DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(8), 851-860 (1992)

AQUEOUS FILM COATING STUDIES OF SUSTAINED RELEASE NICOTINIC ACID PELLETS: AN IN-VITRO EVALUATION

Pai-chang Sheen, Pamela J. Sabol, Gregory J. Alcorn and Kenneth M. Feld

Rhone-Poulenc Rorer Central Research

Horsham, PA 19044

ABSTRACT

Numerous batches of nicotinic acid (niacin) pellets were coated to determine the optimum level of Surelease® coating which would exhibit in-vitro release patterns suitable for BID dosing. Various levels of Surelease, with and without the incorporation of a hydrophilic material, were studied. It was expected that a significantly high level of Surelease would be needed to obtain the desired in-vitro dissolution release rate for the water soluble drug. However, a coating level of 1.2% Surelease coating was found to have an in-vitro dissolution profile approximating that of a BID product. Scanning electron microscopic examination has shown that the surface of coating is smooth and uniform with the coating thickness of about 2 μm. The 2 months stability data showed no significant changes in the dissolution profiles.

INTRODUCTION

Sustained release dosage forms are developed for a variety of reasons (1). The most important reasons are to create a dosage form which not only

can reduce the toxicity and incidence of adverse drug reactions, but also provide continuous therapeutic activity of a drug over a defined period of time.

Nicotinic acid (niacin) belongs to the group of water soluble vitamins widely used for the treatment of hyperlipidemia. According to various studies, a plasma concentration of only 0.5-2 μg/ml of free niacin is sufficient to achieve maximum pharmacological effects provided that they are maintained over a prolonged period of time (2). Because the plasma half-life of niacin is relatively short, about 1 hour, high doses of niacin are necessary to maintain the desired plasma concentrations. The use of high doses of niacin has been limited due to the uncomfortable symptoms of facial flushing and gastrointestinal disturbance (2). Since the symptoms appear to be related to the rate of gastrointestinal absorption, several sustained released niacin products have been developed and marketed to alleviate these side effects.

The purpose of this study was to determine the optimal level of water based Surelease (Colorcon, West Point, PA) coating which would exhibit an in-vitro release pattern approximating that of a BID product.

EXPERIMENTAL

Materials

Niacin pellets were obtained from Armour Pharmaceutical Co. (Kankakee, IL.) The pellets consist of a neutral pellet core alternately layered with a solution of povidone in pharmaceutical glaze and powdered niacin. Surelease is a completely plasticized aqueous polymer dispersion (3). It was chosen as the rate controlling system for a number of reasons; it provides a pH independent release pattern (4), it is easy to use and poses no known safety and health hazards related to that of solvent systems.

Application of Sustained Release Coating

The Aeromatic Strea-1 (Towaco, NJ) fluid bed coating machine with a Wurster column was used to apply Surelease dispersion to the niacin pellets. Five hundred grams of pellets were coated with various levels of Surelease dispersion. The exact amount was calculated on the basis of the solid content of the particular lot of Surelease used. Surelease dispersion was diluted with purified water to 15% solids or it was mixed with various amounts of hydroxypropyl methylcellulose (HPMC) solution and diluted with purified water to 15% Surelease solids. The solution was stirred for 15 minutes before coating. The amount of HPMC in the final film was 2%, 6% or 10%.

The coating parameters were as follows: Spray nozzle orifice, 1.1 mm; column height, approximately 2 cm from the base plate; Masterflex pump (Barrant Co., Barrinton, IL.) with #16 tubing; outlet air temperature, 50 °C; atomizing air, 1.8 bar; fluidizing air, dial setting 13. Coating was applied using a spray rate of approximately 4 ml per minute. When the Surelease application was completed, approximately 20 mL of purified water was used to rinse the container and tubing and this was applied to the pellets. Pellets were then dried in the column until the outlet air temperature reached 54 °C. The same coating operation parameters were used throughout the studies.

