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Influence of Ibuprofen as a Solid-State Plasticizer in Eudragit® RS 30 D on the Physicochemical Properties of Coated Beads

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ABSTRACT

The purpose of this study was to investigate the physicochemical properties of nonpareil beads coated with Eudragit® RS 30 D containing ibuprofen as a multifunctional agent. The influence of the concentration of ibuprofen in the film coating and the effect of the coating level on drug release from coated beads was determined in pH 7.2 phosphate buffer solution. The influence of storage time at 23°C and 60°C on the release of ibuprofen from coated beads was also investigated. The thermal properties of the films were determined using a differential scanning calorimeter. Scanning electron microscopy was employed to image the surface morphology of the coated beads. Infrared spectroscopy was used to study the interaction of Eudragit RS 30 D and ibuprofen. Results from the dissolution studies demonstrated that increasing the amount of ibuprofen in the polymeric film reduced the rate of drug release, mainly because of a more complete coalescence of the polymeric particles of the latex dispersion. The glass transition temperature (Tg) of Eudragit RS 30 D films decreased and the surface of the coated beads became smoother as the concentration of ibuprofen was increased. Hydrogen bonding between the polymer and ibuprofen was demonstrated by Fourier transform infrared spectroscopy. No significant differences were found in drug dissolution between the coated beads stored at 23°C for 12 months and those stored at 60°C for 12 hours. The results of this study demonstrated that the ibuprofen plasticized the Eudragit RS 30 D. Furthermore, the dissolution rate of ibuprofen can be controlled and changes in the drug release rate can be minimized by using the drug-induced plasticization technique with this polymer.

Keywords: Plasticization, Eudragit® RS 30 D, Ibuprofen, Film coating, Stability, Drug release.

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INTRODUCTION

Aqueous film-coating dispersions generally consist of polymeric colloidal particles, a plasticizer, a pigment, and an anti-adherent agent. Most polymers employed for the film coating of pellets and tablets are brittle at room temperature and require the use of plasticizers to improve their handling and processing. These plasticizing compounds reduce the brittleness, increase the flexibility, and improve the toughness and tensile strength of polymers. Plasticizers play an important role in the film formation process. The degree of latex particle coalescence and the quality of the resulting film are dependent on the type and amount of plasticizer added to the coating. The efficiency of a plasticizer is related to its chemical structure and the extent of interaction with the polymer [1] .

The plasticizers currently employed in pharmaceutical coatings include polyols like glycerin, organic esters such as citrate esters and dibutyl sebacate, and oils such as castor oil. However, many of these plasticizers have aging and sticking problems when used for aqueous film coating [2-5] . Mechanical changes in the film coating may occur, especially during the coating process and drying stages. Temperature and moisture may damage many of the polymers currently used in pharmaceutical film coating and ultimately result in changes in the dissolution properties of the drug.

Chowhan and coworkers [6] studied the effects of aging on the in vitro release profiles of ticlopidine hydrochloride tablets coated with an aqueous film-coating formulation. A decrease in the dissolution rate was found in tablets coated with polymethacrylic acid esters stored at 37°C and 95% RH, and greater changes were noted in samples stored at 37°C and 95% RH than those stored at 23°C and 95% RH. Similar observations were obtained by other researchers [7-9] . Such an observation indicates the

importance of temperature and time effects on complete film formation because coalescence is a slow process.

Another problem associated with the plasticization of polymers is the leaching of the plasticizer from the film. Plasticizer leaching is dependent on the dissolution medium and can result in dramatic changes in drug release from coated dosage forms [10] . In vitro dissolution studies with cast films of Eudragit® RS/RL have demonstrated that water-soluble plasticizers leached more readily when the level of the hydrophilic polymer in the film was increased [11] . Therefore, the selection of a plasticizer for a film-coating formulation is very important in the development and optimization of a coated pharmaceutical solid dosage form.

Ibuprofen is a nonsteroidal anti-inflammatory agent widely used in the treatment of rheumatoid arthritis and osteoarthritis. Previous research has shown that ibuprofen functioned as a plasticizer for acrylic films. In that study, the concept of nontraditional plasticization of acrylic polymer was introduced and ibuprofen and methylparaben were demonstrated to have a significant plasticization effect on Eudragit® RS 30 D [12-14] . The objectives of the present study were to investigate and characterize the drug release behavior and stability of beads coated with Eudragit RS 30 D containing ibuprofen as a multifunctional agent (active agent, plasticizer, and stabilizer) and to study the interaction between Eudragit RS 30 D and ibuprofen.

