Bi-Phasic Drug Release from Drug Layered, Extended Release Hypromellose Matrices

INTRODUCTION

Hydroxypropyl methylcellulose (hypromellose, HPMC) is widely used as the rate controlling polymer in hydrophilic matrix tablets for oral extended release (ER) applications. In most therapies, such ER preparations are desirable. However, in certain drug therapies, rapid availability of drug dose in order to relieve the symptoms of the disease is advantageous, followed by the maintenance of an effective drug plasma level for the continuation of the clinical effects.

HPMC matrix/mini-matrix systems have been formulated to achieve such “fast/slow” drug release patterns. These matrices are reported to contain the drug fraction for the extended release phase, while the drug fraction for immediate release was integrated into the matrix/mini matrix via an immediate releasing layer in a double-layer tablet system, incorporated into a release controlling coating over the matrices or incorporated into the voids between compressed mini-matrices.[1-3]

The aim of this work was to demonstrate suitability of a hypromellose (HPMC) matrix system to achieve a bi-phasic release profile: a fast release within 15 minutes (similar to an immediate release preparation) followed by extended drug release, using conventional tableting and coating technologies. In addition, the influence of a color top coat on drug release was investigated. Zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class was selected as the model drug.

METHODOLOGY

Formulation methodology in the present study involved drug layering of HPMC matrices, i.e. simultaneously containing drug in the tablet core and in an outer coating layer. Drug release in each phase is controlled by regulating the dose fraction in the tablet core and the outer coating layer.[2&4]

Zolpidem tartrate (Cadila Pharmaceuticals) 4.25% w/w, 15.19% w/w microcrystalline cellulose (Avicel PH102, FMC), 45.56% w/w spray dried lactose (Borculo Domo Ingredients) and 34.00% w/w HPMC (METHOCEL™, premium cellulose ethers, K100 LV Premium CR, IFF, USA) were wet granulated using a planetary mixer (Kaleweka). The dried granules were then sieved through a 22 mesh BSS (710 µm) screen. Magnesium stearate (Vasa Pharma) 0.50% w/w and fumed silica (Aerosil 200, Degussa) 0.50% w/w were then blended with the granules for one additional minute. Matrices with a target weight of 200mg were compressed using an 8 station rotary press (Rimek 2, Karnavati), fitted with 8 mm standard concave tooling.

Matrices were then coated (drug-layered) using a dispersion containing 4.29% w/w zolpidem tartrate, with or without 0.06% w/w sodium lauryl sulphate (SLS, Stepan) and 1.32% w/w Opadry® II, high performance film

coating system, 85G29119 Clear (Colorcon). Matrices were then top coated using Opadry II 85G50517 Blue (Colorcon) to a 2% weight gain. Drug layering and color coating were carried out in an O'Hara Labcoat-1 (12 inch pan diameter). The process parameters are listed in Table 1.

Breaking force of the tablets was measured using a PTB 311E hardness tester (PharmaTest). Friability testing was carried out by using a USP compliant Friabilator (EF-2, Electrolab). Tablet uniformity testing was carried out according to the USP General Chapter: <905> Uniformity of Dosage Units.[5] Drug release was determined using a USP compliant automated dissolution bath [Erweka DT 800, apparatus 2 (paddles) at 50 rpm and sinkers (Electrolab)]. The dissolution medium (900 ml) was of 0.01M HCl at 37ºC (±0.5ºC). An online dual beam spectrophotometer (Perkin-Elmer) was used for the detection of zolpidem tartrate at a wavelength of 294.4 nm over a 5.5 hour period.

Table 1. Process Parameters Drug Layering Color-Coating

	Drug Layering	Color-Coating
Tablet Charge (g)	450	462
Air Volume (cfm)	150	150
Inlet Temperature (ºC)	55	55
Exhaust Temperature (ºC)	42	42
Product Temperature (ºC)	45	45
Fluid Delivery Rate (g/min)	8	5
Pan Speed (rpm)	9	8
Atomization Air Pressure (bar)	2	2
Coating Solids Content (%)	5.67	20.00
Coating Weight Gain (%)	2.70	2.00

Coated tablets were packaged in foil sealed 100cc HDPE containers, without desiccant and stored at 40ºC/75% RH.