Dissolution Tests

The dissolution method used for screening the formulations was USP paddles at 50 rpm in 900 ml of dissolution medium at 37 °C. The dissolution medium consisted of 0.05 M KH_2PO_4 adjusted to pH 1.2-1.5, with concentrated HCl, which was adjusted after one hour to pH 7.5 using 50% NaOH solution. Capsules containing a weight of niacin pellets equivalent to 250 mg of niacin were added to each dissolution vessel. Samples were removed through a 20 μm filter for analysis at suitable time intervals from 1 to 24 hours. The samples were assayed spectrophotometrically at 261 nm. Each of the dissolution values reported is based on an average of 6 capsules.

Scanning Electron Microscopy (SEM)

The coated pellets were examined under a scanning electron microscope (SEM) (Model SX 40, ISI, Milpitas, Ca.) for morphological evaluation. The pellets were also cross-sectioned for coating thickness measurement. The samples were prepared by gold spattering technique before SEM examinations.

RESULTS AND DISCUSSION

Effect of Coating Level on the Rate of Release

The uncoated niacin pellets showed 100% release in one hour (Figure 1). Initially, Surelease was applied to the pellets at levels ranging from 2.5 to 20% by weight, as was suggested in the product literature (3). Dissolution rates of these coated niacin pellets showed surprising results. After 24 hours, pellets with 2.5% coating showed only 41% niacin released (Figure 1).

In general, water soluble drug pellets require a high level of coating to produce sustained release profiles, because the drug can dissolve during aqueous film deposition and migrate further into the film coat (4). As the amount of drug embedded in the film coat increases, the coating becomes less continuous and more permeable during dissolution. Consequently, a thicker coating is required to achieve the target rate of drug release.

The preliminary studies demonstrated that niacin might not dissolve and migrate into the coating layer during the coating operation. Therefore, a series of low coating levels were conducted to produce the desired release rates. Niacin pellets were coated with 0.3, 0.5, 1 and 1.2% Surelease. The dissolution rates showed fast release of niacin at 0.3 and 0.5% and fairly moderate release at 1 and 1.2% coated pellets (Figure 2). A visual observation found that the coatings of 0.3 and 05% pellets were ruptured during dissolution. The integrity of the coatings of 1 and 1.2% were well

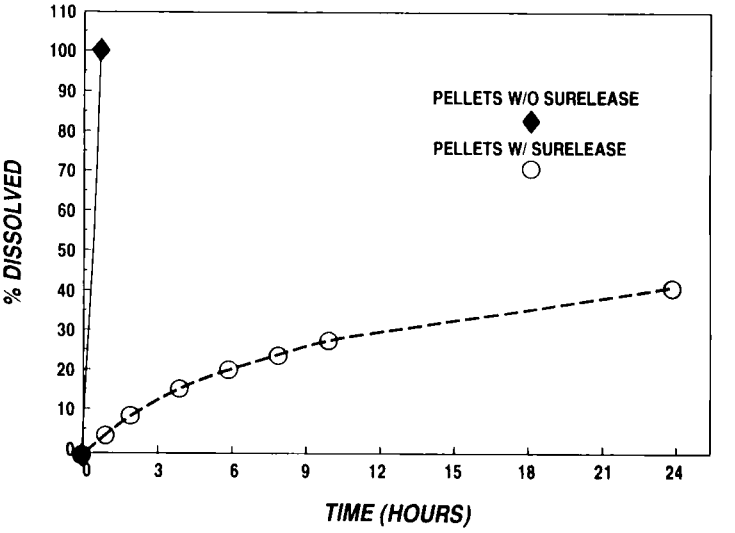

FIGURE 1

Dissolution profiles of immediate release and 2.5% Surelease coated niacin pellets