MATERIALS AND METHODS

Materials

Eudragit RS 30 D was donated by Hüls America Inc (Somerset, NJ). Ibuprofen was obtained from Francis SpA Inc (Varese, Italy). Nonpareil beads (size 16-20 mesh) were donated by Mendell Inc (Patterson, NY).

Preparation of film-coating dispersion

The ibuprofen was first dispersed in water using a Polytron® rotor-stador mixer (Brinkmann Instruments, Westbury, NY) and then added to the Eudragit RS 30 D polymeric dispersion. The coating dispersions were agitated using a magnetic stirrer. The amount of ibuprofen incorporated into the film coating (20%, 30%, or 40%) was based on the dry polymer weight, and water was added to decrease the acrylic solids content to approximately 20%. To ensure sufficient time for plasticization of the polymer, the suspensions were agitated for 4 hours prior to spraying.

Film coating of beads

A 300-g batch of 14 to 20 mesh nonpareil beads was placed in the fluid-bed coater (Uni-Glatt Laboratory Unit, Glatt Air Technique, NJ) and prewarmed for 10 minutes prior to spraying. The inlet air temperatures were held between 45°C and 50°C. The atomizing air pressure was 2.0 kg/cm^2 . The Eudragit RS 30 D dispersion containing ibuprofen was applied at a rate of 2.0 g/min. The aqueous dispersions were stirred continuously throughout the coating process. To promote further coalescence of the polymeric film, the coated beads were tray-dried at 40°C for 24 hours in an air-circulated oven. The dried beads were then stored at 0% RH and 23°C prior to testing. The coated beads were stored in a closed container at 23°C for predetermined time intervals. The samples of the coated beads were also stored at 60°C for 12 hours to determine the influence of the curing conditions on drug release properties.

Thermal analysis of free films

The preparation of free film has been described previously [12] . The thermal properties of the free films were determined using a differential scanning calorimeter (Modulated Temperature DSC, TA Instruments, New Castle, DE). Film samples of 10 mg to 15 mg were accurately weighed into aluminum pans and then sealed. The samples were tested under a nitrogen atmosphere at a heating rate of 10°C/min, at a temperature range of -20°C to 80°C.

Scanning electron microscopy

Scanning electron microscopy was used to study the morphology of the polymeric free films and film-coated beads. Samples were coated with gold-palladium for 70 seconds under an argon atmosphere using a Pelco Model 3 cold sputter module (TED Pella, Tustin, CA) in a high-vacuum evaporator equipped with an omni-rotary stage. Scanning electron microscopy was performed using a Jeol Model 35 scanning electron microscope (Jeol USA, Peabody, MA) at 25 kV.

Fourier transform infrared (FT-IR) spectroscopy analysis

The infrared spectra of ibuprofen, Eudragit RS 30 D dried polymer film, and the ibuprofen plasticized polymer were analyzed with a Nicolet Magna-IR™ system 550 (Nicolet Instrument, Madison, WI). A KBr pellet was formed by first mixing a 2% sample with dried KBr by using mortar and pestle. From this mixture, 100 mg was pressed under 4000 kg force in a punch-and-die set to form a transparent KBr pellet. The pellet was carefully transferred and adhered onto a sample holder on an Econo-Card (Aldrich Chemical, Milwaukee, WI). The card was then inserted into the sample holder in the FT-IR spectroscopy machine and scanned from 400 to 4000 cm^{-1} . The scanning spectrum was analyzed using Omni™ software (West Covina, CA).

Drug release studies

The dissolution properties of ibuprofen from coated beads was determined using USP XXIV Method II (paddle). The dissolution medium consisted of 900 mL of a phosphate buffer solution (pH 7.2) and was maintained at 37°C over a 12-hour period. The medium was agitated at 100 rpm, and samples were extracted at specified time intervals and analyzed spectrophotometrically at 221 nm for drug content.

