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RESEARCH ARTICLE

Effects of Formulation Variables and Post-compression Curing on Drug Release from a New Sustained-Release Matrix Material: Polyvinylacetate-Povidone

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ABSTRACT

A new commercially available sustained-release matrix material, Kollidon® SR, composed of polyvinylacetate and povidone, was evaluated with respect to its ability to modulate the in vitro release of a highly water-soluble model compound, diphenhydramine HCl. Kollidon SR was found to provide a sustained-release effect for the model compound, with certain formulation and processing variables playing an important role in controlling its release kinetics. Formulation variables affecting the release include the level of the polymeric material in the matrix, excipient level, as well as the nature of the excipients (water soluble vs. water insoluble). Increasing the ratio of a water-insoluble excipient, Emcompress®, to Kollidon SR enhanced drug release. The incorporation of a water-soluble excipient, lactose, accelerated its release rate in a more pronounced manner. Stability studies conducted at 40°C/75%RH revealed a slow-down in dissolution rate for the drug-Kollidon SR formulation, as a result of polyvinylacetate relaxation. Further studies demonstrated that a post-compression curing step effectively stabilized the release pattern of formulations containing ≥47% Kollidon SR. The release mechanism of Kollidon-drug

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and drug-Kollidon-Emcompress formulations appears to be diffusion controlled, while that of the drug-Kollidon-lactose formulation appears to be controlled predominantly by diffusion along with erosion.

KEY WORDS: Diphenhydramine HCl; Kollidon SR; Matrix tablets; Polyvinylacetate; Sustained-release.

INTRODUCTION

The use of polymeric materials in sustained/controlled drug delivery is best exemplified by hydroxypropylmethylcellulose (HPMC), due in part to its ready availability of various grades, differing in molecular weights and viscosity, its ability to accommodate host molecules of varying physicochemical properties, and its good regulatory acceptance (1). Other commonly used matrix materials include carbomers (2), methyl/ethylcellulose and derivatives (3), natural gums (4), etc. Polyvinylacetate (PVAc) has also been reported to be effective in controlling the release of various chemical entities, including theophylline (5), nifedipine (6), and chlorpromazine hydrochloride (7). However, the use of PVAc in previous publications all involved a particle coating method, due to the unavailability of a directly compressible material.

Recently, a physical mixture of PVAc and povidone (Kollidon SR) has become commercially available (8). This directly compressible excipient has been demonstrated to effectively retard the release of propranolol HCl and caffeine (9). The material forms a matrix block upon compression as it is composed of eight parts of water-insoluble PVAc and two parts of water-soluble povidone. The povidone component gradually leaches out of the matrix during dissolution thereby creating pores for the active to diffuse out. The compressed PVAc component maintains tablet core structure during the dissolution run.

The amorphous nature of PVAc coupled with its unusually low glass transition temperature of 28–31°C (10) imparts certain unique characteristics to this binary matrix. It is therefore the purpose of this research to examine key formulation and process variables that could affect the release kinetics, by using diphenhdyramine HCl as a model compound. Additionally, the mechanism(s) of release of such a highly water-soluble compound from Kollidon SR matrix tablets, formulated with and without additional excipients, has also been elucidated.

MATERIALS AND METHODS

Materials

Diphenhydramine hydrochloride USP was internally obtained from Parke-Davis Chemical Development. Kollidon SR was obtained from BASF Corporation (Mount Olive, NJ). Lactose monohydrate, Fast-Flo® grade, was obtained from Foremost Farms USA (Baraboo, WI). Calcium phosphate dibasic dihydrate (Emcompress) was purchased from Edward Mendell Co. (Patterson, NY). Magnesium stearate of nonbovine origin was obtained from Mallinckrodt Inc. (St. Louis, MO).

Tablet Preparation

Diphenhydramine HCl, Kollidon SR, and a selected excipient were blended in an 8-qt. Patterson-Kelly (East Stroudsburg, PA) V-blender for 5 minutes. Magnesium stearate was passed through a 30-mesh screen and added to the V-blender. Mixing was continued for an additional 5 min. The blend was compressed on a Korsch (Somerset, NJ) PH106 rotary press using oval-shaped tooling with the dimension of $0.750'' \times 0.390'' \times 0.062''$ at a compression force of ~33 KN. Tablets were compressed to a target weight of 800 mg with each tablet containing 300 mg of diphenhydramine HCl with varying amounts of Kollidon SR, with or without lactose or Emcompress, and 4 mg (0.5 wt%) magnesium stearate as the lubricant.

Tablet Curing

For the curing duration study, the tablets were cured at 60°C in a Hotpack Supermatic oven (Philadelphia, PA) for varying lengths of time ranging from 10 minutes to 18 h. All other batches were cured at 60°C for a fixed time of 15 hours. Dissolution testing and hardness measurements were performed after the cured tablets were cooled to room temperature for overnight or longer.

Stability Testing Protocol

Tablets were packaged in 20s into 90-cc high-density polyethylene bottles. One 1-gm Sorbit® desiccant cartridge (United Desiccants, Belen, NM) was placed into each bottle. The bottles were then closed with 38-400 C/R caps, and induction-sealed using an Enercon LM3620-01 induction sealer (Enercon Industries Corp., Menomonee Falls, WI). The bottles were then placed inside Espec humidity cabinets preequilibrated to 25°C/60%RH and 40°C/75%RH (Tabai Espec Corp., Osaka, Japan). At

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