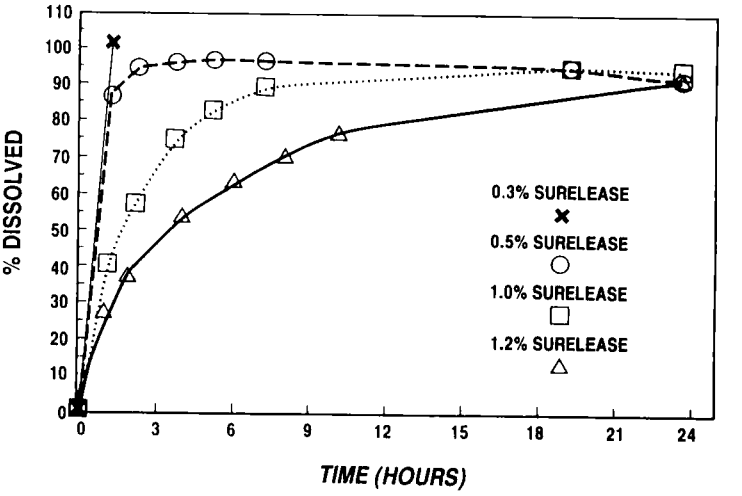

FIGURE 2

Dissolution profiles of niacin pellets coated with low levels of Surelease

preserved throughout the dissolution experiment. Even when the drug was completely depleted from the pellets, the coating shell remained intact.

Incorporation of HPMC in the Sustaining Coat

Due to concern about the uniformity of the coating and potential difficulties with regard to reproducibility at such a low level (1.2%) coating, a slightly different approach was tried. A water soluble polymer, hydroxypropyl methylcellulose (HPMC) was added to Surelease at the 2.5% coating level in an attempt to create pores in the coating. An increase in the drug release rates would be expected when the pellets are exposed to dissolution medium. The pellets coated with Surelease dispersion that contained 2 and 6% of HPMC based on Surelease solids, yielded only slightly faster rate of release than those coated with Surelease alone (Figure 3). As expected, the presence of the water-soluble HPMC in the coating leads to the formation of pores during dissolution, which enhances the access of the dissolution medium to the pellet cores (5). However, at 10% HPMC, the integrity of the film was lost and release of niacin was quite rapid (Figure 3). This indicates that incorporation of HPMC in Surelease coating may need to be optimized to produce the desired release rate. However, this approach may not be a practical method for increasing the release rate of a water soluble drug, such as niacin; because the coating system will be easily ruptured due to the presence of higher concentration of HPMC (i.e. 6 to 10%) and cause a rapid release of drug.

Reproducibility of 1.2% Surelease Coating

In order to produce the desired sustained release profiles, uniform and complete Surelease coating must be applied to water soluble niacin pellets. To study the reproducibility of the dissolution rates of niacin from Surelease coated pellets from batch to batch, three batches of pellets were coated with 1.2% Surelease and the dissolution data generated. As shown in Figure 4, the dissolution rates was found to be reproducible indicating the coating membrane

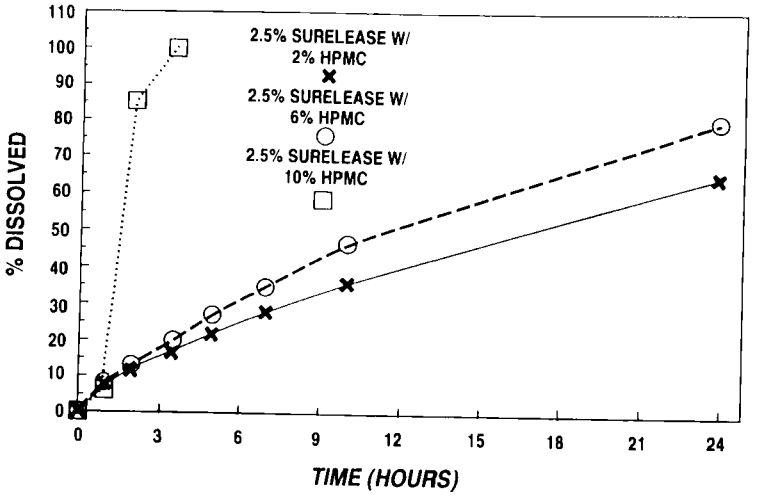

FIGURE 3

Dissolution profiles of niacin pellets coated with 2.5% Surelease containing various concentrations of HPMC

