DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(15), 1781-1787 (1995)

USE OF COLLOIDAL SILICA AS A SEPARATING AGENT IN FILM FORMING PROCESSES PERFORMED WITH AQUEOUS DISPERSION OF ACRYLIC RESINS

Vecchio C.(*), Fabiani F.(**) and Gazzaniga A.(**)

(*) R&D Pharmaceutical Development, Farmitalia Carlo Erba, Via Giovanni XXIII 23, 20014 Nerviano (MI), Italy; (**) Pharmaceutical Chemistry Institute, University of Milan, Viale Abruzzi 42, 20131 Milan, Italy

ABSTRACT

Aqueous dispersion of polymers are going to take the place of the corresponding organic solution in the film forming process of tablets, pellets and granules, because of some definite advantages.
Among the additives used in formulation techniques, talc, that is normally utilized as an antiadherent and polishing agent, presents some problems connected with its tendency to form sedimentation. For this reason, during the film coating operation, the dispersion must be always kept under constant and proper agitation, however, the danger of blocking the piping and the spraying system of the equipment employed cannot be completely avoided.
On the bases of these observations, the aim of this research work is to evaluate the possibility of substituting talc with colloidal silica as separating agent in aqueous dispersion of film acrylic resins, normally used in the preparation of prolonged release systems.
Results concerning fluid bed coating processes of pellets prepared by extrusion-spheronization technique have been reported, with particular attention to usable concentration of colloidal silica and to possible influence of these on the drug release characteristics of the systems obtained.

INTRODUCTION

Film coating of solid pharmaceutical dosage forms is generally used to modify the drug release pattern. As far as extended-release dosage forms are concerned, the factors which influence drug delivery in terms of rate, duration and

(*) Present address: Pharmaceutical Technologies R&D, Via Comignago 2B, 28010 Revislate-Veruno (NO), Italy

reproducibility include raw material quality, substrate preparation and both formulation and process variables.

The choice of a proper film coating composition represents a fundamental step of the manufacturing, since the film is the diffusive covering which controls the release of the drug.

The properties of the coating membrane are influenced by the polymer characteristics, the additives, the solvents or the vehicles, the structure and the thickness (1).

The polymers are the main components of the membrane and are responsible for the hydrophilic/hydrophobic balance, and consequently determine permeability.

The solvents can also play an essential role in defining the final coating characteristics through the polymer solvation which affects the extension capability of the polymer chains. At present the aqueous polymeric dispersions are substituting the organic solutions in the film coating process for ecological as well as economical reasons.

Among the additives of the aqueous polymer dispersion formulation, talc, usually employed as an antiadherent, separating and polishing agent, creates technological problems due to its evident tendency to settle.

For this reason the aqueous polymer dispersions must always be stirred under proper and constant agitation during the spraying process. Nevertheless this procedure does not completely eliminate the risk of blocking up the piping and spraying system of the equipment.

The aim of this study was to evaluate an alternative coating formulation with a simpler application procedure of the aqueous polymer dispersions during the coating process.

In order to solve the technological problems of sedimentation, we have thought to substitute talc with colloidal silica, as a separating agent, in aqueous acrylic resin dispersion generally employed to prepare drug prolonged release systems.

In this paper we report results concerning film coating processes carried out on d-Indobufen pellets and data relevant to the influence of colloidal silica on release characteristics of coated pellets.

MATERIALS AND METHODS

The pellets forming the core of the extended-release form were prepared by extrusion-spheronization technique using d-Indobufen, microcrystalline cellulose and lactose (2,3). Pellets' composition and manufacturing process are reported in a previous study (3).

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

- copolymers of methacrylic esters (Eudragit RL/RS 30D, Rohm Pharma, Germany)
- triethyl citrate (Citroflex 2, Pfizer, USA)
- talc (Talco e Grafite, Milan, Italy)
- colloidal silicon dioxide (Syloid 244, W.R. Grace, USA)
- polyethylene glycol (PEG 6000, Hoechst, Germany)
- simethicone emulsion (Carlo Erba, Milan, Italy)

Coating Method

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

- pellets load	1000 g
- air inlet temperature	55°C
- air outlet temperature	33°C
- pumping rate	20 mL/min
- atomizing air pressure	1.4 atm
- drying temperature	55°C
- drying time	60 min

The granules were taken out when pellet weight increased by 3, 6, 9 % w/w. The formulation of polymeric dispersions used in the coating process were those suggested by the manufacturer, and are reported in table 1.

Physical Tests of Pellets

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

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

RESULTS AND DISCUSSION

The spraying of acrylic dispersion coating (Eudragit RL 30D and RS 30D) using colloidal silica instead of talc was performed without problems of sedimentation, which made vigorous agitation unnecessary while it is usually indispensable when talc is employed. Moreover no sticking tendency and pellet aggregation was observed during the application of the film.

