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EVALUATION OF THERMAL AND FILM FORMING PROPERTIES OF ACRYLIC AQUEOUS POLYMER DISPERSION BLENDS : APPLICATION TO THE FORMULATION OF SUSTAINED-RELEASE FILM COATED THEOPHYLLINE PELLETS

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ABSTRACT

Aqueous acrylic polymer dispersions were blended in order to improve processing and film formation from acrylic polymers with poor film forming properties and/or to obtain sustained-release film coated pellets with optimal barrier properties according to the physico-chemical and pharmacokinetic requirements of the active substance.

Heterogeneous film structures are generally obtained from blends containing an association of hard acrylic polymers (Eudragit® RS30D, S100) with the soft Eudragit® NE30D when the drying temperature is lower than the minimum film forming temperature (MFT) of the hard acrylic polymers. The Tg and MFT values of the hard acrylic polymers are not modified in the presence of the soft polymer as shown by the thermograms of these blends which are generally characterized by two individual glassy transitions.

On the other hand, a wide range of drug dissolution profiles can be obtained from film coated pellets either by using, in different proportions, the insoluble but readily permeable Eudragit® RL30D in association with the less permeable Eudragit® RS30D in order to obtain pH-independent permeability membrane, or by mixing the anionic methacrylic acid copolymers (L30D, S100) with the neutral NE30D in order to obtain pH-dependent permeability film coated pellets showing higher dissolution release rates at intestinal pH values.

INTRODUCTION

When formulating modified-release film coated oral dosage forms, it is unlikely to meet the objectives set for the final product by using one single polymer.
The development of these forms indeed requires the knowledge of the physico-chemical and pharmacokinetic properties of the active substance, especially the solubility at the physiological pHs and the absorption rate and extent at the different sites of the gastrointestinal tract.
It is thus obvious that the formulation of sustained-release forms like film coated pellets requires specific membrane properties for each particular case. The great deal of flexibility in formulation of these forms allows to design, for most drugs, high quality pharmaceutical dosage forms (1).
The use of pharmaceutical film coating additives like plasticizers (2-4), insoluble powders (5-7) or pore forming agents (8, 9), is often necessary to improve the workability and to obtain optimal barrier properties.
For the same reasons, the use of polymer blends, might offer a wide range of applications for the formulation of film coated controlled-release dosage forms.
As examples, acrylic polymers in form of aqueous dispersions (30 % solids) or dispersible powders (10) like neutral ethylacrylate-methylmethacrylate copolymer (Eudragit® NE30D), slightly cationic hydrophilic polymethacrylates (Eudragits® RS30D and RL30D) and anionic methacrylic acid copolymers (Eudragits® L30D, L100-55, L100 and S100) can be mixed together without major difficulties (11).
As for the blends of polymer solutions, care must be taken when aqueous polymeric dispersions are mixed, especially when ionic interactions are expected. Furthermore, additional special attention is required when using latex aqueous dispersions stabilized by different emulsifier systems and/or having different pHs (12).
In some cases, a moderate agglomeration of latex particles can be observed, however this phenomenon does not remarkably affect the workability of the mixed dispersions.
Some of the properties of acrylic polymers, which might influence the mixing of latices, are summarized in table 1.
Eudragit® NE30D is a very soft and flexible material which could be blended with aqueous dispersions of hard polymers in order to lower the softening temperature (Ts) or the minimum film forming temperature (MFT) of the combined film (10, 13) resulting in improved processing and better film properties.
In the same manner, it is possible to obtain films of graded pH-independent permeability by mixing, in any proportions slightly cationic hydrophilic (RS30D, RL30D) and neutral (NE30D) acrylic polymers.
Finally, the anionic acrylic polymers with graded solubility in the pH-range of 5.5 to 7.0 can be mixed without any problems with the neutral or in limited amounts with the cationic hydrophilic acrylic polymers. The permeability of films obtained from these blends increases at intestinal pHs as a function of the content of

TABLE 1
Some Properties and Miscibility Characteristics of Commercially Available Acrylic Polymers used in Aqueous Film Coating