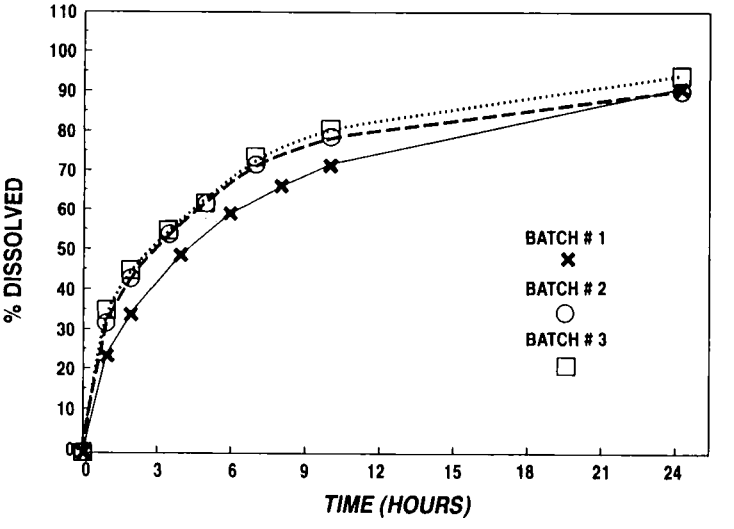

FIGURE 4

Dissolution profiles of different batches of niacin pellets with 1.2% surelease coating

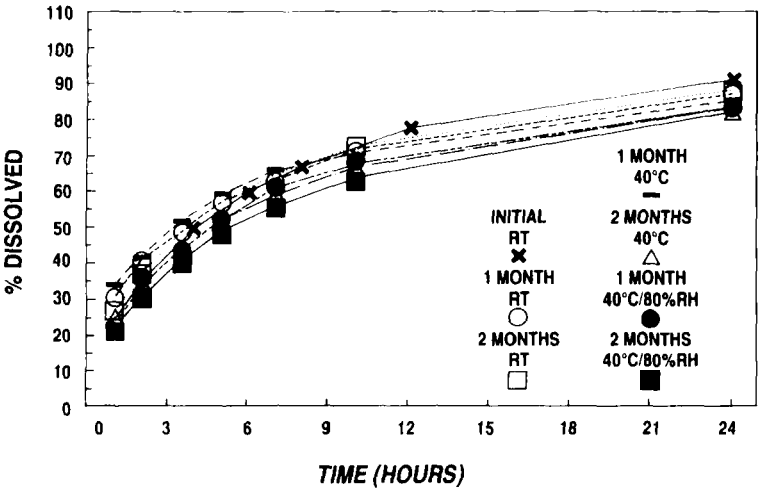

FIGURE 5

Dissolution profiles of aged niacin pellets coated with 1.2% Surelease

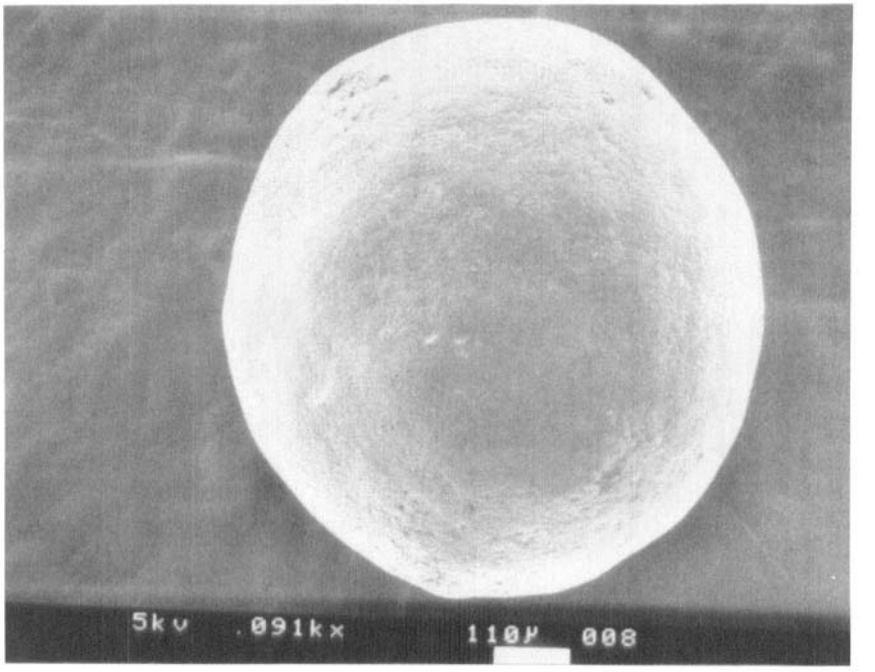

FIGURE 6

The surface of a niacin pellet coated with 1.2% Surelease (magnificient : 91X)