From the morphological point of view, it seems that there are no differences between the films obtained from dispersions containing talc or colloidal silica as separating agents. Talc and silica are characterized by different physical and chemical properties. Talc is a very fine crystalline powder, which shows hydrophobic surface characteristics; it exhibit a large surface area (12 m^2/g) in relation to its mass of platelike structure and the value depends on the fineness of the product, generally about a few microns.

Colloidal silica is a submicroscopic amorphous powder, which is hygroscopic, but absorbs large quantities of water and in water forms a colloidal dispersion.

Release profiles of d-Indobufen from pellets coated with aqueous dispersion containing talc or silica are shown in figure 1. The presence of colloidal silica determined an increase of dissolution rates; such behavior was verified either with Eudragit RL or mixture Eudragit RL/RS containing dispersions.

In addition, the presence of the colloidal silica seems to uniform the permeability characteristics of the film obtained; the introduction of less permeable Eudragit RS, practically, has no influence on the release profile. The increase of dissolution rate could be reasonably ascribed to the well-known adsorption capacity of the colloidal silica which combines a considerable specific surface area with a strong affinity for polar compound like water.

TABLE 1: Qualitative and Quantitative Composition of the Polymeric Dispersion

Formulae	**1**	**2**	**3**	**4**	**5**	**6**
Eudragit® RL30D (g)	200	160	200	160	160	160
Eudragit® RS 30D (g)	-	40	-	40	40	40
Talc (g)	50	50	-	-	-	-
Colloidal Silica (g)	-	-	18	18	18	36
Triethylcitrate (g)	12	12	12	12	12	12
Poliethylenglycol (g)	-	-	-	-	6	6
Simethicone (g)	-	-	0.3	0.3	0.3	0.3
Deionized water (g)	338	338	369.7	369.7	363.7	345.7

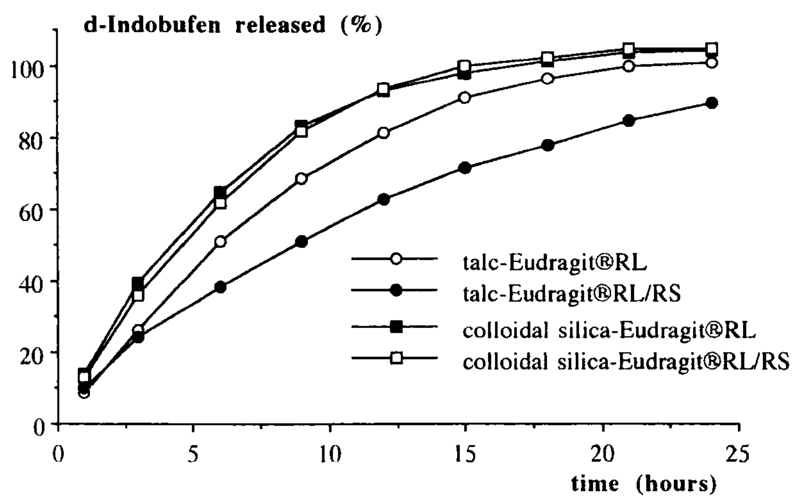

FIGURE 1
Release profiles of d-Indobufen from pellets coated with acrylic aqueous dispersions containing talc or colloidal silica.

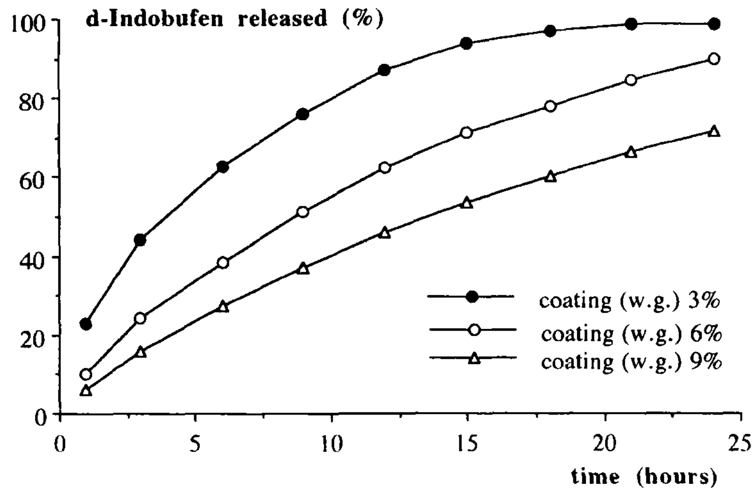

FIGURE 2

Release profiles of d-Indobufen from pellets coated with increasing amounts of acrylic aqueous dispersions containing talc (w.g.= weight gain).

The drug diffusion through the coating membrane could be therefore favored by the large uptake of water, which occurs through the pores or the swelled segments of the acrylic polymeric chains.

The release profiles relevant to pellets coated with different film thicknesses prepared with dispersions containing colloidal silica or talc are shown in figures 2 and 3. As expected, by increasing the thickness the drug release rate decreased. Such an effect appeared evident with the talc containing formulations (Fig.2); conversely small differences in release rate can be observed when talc is substituted by colloidal silica (Fig.3).