RESULTS AND DISCUSSIONS

Physical Characterization of the Matrices

Good physical properties were obtained for the compressed matrices (core). Tablet breaking force increased with the subsequent drug-layering and color-coating processes (Table 2).

Table 2. Physical Properties of Zolpidem Tartrate ER matrices (n=10)

Tablet Properties	Tablet Parameters		
	Core	Drug Layered	Color-Coated
Thickness (mm)	3.96 ± 0.05	4.08 ± 0.02	4.09 ± 0.03
Weight (mg)	201 ± 3	206 ± 2	210 ± 3
Breaking Force (kp)	7.14 ± 0.50	7.55 ± 0.52	8.40 ± 0.66
Friability (%)	0.09	0.05	0.09

Drug Content Uniformity Testing

Individual tablets assayed for actual drug content complied with the USP requirements for content uniformity.

Drug Release Characterization

Zolpidem tartrate release, from drug layered HPMC matrices, was biphasic as shown in Figure 1. The zolpidem in the outer drug layer is believed to be released as the first pulse through dissolution of the coating,

while the second phase of the release is controlled by the HPMC matrix core. Increasing the drug layering dose fraction to 32% (core containing 68% zolpidem tartrate) from 20% (core containing 80% zolpidem tartrate) increased the release from 32% to 47% in the first 15 minutes, indicating that the dose fraction in each phase can be adjusted to achieve the desired fast/slow release. The remainder of the drug is released over a 5.5 hour period. Comparative drug release profiles (Figure 2) show that incorporation of SLS in the drug layering dispersion resulted in an enhanced wetting and solubility of the drug contained in the coating layer. This indicates that solubilizers or other additives can be used to enhance initial release of poorly soluble drugs from the coating layer.[2]

Figure 1. Effect of Drug Fraction in the Coating on Drug Release Profiles

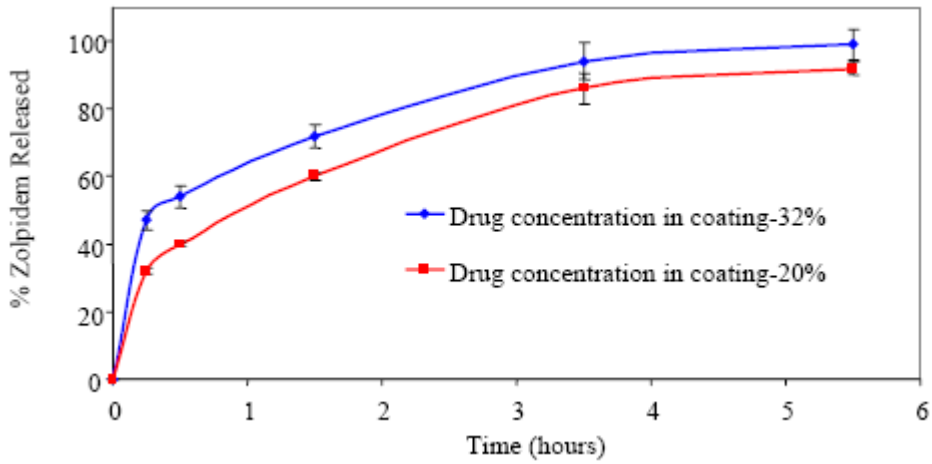
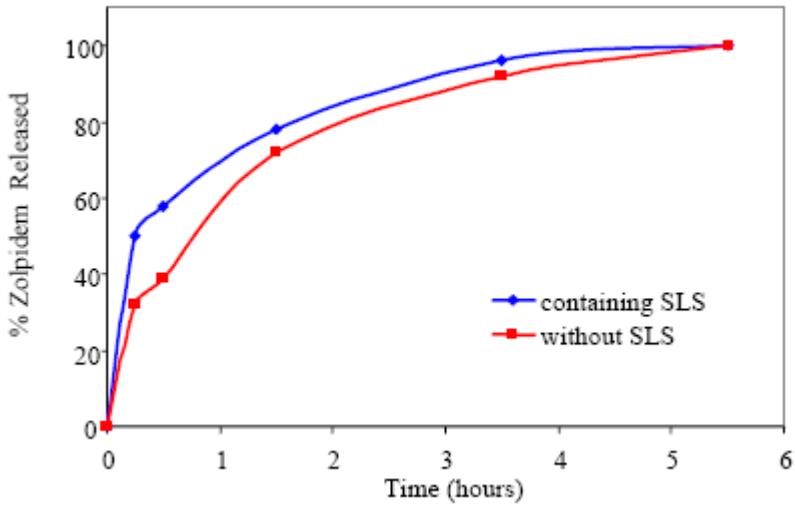