Eudragit types	Dispersion type	Characteristics	Additives and pH	Miscibility and special precautions
Neutral methacrylic ester copolymer (neutral) Eudragit NE30D	Latex	soft, medium permeability	PNP pH ~ 7.5	In any proportions with anionic and cationic polymers, adjust pH to 5-6
Hydrophilic methacrylic ester copolymers (cationic)	Pseudolatex (solvent change)	medium	Sorbic acid pH ~ 5	Critical with anionic polymers, addition of neutral surfactant
Eudragit RS30D		low permeability		
Eudragit RL30D		high permeability		
Methacrylic acid copolymers (anionic)				In limited amounts with cationic polymers,
Eudragit L30D	Latex	medium, soluble pH > 5.5	Tween 80 + SLS pH ~ 2.5	cationic latex particles have to be stabilized
Eudragit L100-55	dispersible	medium, soluble pH > 5.5	-	with a solution of
Eudragit L100	powders	hard, soluble pH > 6.0	-	anionic polymer,
Eudragit S100	(spray dried)	hard, soluble pH > 7.0	-	adjust pH to ~ 5

PNP : Polyoxyethylene nonyl sulfate
SLS : Sodium lauryl sulfate

anionic enterosoluble polymers. Such coatings could be especially useful for drugs like theophylline (14, 15) or metoprolol (16) which are well absorbed through the GI tract but with a slower absorption rate in the colon (small absorptive area) or for drugs showing reduced solubility at intestinal pH values.

The aim of this study is to determine the influence of the use of blends of acrylic aqueous dispersions on the properties of the films obtained using theophylline as the model drug whose solubility is pH-independent.

The influence of mixing a soft acrylic polymer (NE30D) with a medium (RS30D) or a hard polymer (S100) on the thermal and film forming properties of the blends was firstly studied.

Then, sustained-release film coated pellets were prepared by mixing acrylic polymers presenting different permeability properties (pH dependent or pH independent) in order to obtain a wide range of dissolution profiles.

EXPERIMENTAL

Materials

The different acrylic polymers in the form of aqueous dispersions or dispersible powders (Eudragits®) were supplied by Röhm Pharma GmbH (Darmstadt, Germany). Pharmacoat 606® (hydroxypropyl methylcellulose, Seppic, France) is used after dispersion in distilled water (10 % w/w). Talc with a mean particle size of approximately 9 μm (Aldrich chemical Co Ltd, England), Citroflex A2® (acetyl triethylcitrate, Reilly chemicals, Belgium) and antifoam emulsion (silicone emulsion,Vel S.A. Belgium) were used as received. Theophylline pellets containing 80 % drug and obtained by the extrusion-spheronization process were supplied by SMB Technology, Brussels.

Methods

Preparation of Coating Dispersions

The blends of the acrylic polymers were prepared taking into account the composition and the pH of each aqueous dispersion (12) in order to avoid excessive agglomeration of the latex particles. The following aqueous dispersion blends were prepared :

Eudragits® RS30D/RL30D :	(10:0), (9:1), (8:2), (7:3), (5:5), (0:10)
Eudragits® NE30D/L30D :	(10:0), (9:1), (8:2), (7:3)
Eudragits® NE30D/S100 :	(10:0), (9:1), (8:2), (7:3)
Eudragits® NE30D/L30D/S100 :	(8,5:0.5:1), (8:1:1), (7:1:2), (7:2:1)

The different aqueous dispersions used for coating the theophylline pellets are given in table 2.
Talc was previously dispersed in water in presence of an antifoam agent and mixed with the required quantities of Pharmacoat 606.
Dispersions containing Eudragit® RS30D and RL30D, require the addition of 20% (related to film former) acetyl triethylcitrate (ATEC) as plasticizing agent. The plasticizer was added to the polymer aqueous dispersions under gentle stirring. Then all the components of the coating dispersion were blended and the stirring was continued for one hour before starting the coating process.
Each coating dispersion contains 12.5% w/w acrylic polymer blend.

