	0.07 ± 0.03	0.22 ± 0.09
PMA 0.5:4.5:5	69.45 ± 4.39	0.69 ± 0.04	0.76 ± 0.33	1.51 ± 0.53
PLA 0.5:4.5:5	68.32 ± 3.41	0.69 ± 0.03	0.24 ± 0.06	0.49 ± 0.08
PCA 0.5:4.5:5	81.27 ± 11.51	0.82 ± 0.12	1.33 ± 0.78	1.82 ± 0.66
PBA 0.5:4.5:5	122.63 ± 16.83	1.21 ± 0.69	3.09 ± 1.19	2.03 ± 0.46

Results are the mean and standard deviation of six replicates.

variables. Looking back to the interranging communality values it is obvious that the dissolution performance of the model drug was influenced by the independent variables to a certain degree, but also here are unknown influence factors to consider.

3.3.3. Interranging communalities d

The values calculated are as shown in Table 10, indicating that at least some of the independent variables had an influence on the dissolution performance of the pellets. It can be expected however, that some of the variability observed cannot be explained fully as the values of d indicate an interdependence on the interdependent variables of about 64%, the remaining 36% remaining resolved.

3.3.4. Significant influence factors

1. AUC: this dependent variable was shown to be influenced by the drug solubility ($P = 0.006$), drug level ($P = 0.021$) and the presence of a coat ($P < 0.001$).
2. MDT: in the same way as obtained for the AUC, the MDT values are also statistically dependent on the drug solubility ($P = 0.005$), drug level ($P = 0.018$) and the presence of a coat ($P < 0.001$).

For both dependent variables the coat level appeared as the most important influencing factor. This is not surprising because with respect to coated pellets it is assumed that the membrane is actually the sustained release device. However, it is also important to notice that the drug solubility also showed a high level of significance, which proves that the choice of a coat membrane should take into consideration the type of drug to be incorporated. To a lesser extent, it is important to underline the influence of the amount of the drug. This result can provide helpful information in the

Table 6
ANOVA for AUC (area under the dissolution profile curve expressed in mg l^{-1} h) of preparations of Group I, II, III and IV, by comparison with formulation PLA 2:3:5

Group	Preparation	F ratio 0% coat (1)	5% coated (2)
I	PLA 2:3:5	Standard	Standard
	ILA 2:3:5	96610***	2384.83***
	PaLA 2:3:5	15.64***	9.95*
	ELA 2:3:5	206.60***	313.81***
	SLA 2:3:5	357.60***	849.72***
II	PLA 0.5:4.5:5	365.18***	718.49***
	PLA 1:4:5	238.82***	471.16***
	PLA 3:2:5	44.18***	248.50***
	PLA 4:1:5	74.66***	697.10***
	PLA 5:0:5	77.56***	754.58***
III	PGA 2:3:5	228.66***	593.14***
	PMA 2:3:5	147.15***	594.81***
	PCA 2:3:5	204.22***	741.65***
	PBA 2:3:5	127.68***	487.18***
IV	PGA 0.5:4.5:5	346.37***	869.72***
	PMA 0.5:4.5:5	127.68***	706.99***
	PCA 0.5:4.5:5	228.66***	592.31***
	PBA 0.5:4.5:5	1.00	270.84***

Variance between classes: $12609.79^{(1)}$; $56572^{(2)}$; Variance in the class: $1.086^{(1)}$; $82.64^{(2)}$; F values: $11606^{(1)}$; $684.51^{(2)}$. 1st DF 17 (FG1 = 1); 2nd DF 90 (FG2 = 10).

* $P \leq 0.05$.

*** $P \leq 0.001$.

Table 7
ANOVA for MDT (mean dissolution time in hours) of preparations of Group I, II, III and IV, by comparison with formulation PLA 2:3:5

Group	Preparation	*F* ratio	
		0% coat (1)	5% coated (2)
I	PLA 2:3:5	Standard	Standard
	ILA 2:3:5	38683***	460.30***
	PaLA 2:3:5	4.15	13.80**
	ELA 2:3:5	66.46***	120.11***
	SLA 2:3:5	125.66***	273.31***
II	PLA 0.5:4.5:5	125.66***	234.85***
	PLA 1:4:5	84.12***	164.28***
	PLA 3:2:5	16.62**	96.92***
	PLA 4:1:5	25.96***	234.85***
	PLA 5:0:5	25.96***	252.24***
III	PGA 2:3:5	84.12***	201.93***
	PMA 2:3:5	50.89***	204.58***
	PCA 2:3:5	66.46***	249.30***
	PBA 2:3:5	37.39***	171.50***
IV	PGA 0.5:4.5:5	125.66***	279.49***
	PMA 0.5:4.5:5	37.39***	234.85***
	PCA 0.5:4.5:5	84.12***	199.30***
	PBA 0.5:4.5:5	1.00	110.15***

Variance between classes: $1.334^{(1)}$; $5.860^{(2)}$; Variance in the class: $0.00028^{(1)}$; $0.00347^{(2)}$; *F* values: $4618^{(1)}$; $168.52^{(2)}$. 1st DF 17 (FG1 = 1); 2nd DF 90 (FG2 = 10).