RESULTS AND DISCUSSION

Plasticizers are used to improve the processibility, flexibility, and elasticity of polymers. These compounds alter the thermal properties of the polymer by disrupting the intermolecular interactions of the polymer chains. Plasticization of a polymer will result in a reduction of the glass transition temperature (Tg) of the polymeric film. Below this temperature, the polymer exists in a glassy state that is characterized by a substructure with minimal polymer chain movement. Above the glass transition temperature, a polymer is in a rubbery state, which is usually characterized by regions with increased polymer chain movement and polymer elasticity. **Figure 1** shows the influence of ibuprofen concentration on the glass transition temperature of cast films of Eudragit RS 30 D. It can be seen from this figure that ibuprofen was very effective in lowering the Tg of the acrylic polymer and plasticizing the acrylic film. Due to the low dose of

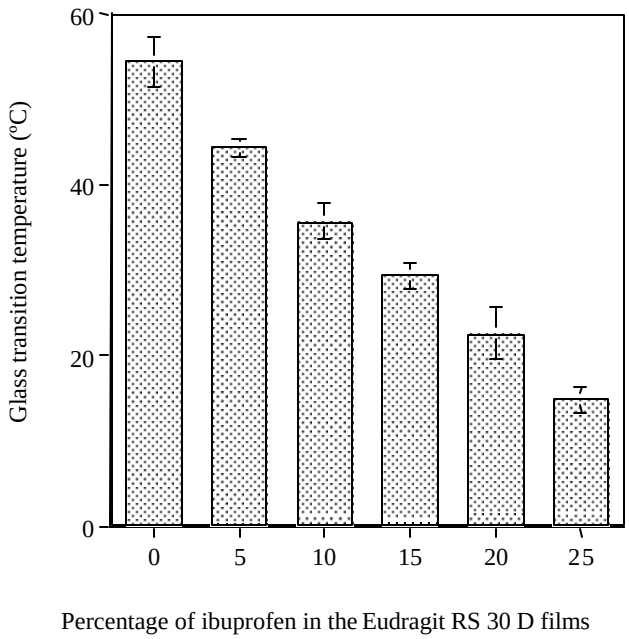

Figure 1. Influence of ibuprofen on the glass transition temperature of Eudragit® RS 30 D films (n = 6).

ibuprofen in the polymer layer, ibuprofen controlled-release dosage forms can be developed by presenting ibuprofen in both the core bead and the outer polymer layer, where ibuprofen will function both as the active ingredient and as the plasticizer for the polymer.

The solubility parameter is directly related to the cohesive energy density of a compound. Generally, the smaller the difference in the solubility parameters between 2 compounds, the greater their miscibility will be. The difference in the solubility parameters is therefore a useful guide to the compatibility and miscibility of a plasticizer with a particular polymer [13,15] . Reports from the literature have suggested that in order to obtain good miscibility between 2 compounds, the difference in the solubility parameters should not be greater than 6.3 $(J/cm^3)^{1/2}$ [16] . The solubility parameters for Eudragit RS 30 D (19.0 $(J/cm^3)^{1/2}$) and ibuprofen (19.2 $(J/cm^3)^{1/2}$) are very similar, thus indicating a good miscibility between the polymer and ibuprofen. As a small molecule, ibuprofen can position between polymer chains to plasticize the polymer. The drug was taken up completely by the polymer particles. In addition, the surface and cross-sectional topographs of Eudragit RS 30 D film containing ibuprofen exhibited a smooth, uniform surface and a compact

internal texture, further demonstrating the plasticizing properties of the active ingredient for the Eudragit RS 30 D polymer.

An active ingredient can be present in a cast film as a crystal embedded in the hardened polymer matrix or as a solid solution in the film. For solid solutions or molecular dispersions, there are no embedded crystals of active drug to refract light, with the result being a transparent film. In the current study, the acrylic films plasticized by ibuprofen were transparent, which demonstrated that the ibuprofen was dissolved or present in an amorphous state within the Eudragit RS 30 D polymer. This finding was also supported by the scanning electronic micrographs of the cast films that are shown in **Figure 2**. The crystallinity of ibuprofen is evidenced in the top photograph (**Figure 2A**) while the amorphous state of the plasticized polymer is seen in the bottom photograph (**Figure 2C**). This result is also in agreement with our previous findings [13], where the x-ray diffraction patterns from cast Eudragit RS 30 D films containing ibuprofen were found to be identical to those of the pure polymer, as the drug was dissolved or present in an amorphous state within the polymeric matrix.