Preparation of Coated Pellets

Known weight of pellets (800 g) was transferred into the fluidized-bed coating apparatus (Uni-Glatt, Glatt GmbH, Germany), equipped with a bottom-

TABLE 2
Sustained-Release Formulations used for the Coating of Theophylline Pellets

Formulation	NE30D/L30D blends	NE30D/S100 blends	NE30D/L30D/S100 blends	RS30D/RL30D blends
Acrylic polymer (dry basis)	100.0	100.0	100.0	100.0
Citroflex A2 (g)	-	-	-	20.0
Pharmacoat 606 (g)	5.0	2.0	2.0	2.0
Talc (g)	25.0	25.0	25.0	25.0
Antifoam (g)	1.0	1.0	1.0	1.0
Water (g)	669.0	672.0	672.0	652.0
Solids content (%w/w)	16.3	15.9	15.9	18.4
Coating level (%)	9.2	11.9	11.7	9.9

spray coating process in a Würster column (17, 18), and coated with the various dispersions until the desired film weight was deposited.

During the coating operations, the aqueous dispersions were stirred continuously to prevent sedimentation of the insoluble particles. The inlet and the outlet temperatures of the drying air during the coating procedure were respectively 35 $\pm$ 1°C (40 $\pm$ 1 °C for RS30D:RL30D blends) and 28 $\pm$ 1°C (32 $\pm$ 1 °C for RS30D:RL30D blends). Coating dispersions were pumped at a flow rate of 10 ml/min and the pneumatic spraying pressure was 1 bar. The total spraying time laid between 50 to 70 minutes.

The coated pellets were dried in the same apparatus during 10 minutes at the same inlet temperature and then were cured at 60 °C and 50% relative humidity for 24 hours.

The coating level of each batch of coated pellets was determined by measuring the drug content of the uncoated and coated pellets. The drug loading determined for each individual batch of coated pellets was used in dissolution studies as the value representing 100% of the drug released from pellets.

In vitro Dissolution Studies

In vitro dissolution tests were performed using the USP dissolution apparatus n° 2 (paddle) at 37.0 °C with a stirring rate of 60 rpm. The dissolution medium was a phosphate-acetate buffer (0.05 M) containing 0.05% w/w Polysorbate 20.

The dissolution tests were conducted in test media simulating the pH variations in the GI tract. The initial volume and pH of the dissolution media were respectively 900 ml and 1.3.

At predetermined intervals, 4N NaOH solution was added with an automatic burette (Radiometer ABU80) connected to an automatic titrator (Radiometer TTT80) and a pH Meter (Radiometer pHM 82) in order to carry out variation of the pH programmed as follows: 0-1.0 h, pH 1.3; 1.0-1.5 h, pH 5.0; 1.5-4.5 h, pH 6.3; 4.5-7.5 h, pH 6.9; 7.5-12 h pH 7.2.
Samples of coated pellets (n=5), equivalent to 100 mg of theophylline, were placed in the dissolution medium and the drug release was assayed spectrophotometrically (272 nm) using the Philips PU 8605/60 Tablet Dissolution Monitoring System.
On the other hand, in-vitro dissolution tests were performed at different constant pHs (1 to 7) using the same buffer composition, in order to determine the influence of pH on drug release from coated pellets. The drug release profiles obtained are presented under a multi-dimensional topographic representation (19).

Differential Scanning Calorimetry

Thermal analysis was performed on the different acrylic polymers alone and on the different blends using a Perkin Elmer DSC-7 differential scanning calorimeter / TAC-7 thermal analysis controller with an intracooler-2 cooling system for subambient determinations (-70°C). Aluminium pans and lids were used for samples and temperature calibrations were performed using cyclohexane and indium as standards. Aqueous dispersed samples were dried (5 hrs at 40 °C) after the mixing operation in the aluminium pans and then sealed. All samples were run at a scanning rate of 10°C/min using nitrogen as effluent gas.
The determinations of transition temperatures (Tg_{onset}, n=3) and spreads (Tg_{spread}) were carried out by a computerized procedure.
The determinations of the minimum film forming temperature (MFT) were carried out using an isothermal mode procedure. The aqueous dispersions were placed in open pans and the minimum temperature above which a continuous, transparent film is formed was determined.