** $P \leq 0.01$.

*** $P \leq 0.001$.

formulation design. As pellets are considered a suitable carrier form for high dosage products it should be interesting to look at the prediction of the release profile from these influence factors.

3.4. Calculation of the regression equations

AUC—The effect of the independent variables studied on the AUC can be expressed by the following equation:

$$\mathrm{AUC} = 29.435 \times \mathrm{coat} - 0.0184 \times (\mathrm{drug\ level})^2 - 31.969 \times \ln(\mathrm{drug\ sol.}) + 150.993$$

which is characterised by a $F = 66.77$. Although the statistical significance ($P < 0.001$) of this equation is high, the RMS value obtained (47.43%) denotes that other factors outside of the experimental design are involved.

Table 8
Influence of the independent variables filler level and type on the MDT (h) of propranolol hydrochloride calculated from uncoated pellets made with formulations of Group III and IV

Variables	SS	DF	*F* values
Filler level[a]	0.018	1	159.06[c]
Filler type [b]	0.070	4	156.26[c]
Level * Type	0.034	4	75.09[c]

[a] Filler level: L1, 30% on a weight basis; L2, 45% weight basis.

[b] Filler type defined according to its solubility: F1, glucose; F2, mannitol; F3, lactose; F4, calcium phosphate: F5, barium sulphate.

[c] $P = 0.001$; DF, degrees of freedom for variance within the group: 50; degrees of freedom for total variance, 59; SS, some of squares.

The regression analysis makes the assumption that the AUC increases as the coat level increases. However, when the drug level increases, the AUC decreases which suggests that high drug loaded pellets show a faster release. The relation of AUC with the drug solubility also suggests that an increase in the solubility provides a faster release. However, this being a logarithmic relationship, this variable shows high influence for small changes in the range of drug solubility, as well as small changes when the solubility is high.

MDT—the application of the same concepts as for AUC, leads to the equation

Table 9
Influence of the independent variables filler level and type on the MDT (h) of propranolol hydrochloride calculated from pellets coated with Surelease E-7-7050 at 5% weight gain, made from formulations of Group III and IV

Variables	SS	DF	*F* values
Filler level[a]	1.432	1	117.42[c]
Filler type [b]	6.135	4	125.74[c]
Level * Type	7.318	4	150.00[c]

[a] Filler level: L1, 30% on a weight basis; L2, 45% weight basis.

[b] Filler type defined according to its solubility: F1, glucose; F2, mannitol; F3, lactose; F4, calcium phosphate: F5, barium sulphate.

[c] $P = 0.001$; DF, degrees of freedom for variance within the group: 50; degrees of freedom for total variance, 59; SS, some of squares.

Table 10
d-values and their significance levels for the range of variables assessed by canonical analysis

Variables	d value	Significance level
d^2_{AUC}	0.638	$P<0.001$
d^2_{MDT}	0.639	$P<0.001$

$$\mathrm{MDT} = 0.3007 \times \mathrm{coat} - 0.0002 \times (\mathrm{drug\ level})^2 - 0.3278 \times \ln(\mathrm{drug\ sol.}) + 1.5517$$

which is characterised by a F of 66.54. Again the level of significance ($P < 0.001$) denotes the influence of these independent variables on the dissolution behaviour of the drug. The assumptions made for the AUC are valid for the MDT although the high variability of the results still remains (RMS = 47.79%).

4. Conclusions

The analysis of the influence of the pellet formulation as well as a coating membrane shows that the drug release from uncoated pellets is mainly influenced by the solubility of the drug. When soluble and slightly soluble drugs are present the release is almost instantaneous, when there is no coat. The different fillers have no influence on sustaining the release of drugs from uncoated pellets.

Although specific mechanisms of drug release were found for some preparations, it is not possible to attribute a general mechanism for drug release from uncoated pellets.

Except for the lowest soluble drugs, the total drug recovered from uncoated pellets reaches 100% within 1 h. Differences in the release profiles were only noticed at the first sample collections. However, a high level of insoluble fillers can extend this interval slightly.

Pellets coated with an ethylcellulose dispersion at a 5% weight gain showed an influence of the coat membrane on the drug release. Although the drugs followed the 'solubility rule', unexpected results could be explained by analysing the physical characteristics of the core of the pellet such as porosity and specific surface area. The knowledge of the pellet structure, such as pore diameter and volume is of great importance as a porous structure could decrease the film adhesiveness.

The amount of polymer applied was insufficient to ensure that for all the drugs, the release kinetics followed a diffusion control mechanism. Very soluble drugs were released faster than low soluble drugs and although the coat delayed the release this effect did not last for more than 2 h. The amount of drug present (drug load) was an interacting factor. High soluble fillers gave the fastest release. However, the compacted structure of the pellet obtained with mannitol can influence the drug release constant. The osmotic pressure generated inside the coat membrane is responsible for its rupture with consequent effect on the release profile. The insoluble fillers showed poor film adhesion, which led to the disintegration of the membrane in a process that was seen as time dependent. The influence of the filler solubility was less important when the fillers were used at a lower level. This is in agreement with the diffusional process that is expected from coated pellets. However, the high content of insoluble fillers together with lower levels of the drug led to the formation of a complex structure that resulted in difficulties in drug release. The complex aspect of the insoluble material present inside the core after the dissolution test can explain the delay observed with these preparations.

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