The brittle and ductile behavior of the Eudragit RS 30 D polymer can also be seen in **Figure 2**, where there is a significant visible difference between the unplasticized (**Figure 2B**) and plasticized polymer films (**Figure 2C**). In general, the ability of a material to crystallize depends on the regularity of its molecular structure. A regular structure is potentially capable of crystallization, but an irregular structure will tend to exist in an amorphous state. The mechanism of plasticization is considered to be a decrease in the cumulative intermolecular forces between the polymer chains [17] . Crystallization of polymer chains promotes intermolecular forces, thus increasing the rigidity and brittleness of the polymer. This mechanism was proposed earlier by Heinamaki and co-workers [17] . The addition of ibuprofen enhanced the plasticization of the Eudragit RS 30 D polymer and thus resulted in a highly amorphous polymer structure due to the disordered placement of the polymer chains in the polymeric matrix.

Eudragit RS contains ammonium and ester groups that are capable of interacting with other molecules through hydrogen bonding, as well as through electrostatic and dispersion forces. The carboxylic

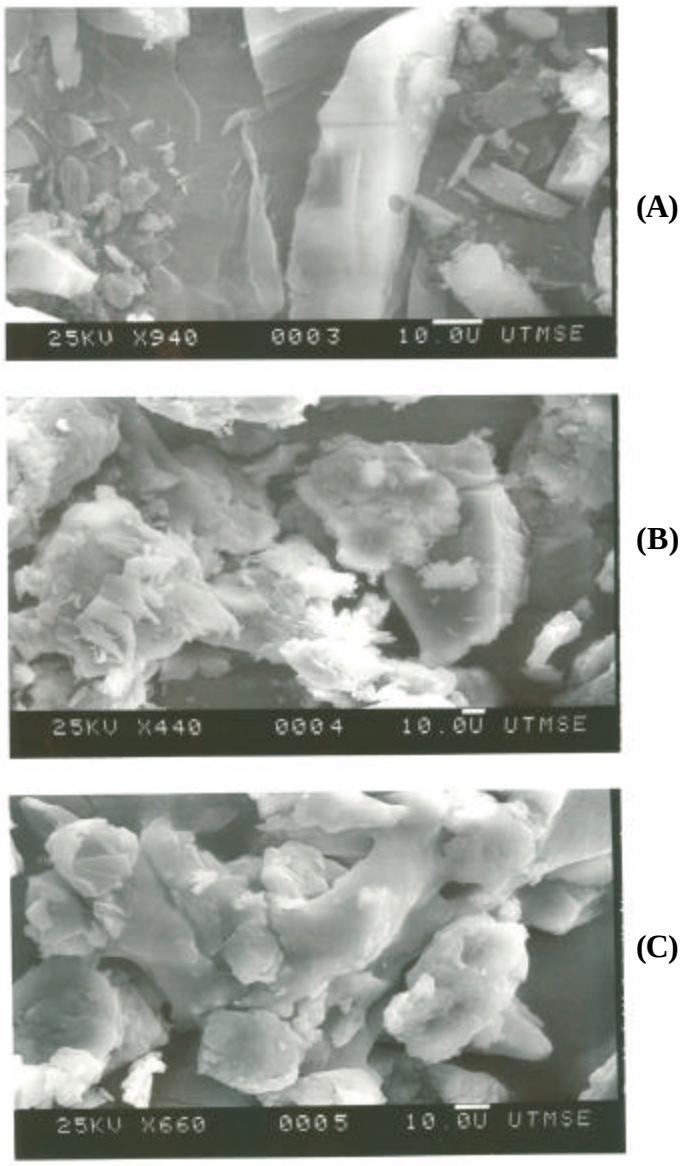

Figure 2. Scanning electronic micrographs of (A) ibuprofen, (B) Eudragit® RS 30 D polymer alone, and (C) Eudragit RS 30 D plasticized with ibuprofen.

acid functional group of ibuprofen also has a potential to interact through hydrogen-bond formation. The ibuprofen disrupted interactions between the chains of the Eudragit RS polymer through hydrogen-bond formation, and this disruption was responsible for the plasticizing effects. These theories are supported by the infrared spectra shown in **Figure 3**. **Figure 3A** shows the FT-IR absorption peaks of ibuprofen at 1710 and 2955 cm^{-1} caused by the carbonyl stretching vibration and the hydroxyl stretching vibration. Once the interaction occurred between ibuprofen and Eudragit RS 30 D, these two peaks shifted to the higher wave number.