RESULTS AND DISCUSSION

Glass Transition and Minimum Film Forming Temperatures of Polymer Blends

Considering that the deformability of the polymer latices under specified conditions is one of the most important parameters of the film formation mechanism(20, 21), the soft acrylic polymer dispersion (NE30D) was blended with the hardest acrylic polymers in order to decrease the thermal-mechanical properties of the latter and consequently, to improve their film forming properties.
The thermogram of a polymer (22, 23) generally presents an endothermic jump in the heating curve (second order transition) which can be characterized by a

point, i.e. the onset (Tg_{onset}), the mid point (Tg) or the end point (Tg_{end}) of the glass transition. A relatively large spread may exist between the beginning and the end of the transition (Tg_{spread}).

The glass transition and minimum film forming temperatures of the different acrylic polymer blends determined by DSC are shown in table 3. The thermograms of the blends are characterized by two individual glass transition temperatures unlike what is usually observed with blends of totally miscible and compatible polymers which are characterized by only one intermediate transition temperature. The first transition temperature of the blend (Tg_a) corresponds to the Tg_{onset} of the soft acrylic polymer (NE30D) and the second one (Tg_b) to the Tg_{onset} of the hardest polymer (RS30D or S100).

Furthermore, the temperature spreads between the beginning and the end of the transition of the softer polymer (Tg_{spread}) are increased for the blends (respectively 84 and 85 °C for NE30D/S100 and NE30D/RS30D (5:5) blends) in comparison with the Tg_{spread} value (38 °C) observed for the softer polymer alone. Because of this increase of the transition spread, the second endothermic jump due to the hard polymer is difficult to evaluate, especially when the Tg values of the two polymers are close to one another. As examples, the second transition temperature of NE30D/RS30D blends is only apparent for high concentrations (2:8) of the hardest polymer whereas for the NE30D/S100 blends it can be evaluated already at low contents of the hard polymer (Table 3).

Finally, despite the fact that film formation is effective at relatively low temperatures, the films obtained from these blends are generally cloudy (heterogeneous) when the drying temperature is several degrees under the MFT of the hardest acrylic polymer. Considering the MFT as the temperature above which a continuous and transparent film is formed, the MFT values of the blends were practically not decreased in presence of the soft polymer.

Regarding these results, we can assert that the use of the soft acrylic polymer does not have any effective plasticizing effect on the Tg and MFT of the hard acrylic polymer. Therefore, the films obtained from blends are heterogeneous as they contain a continuous phase of the soft polymer in which is embedded uncoalesced latex particles of the hard polymers. In order to avoid the formation of highly porous films, it is recommended to use blends with low hard acrylic polymer contents.

The formation of a continuous film is possible either by increasing the drying temperatures above the film forming temperature of the blends or by adding effective plasticizers (2, 3, 20) in order to decrease the Tg and MFT values of the hardest polymer.

Blends of Eudragit® RS30D and RL30D, having very close thermal properties, were also realised. The thermograms obtained are totally superposable whatever the composition of the blends. The film formation properties of these blends are equivalent to those of the polymers considered separately.

Pellets Coated with pH-independent Permeability Polymer Blends

The hydrophilic slightly cationic pseudolatices (RS30D and RL30D) have similar composition and pH values and therefore, can be mixed together in any

TABLE 3
Glass Transition and Film Forming Temperatures of different Acrylic Polymer Blends determined by DSC

Acrylic polymer blends	Tg_a (°C)	Tg_{spread} (°C)	Tg_b (°C)	MFT (°C)
Eudragit NE30D	- 8	38	-	< 10
NE30D/S100 (8:2)	- 9	54	148	75
NE30D/S100 (5:5)	- 10	84	151	83
NE30D/S100 (2:8)	- 9	58	149	81
Eudragit S100	146	18	-	84
NE30D/RS30D (8:2)	- 9	62	-	30
NE30D/RS30D (5:5)	- 8	85	-	32
NE30D/RS30D (2:8)	- 11	60	28	35
Eudragit RS30D	52	31	-	35

proportions, without special precautions, to obtain graded permeability films (24). The permeability of these films does not depend on the pH of the dissolution media (11) and the diffusion rate through such films depends to some extent on the nature of the drug.