The polyethylene glycol, which was added to the colloidal silica based formulation, leaded to an increase of the drug release rate (Fig.4, Table 1), that can easily be attributed to the property of the polyethylene glycol as a canalizing agent.

By increasing the concentration of the colloidal silica in formulation 5, a reduction of the d-Indobufen release rate was obtained, the release of the drug was not completed at the 24th hour (Fig.4).

This phenomenon may be due to the barrier effect caused by the increase in thickness of gel formed by the high amount of colloidal silica present in the formulation.

As long as the amount of the colloidal silica is kept low, the gel layer which forms among the polymeric particles does not constitute an obstacle to the outward diffusion of drug molecules.

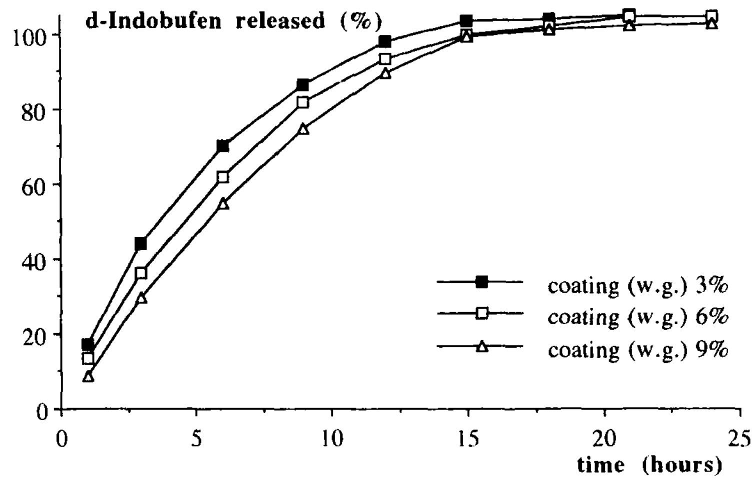

FIGURE 3
Release profiles of d-Indobufen from pellets coated with increasing amounts of acrylic aqueous dispersions containing colloidal silica (w.g.= weight gain).

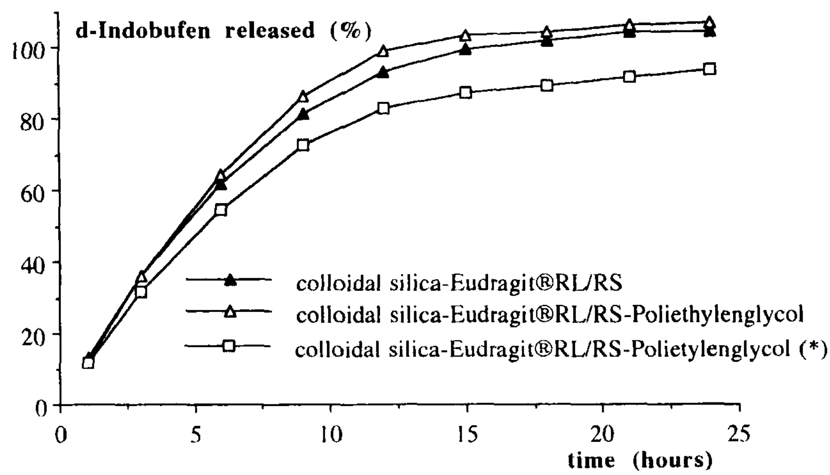

FIGURE 4
Release profiles of d-Indobufen from pellets coated with acrylic aqueous dispersions containing colloidal silica and polyethylene glycol. (*) double amount of colloidal silica (formula 6).

The use of colloidal silica into acrylic dispersions, instead of talc, overcomes the technological problem represented by the tendency of sedimentation. In fact the agitation of the polymeric dispersion during the spraying process is no longer necessary, avoiding the problems concerning the blockage of piping and the spraying system.
The technological properties of the coated pellets confirmed that colloidal silica is effective as a separating agent; however its use, due to the strong influence on release patterns, has to be thoroughly evaluated in defining drug release modulation.

CONCLUSIONS

This study has further given the indications for the development of the film coating technique by using colloidal silica containing dispersions. Colloidal silica resulted an effective separating agent, which simplified considerably the application of the acrylic dispersion on the d-Indobufen pellets. With the use of the colloidal silica the settling in coating dispersion and the clogging of the spray system did not occur during the coating process, and films with good characteristics were obtained.
These promising results will have to be confirmed with the scaling up of coated pellets preparation in order to verify the possibility of a future industrial application.

ACKNOWLEDGEMENTS

The authors appreciate the collaboration of A.Capoccia, G.Cristina, G.Bruni, S.De Luigi, G.Orizio e G.Rossi.

REFERENCES

1. J.W. McGinity, "Aqueous Polymeric Coating for Pharmaceutical Dosage Forms", Marcel Dekker, INC. New York and Basel, 1989.
2. R. Bianchini and C. Vecchio, Il Farmaco, 44 (6), 645 (1989).
3. R. Bianchini, G. Bruni, A. Gazzaniga, C. Vecchio, Drug Dev. Ind. Pharm., 18, 1485 (1992).