The two unique, strong, stretching bands at 1160 and 1250 cm^{-1} of Eudragit RS, shown in **Figure 3B** , are attributed to the carbonyl stretching vibration of the ester group. The formation of intermolecular hydrogen bond between the carboxylic acid group in the ibuprofen and the ester group in Eudragit RS polymer would result in a decrease in the electron density on oxygen; therefore, the intensity of the carbonyl bond (1160 cm^{-1} and 1250 cm^{-1}) would be weakened. These changes in the IR spectra demonstrate that ibuprofen interacted with the Eudragit RS 30 D polymer through the carboxyl acid groups.

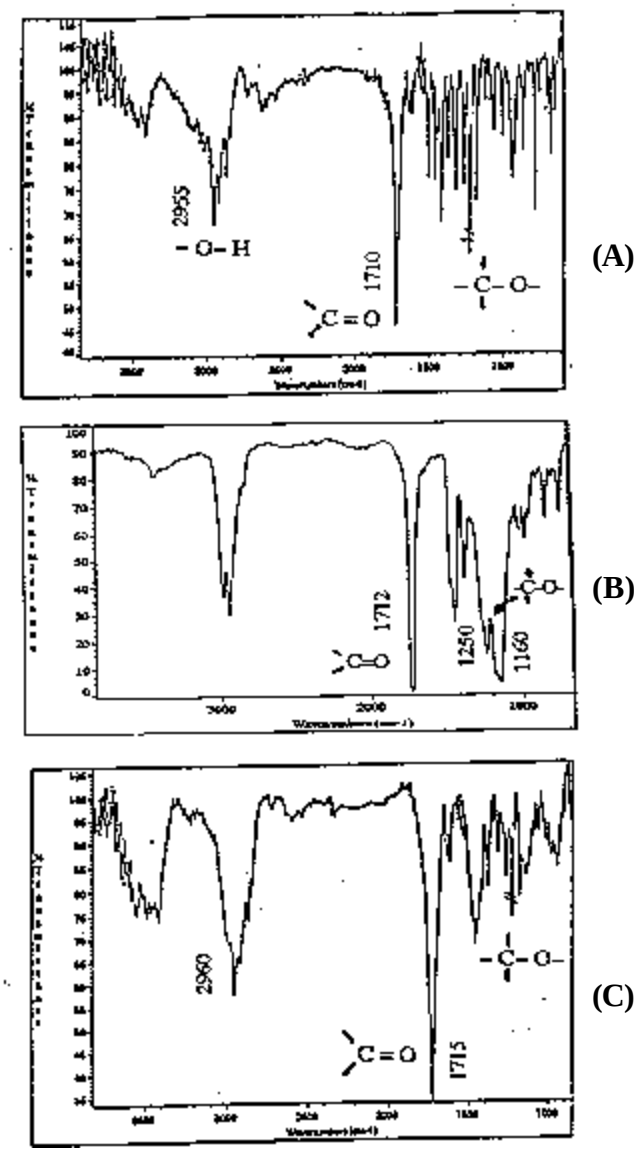

Figure 3. Infrared spectra of (A) ibuprofen, (B) Eudragit® RS 30 D, and (C) acrylic polymer plasticized with ibuprofen.

The surface morphology of nonpareil uncoated beads and beads coated with Eudragit RS 30 D containing ibuprofen are seen in **Figures 4A** through **4C** . The rough surface of the uncoated beads is readily evident. The surface of the film became relatively smoother as the concentration of ibuprofen in the film coating increased. These results demonstrate that a greater degree of coalescence of the latex particles was obtained during film formation, when higher levels of ibuprofen that functioned as a plasticizer were present in the dispersion.