The drug release rates from theophylline pellets coated by using these polymeric blends are shown in figure 1. A wide range of dissolution profiles is obtained simply by changing the ratios of the two polymers. Compared to the dissolution results of the uncoated pellets, the theophylline release is very slow and practically linear as a function of time with Eudragit® RS30D while practically unmodified with Eudragit® RL30D coated pellets.

Therefore, the use of the readily permeable Eudragit® RL30D appears to be as effective as the use of pore forming agents or hydrosoluble polymers for controlling the membrane permeability, so that the design of film coated pellets can be easily realised by selecting the proper RS30D/RL30D ratio and coating thickness.

Pellets Coated with pH-dependent Permeability Polymer Blends

The mixing of neutral acrylic polymer (NE30D) and anionic methacrylic acid copolymers (Eudragits® L30D, L100-55, L100 and S100) is possible in any proportions, when the pH of the anionic polymer dispersions is adjusted to 5. The mixing of hydrophilic slightly cationic acrylic polymers with anionic acrylic polymers is critical (ionic interactions) because it may induce some agglomeration of the latex particles. The mixing operations (12) for these blends are tedious and therefore was not considered in this study.

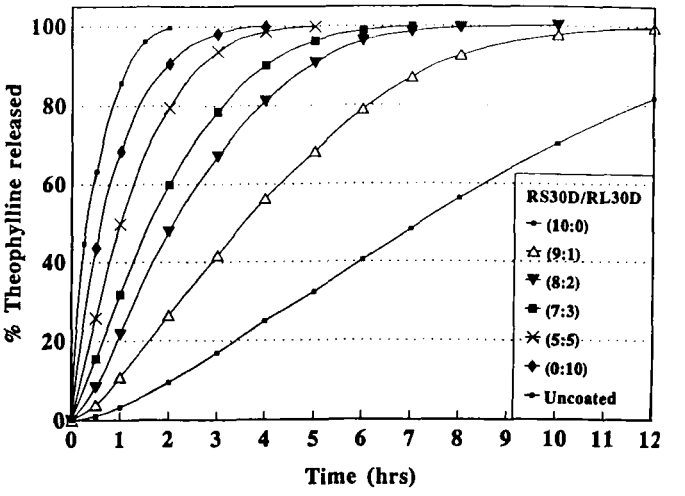

FIGURE 1

Influence of mixing different proportions of Eudragits® RS30D/RL30D on theophylline release profiles from film coated pellets at pH 7 (9.9% coating level)

The effect of blending, in different proportions, Eudragit® NE30D with L30D or aqueous dispersed S100 on the theophylline release rates in the pH-gradient dissolution media are shown in figures 2 and 3 respectively.

In each case, the drug release rate was significantly accelerated when the pH of the dissolution media is progressively increased up to the dissolution pH of the anionic acrylic polymer contained in the blend. This phenomenon can be explained by the higher porosity and permeability of these films after dissolution of the enteric fraction at intestinal pH values.

The acceleration of the drug release is obviously dependent on the proportion of the enteric polymer present in the blend, the higher is the enteric polymer content, the higher is the dissolution pH-dependency of the dosage form.

On the other hand, the drug release is much more delayed in the case of NE30D/S100 blends when compared with the NE30D/L30D because the pH of dissolution of Eudragit® S100 is higher than that of Eudragit® L30D.

In order to decrease the dependency of release rates on the pH variations and to optimize the drug release profiles, blends containing the three above mentioned acrylic polymers were used. As shown in figure 4, a practically constant theophylline release rate is obtained during the pH-gradient dissolution tests for the lowest content (8.5:0.5:1) of anionic polymers, with a very slight increase of the drug release rate occurring when the pH of the dissolution fluid is increased from 5.0 to 7.2.