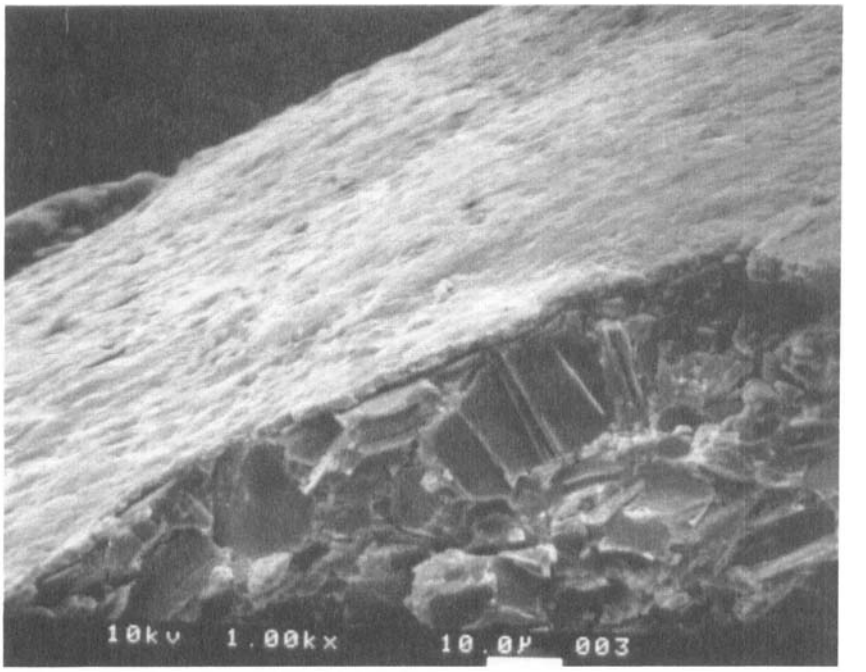

FIGURE 7

Cross-sectional view of a 1.2% Surelease coated niacin pellet (magnification = 1,000X)

is uniform and completely covers the pellet cores even at this level of coating. Evidently, the Wurster process used for these studies was quite efficient in apply the coating dispersion to the surface of pellets to produce the satisfactory coating.

Effect of Aging on Rate of Release

The release profiles of the coated pellets that were stored at controlled room temperature (25 °C), 40 °C and 40 °C/80% RH (Relative Humidity) for up to 2 months are shown in Figure 5. The release rates showed no gross changes in dissolution profiles, although a slight slowing was noted after storage at 40 °C and 40 °C/80%RH. These results imply that film-formation of the Surelease dispersion is completed during the coating process and that further

curing at elevated temperature is not required to enhance the coalescence of the ethylcellulose particles.

Scanning Electron Microscopy(SEM)

According to SEM examination, the surface of the coated pellets appears smooth, compact and continuous (Figure 6). A cross-sectioned view of the coated pellets showed a distinctive interface between the core and the coating. The coating thickness is about 2 μm (Figure 7).

CONCLUSION

Various levels of Surelease, with and without the incorporation of HPMC, were applied on niacin pellets. It was surprising that the release rate of water soluble niacin was able to be well controlled by a low level of Surelease coating (1.2%). The results of short term stability studies showed no significant changes in dissolution rates, possibly due to the complete curing of Surelease coating during the coating process.

ACKNOWLEDGMENT

Thanks are due to Ms. Suzzanne Ciancia for generating the dissolution data.

REFERENCES

1. A. C. Cartwright, Mfg. Chem. 58 (5), 33 (1987).
2. W. Hotz, Adv. Lipid Res., 20,195 (1983).
3. Surelease (Colorcon, West Point, Pa).
4. G. S. Rekhi, R. W. Mendes, S. C. Porter and S. S. Jambhekar, Pharm. Tech., 13, 113 (1989).
5. I. Ghebre-Sellusi, U. Iyer, D. Kubert and M. B. Fawzi, ibid, 12, 96 (1988).