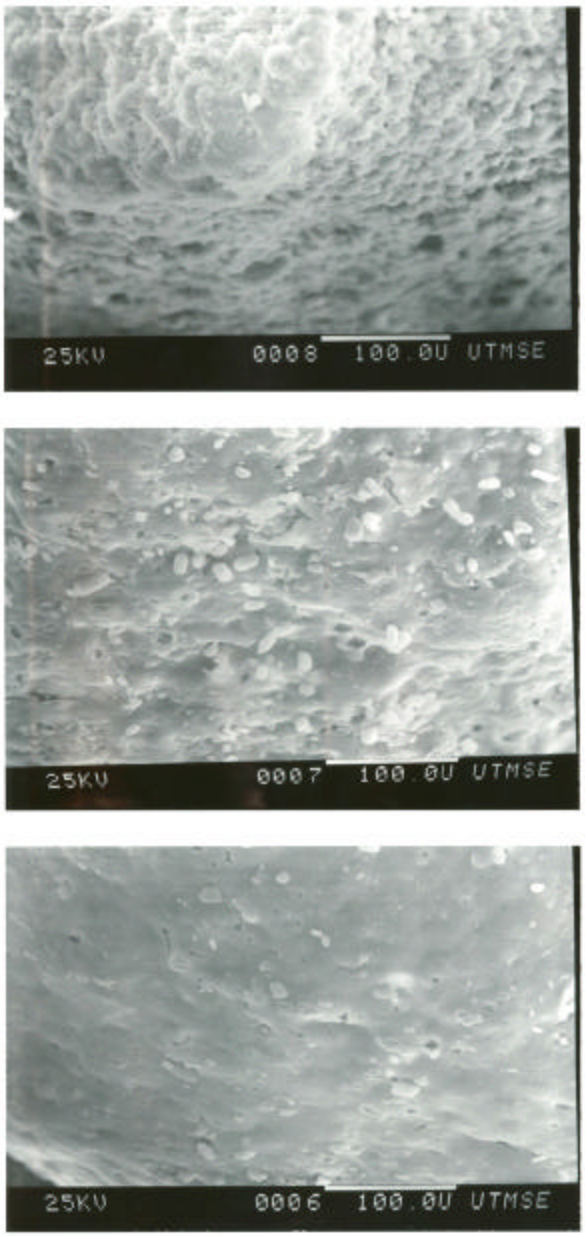

Figure 4. Surface morphology of nonpareil beads uncoated and coated with Eudragit® RS 30 D containing different levels of ibuprofen in the latex dispersion: (A) uncoated, (B) 20% ibuprofen, and (C) 30% ibuprofen.

Figure 5 shows the influence of the coating level on drug release from coated beads. When the polymer contained 30% ibuprofen, increasing the coating level from 5% to 20% led to a decrease in the rate of drug release, indicating that the film was controlling the release process. Further increase in polymer weight showed no significant change in drug release. At low coating levels, the membrane was relatively porous and drug molecules took the route of least resistance for the release of ibuprofen from the film coating. In drug-loaded films, it is typical for the release to decrease with increasing thickness of the films. As the coating level increases, fewer pores are available for drug transport, resulting in a retarded drug release [18] . It is more likely that drug release is controlled by diffusion across the polymeric membrane rather than by diffusion through pores or channels or imperfections within the coating film [19] . In film coating, a continuous membrane is formed by the buildup of the overlapping segments. Above a critical coating level, it can be assumed that all the "holes" are covered and a continuous and complete membrane has enveloped each individual bead.

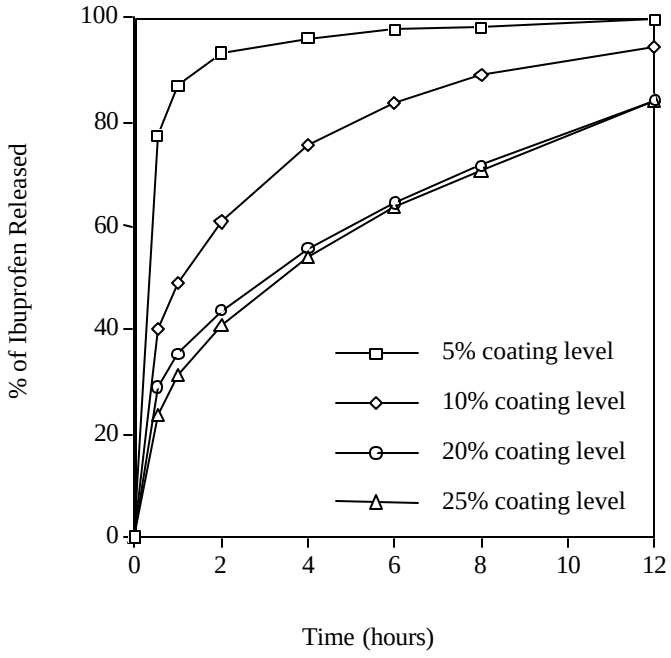

Figure 5. Dissolution profiles of ibuprofen from nonpareil beads coated with different levels of Eudragit® RS 30 D polymer containing 30% ibuprofen (n = 6).