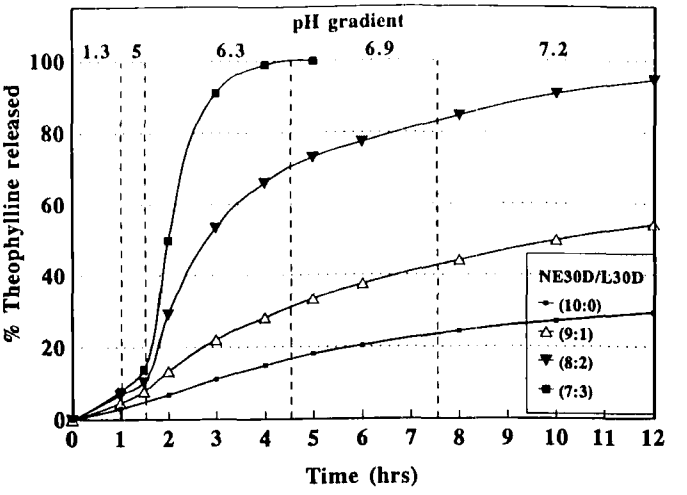

FIGURE 2

Theophylline release profiles from pellets coated with blends containing different proportions of Eudragits® NE30D/L30D in the pH-gradient dissolution medium (9.2 % coating level)

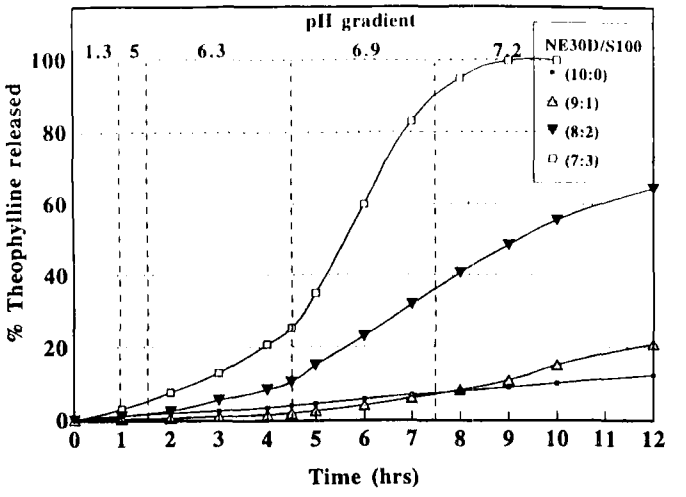

FIGURE 3

Theophylline release profiles from pellets coated with blends containing different proportions of Eudragits® NE30D/S100 in the pH-gradient dissolution medium (11.9 % coating level)

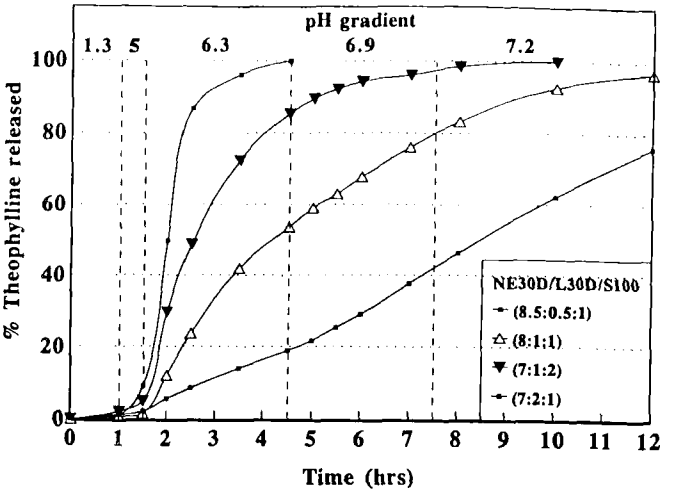

FIGURE 4

Theophylline release profiles from pellets coated with blends containing different proportions of Eudragits® NE30D/L30D/S100 in the pH-gradient dissolution medium (11.7 % coating level)

The tridimensional topographical representation of the drug release *vs* time and pH for theophylline pellets coated with NE30D/L30D/S100 (8.5:0.5:1) blend is shown in figure 5. This multidimensional representation appears to be more striking and accurate than the classical two dimensional plots for the evaluation of the influence of pH on drug release from controlled-release dosage forms. Consequently, this method is also useful to predict the in vivo release of drug at the different sites of the GI tract and to evaluate the potential influence of foods on drug absorption.