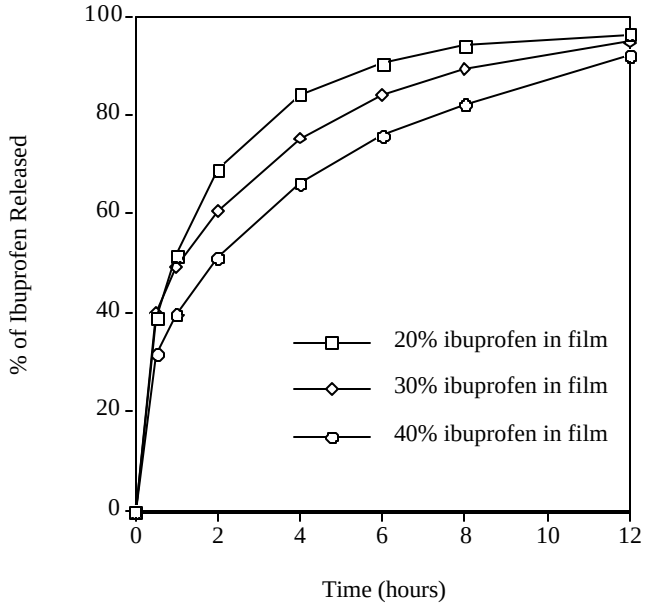

Figure 6. Dissolution profiles of ibuprofen from nonpareil beads coated with 10% Eudragit® RS 30 D polymer containing different levels of ibuprofen as a nontraditional plasticizer (n = 6).

Figure 6 shows the dissolution profiles of ibuprofen from nonpareil beads coated with Eudragit RS 30 D containing different levels of ibuprofen as a solid-state nontraditional plasticizer. The rate of drug release decreased when the ibuprofen levels were increased from 20% to 40%. These findings are in agreement with previous reports in which authors have demonstrated that higher levels of traditional plasticizers in polymeric films reduce the rate of drug release [5,] [20-22] .

The process of film formation from aqueous colloidal latex dispersions requires the evaporation of water, the coalescence of latex particles, and the interdiffusion of polymeric chains to form a continuous film [23] . The final step in the film formation process is known as "curing" or temperature equilibration, and the physical stabilization of the coating film can proceed for an extended time period after the coating process has been completed [24-25] . Several reports have demonstrated the effect of storage conditions on the release patterns of drugs from coated dosage forms due to changes in film properties [20, 26-28] . Curing or equilibrating the coated dosage forms at a temperature above the glass transition temperature of the polymer can significantly alter the drug release

rate. The extent of these changes is dependent on the type and amount of plasticizer, the coating processing conditions, and the storage conditions [5-6, 8] . The nonpareil beads coated with 10% Eudragit RS 30 D containing 40% ibuprofen as plasticizer were stored at 23°C for 12 months, and the effect of this storage time on the dissolution rate of ibuprofen is shown in **Figure 7**. No significant differences were found between the initial drug release rate and the dissolution profiles of the aged samples. These results demonstrate that ibuprofen stabilized the Eudragit RS 30 D polymer. The influence of storage time on the dissolution properties of ibuprofen from nonpareil beads coated with 10% Eudragit RS 30 D containing 40% ibuprofen and cured at 60°C can be seen in **Figure 8** . No significant differences were found in the dissolution profiles of ibuprofen from coated beads after 12 hours of curing at the elevated temperature.

Sticking will occur during coating when the cohesive and adhesive forces acting at pellet-pellet interfaces are greater than the forces tending to separate the pellets-in other words, forces arising from the fluidization in a fluidized bed. Sticking can be observed between pellets if they are overwetted while being coated in a fluidized bed. The action of a plasticizer is to lower the glass transition temperature. It was reported that some plasticizers did not have a significant effect on the film/substrate adhesive force [29] . Interestingly, the 40% ibuprofen coating cured at 60°C exhibited no sticking during the coating process and subsequent storage. The presence of ibuprofen in the coating formulations reduces the extent of sticking, which could be due to a reduction in the cohesive forces between droplets on the pellet surface. This observation suggests that ibuprofen also functions as an anti-adherent in the film coating.