Figure 5 shows that the theophylline release occurs at pH values ranging from 1 to 7, with a significant increase of the drug release rates above pH 5, when the enteric polymers start to dissolve. On the contrary, the theophylline release rate from the Eudragit® NE30D coated pellets is practically independent on pH because this polymer is totally insoluble in the GI fluids (figure 6).

Careful examination of the results shown in figures 5 and 6 indicates that, despite the same coating levels, the drug release rate at pH 1-4 is higher for pellets coated with the NE30D/L30D/S100 (8.5:0.5:1) blend (approximately 60 % theophylline release within 20 hrs) than for pellets coated with Eudragit® NE30D alone (approximately 20 % theophylline release within 20 hrs) although both coating materials are insoluble at this pH range.

This phenomenon can be explained by the heterogeneous and thus more porous

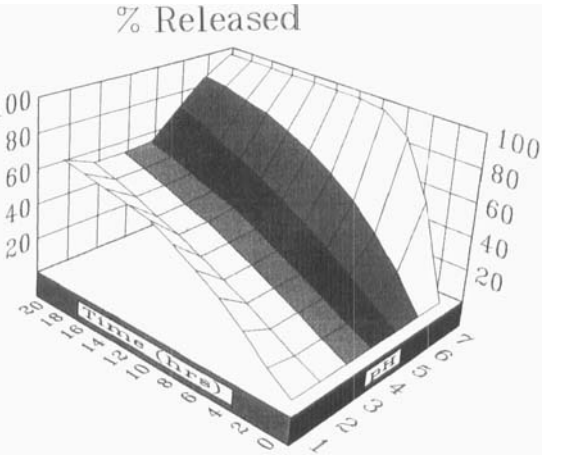

FIGURE 5

Tridimensional topographic representation of theophylline release as a function of time and pH for pellets coated with Eudragits® NE30D/L30D/S100 (8.5:0.5:1) mixture (11.7 % coating level)

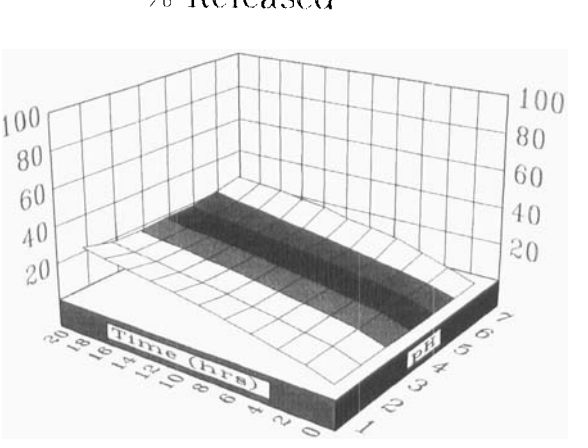

FIGURE 6

Tridimensional topographic representation of theophylline release as a function of time and pH for pellets coated with Eudragits® NE30D (11.9 % coating level)

film structure obtained when a hard polymer like Eudragit® S100 is used in polymer blends. Nevertheless, the increase of the drug release rate resulting from a higher porosity of the membrane can be easily compensated by increasing the coating thickness.

CONCLUSIONS

The use of mixtures of aqueous acrylic polymer dispersions in the formulation of sustained-release film coated pellets seems to be a very useful formulation tool in order to either improve film formation properties of acrylic polymers with poor film forming characteristics (Eudragit® S100) at the usual working temperatures or to control the release rate of drugs according to their solubility and pharmacokinetic requirements.

Membrane permeability of film coated theophylline pellets can be controlled by mixing, in any proportions, the insoluble but readily permeable Eudragit® RL30D with the less permeable Eudragit® RS30D in order to obtain a wide range of drug release profiles

In the same manner, the association of anionic methacrylic acid copolymers (Eudragits® L30D, S100) with the neutral acrylic polymer (NE30D) allows to obtain pH-dependent permeability film coated pellets showing higher release rates at intestinal pH values.

Although the film formation and the properties of the films are improved by the use of soft acrylic polymers, heterogeneous film structures are obtained with blends containing hard acrylic polymers. Nevertheless, the protective properties of the release controlling membrane are not remarkably affected when using blends with low hard polymer contents.

REFERENCES

1. Porter S.C., in "Multiparticulate oral drug delivery," Ghebre-Sellassie I., Drugs and pharmaceutical science, vol. 65, Marcel Dekker, Inc., New York, p 217 (1994).

2. Guttierrez-Rocca J.C. & Mc Ginity J.W., Int. J. Pharm., 103, 293 (1994).

3. Schmidt P.C. & Niemann F., Drug Dev. Ind. Pharm., 19, 1603 (1993).

4. Lippold B.C., Lippold B.H., Sutter B.K. & Gunder W., Drug Dev. Ind. Pharm., 16, 1725 (1990).

5. Appel L.E. & Zentner G.M., Pharm. Research, 8, 600 (1991).

6. Ghebre-Sellassie I., Gordon R.H., Middleton D.L., Nesbitt R.U. & Fawzi M.B., Int. J. Pharm., 31, 43 (1986).

7. Ghebre-Sellassie I., Gordon R.H. & Fawzi M.B., Int. J. Pharm., 37, 211 (1987).

8. Porter S.C., Drug Dev. Ind. Pharm., 15, 1495 (1989).

9. Gilligan C.A. & Li Wan Po A., Int. J. Pharm., 73, 51 (1991).

10. Lehmann K., Acta Pharm. Technol., 31, 96 (1985).

11. Lehmann K., in "Aqueous polymeric coatings for pharmaceutical dosage forms", Mc Ginity J.W., Drugs and pharmaceutical science, Marcel Dekker, Inc., N.Y. and Basel, Vol. 36, 1 (1989).

12. Lehmann K. & Dreher D., Drugs Made in Germany, 31, 101 (1988).

13. Fukumori Y., Yamaoka Y., Ichikawa H., Takeuchi Y., Fukuda T. & Osako Y., Chem. Pharm. Bull., 36, 4927 (1988).

14. Yuen K.H., Deshmukh A.A., Newton J.M., Short M.D. & Melchor R., Int. J. Pharm., 97, 61 (1993).

15. Staib A.H., Loew D., Harder S., Graul E.H. & Pfab R., Eur. J. Clin. Pharmacol., 30, 691 (1986).

16. Godbilon J., Evard D., Vidon N., Dural M., Schoeller J.P., Beuruier J.J., & Hirtz J., Br. J. Clin. Pharmacol., 19, 113 (1985).

17. Jones D., Drug Dev. Ind. Pharm., 20, 3175 (1994).

18. Lehmann K. & Dreher D., Int. J. Pharm. Tech. Prod. Manuf., 2, 31 (1981).

19. Skelly J.P., Yamamoto L.A., Shah V.P., Yau M.K. & Barr W.H., Drug Dev. Ind. Pharm., 12, 1159-1175 (1986).

20. Bindschaedler C., Gurny R. & Doelker E., Labo Pharma-Probl. Tech., 31, 389 (1983).

21. Fukumori Y., in "Multiparticulate oral drug delivery", Ghebre-Sellassie I., Drugs and pharmaceutical science, vol. 65, Marcel Dekker, Inc., New York, p. 79 (1994).

22. Flynn J.H., in "Polymers : Polymer characterization and analysis", Kroschwitz J.I., Wiley-Interscience, New York, p. 837 (1990).

23. Richardson M.J. & Savil N.G., Br. Pol. J., 11, 123 (1979).

24. Lehmann K., Acta Pharm. Technol., 32, 146 (1986).