CONCLUSION

Ibuprofen was found to plasticize Eudragit RS 30 D films and to stabilize the polymer to prevent changes during high-temperature curing. Higher concentration of ibuprofen in the film produced a relatively smooth surface. Ibuprofen interacted with the Eudragit RS 30 D polymer through hydrogen bonding. The glass transition temperature of the Eudragit RS 30 D polymer decreased with increasing levels of ibuprofen in the polymeric film. The drug release rate was reduced by increasing the amount of ibuprofen in

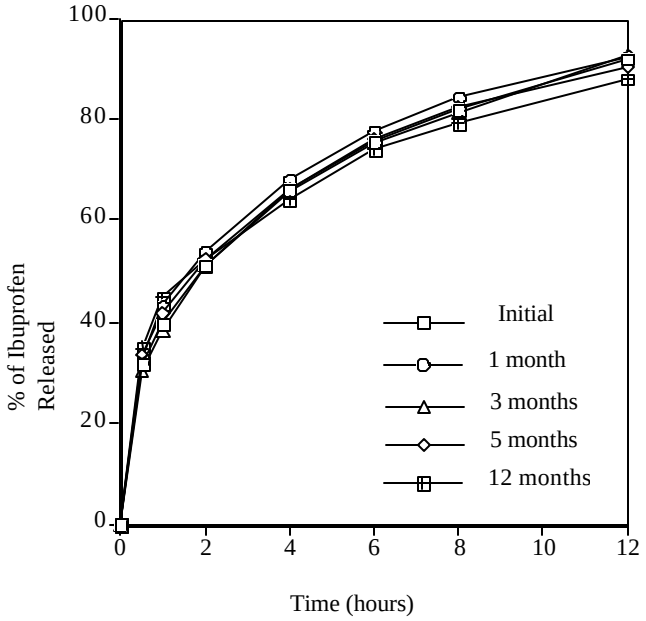

Figure 7. Effect of storage time at 23°C on the dissolution rate of ibuprofen from nonpareil beads coated with 10% Eudragit® RS 30 D polymer containing 40% ibuprofen (n = 6).

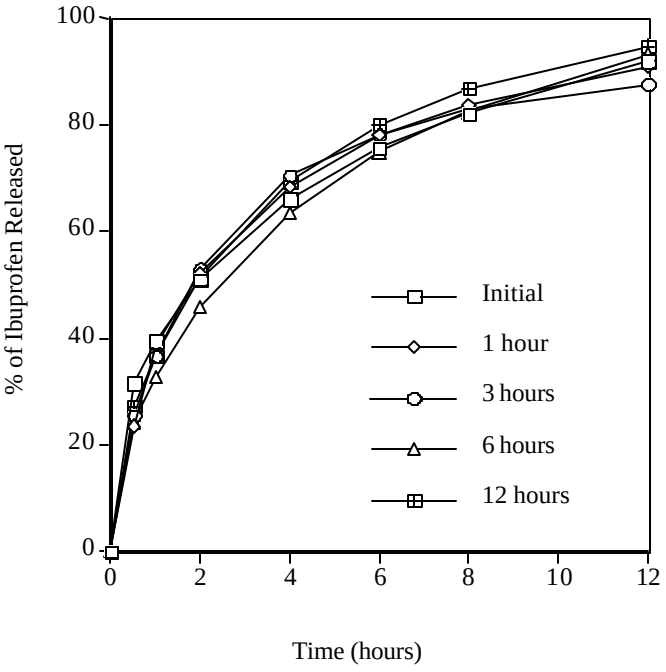

Figure 8. Effect of curing time at 60°C on the dissolution rate of ibuprofen from nonpareil beads coated with 10% Eudragit® RS 30 D polymer containing 40% ibuprofen (n = 6).

the polymeric film and by increasing the coating level on the nonpareil bead. Because the coated pellets did not agglomerate during processing or storage, no additional overcoat was required for these formulations to prevent the sticking that is seen with pellets coated with Eudragit RS 30 D polymer plasticized with a high level of triethyl citrate. Nonpareil pellets coated with Eudragit RS 30 D containing ibuprofen demonstrated no change in release rate when stored at 60°C for 12 hours. In conclusion, the dissolution rate of ibuprofen could be controlled and stabilized by use of the polymeric plasticization technique with this nontraditional plasticizer.

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