Figure 2. Effect of SLS in the Drug Layering Dispersion



Dissolution from drug layered, color coated matrices (Figure 3) was found to be similar to matrices without the color coat (f2=98.9). An f2 value between 50 and 100 indicates that two profiles are similar.[6]

Stability Studies

Drug release from coated matrices remained unchanged (Figure 4) when stored at accelerated stability conditions (6 months at 40ºC/ 75% RH) with a similarity factor, f2 of 73.02.

Figure 3. Effect of Color-Coating on Drug Release Rate

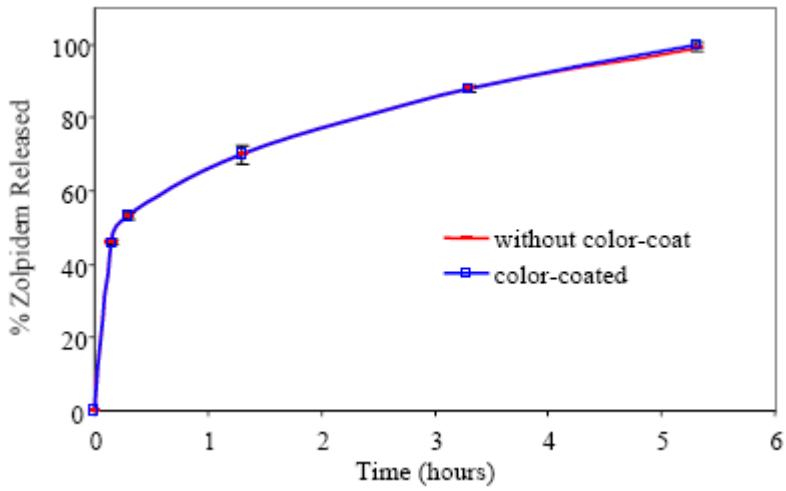
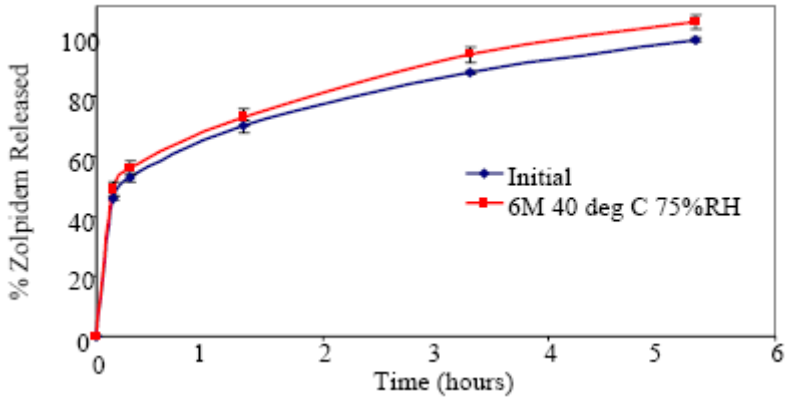


Figure 4. Effect of Storage Conditions on Drug Release Rate



CONCLUSIONS

HPMC matrices were modulated to achieve a biphasic drug release profile. Percent drug released at each phase can be tailored, depending on the dose fraction in the matrix and in the coating. A larger first pulse can be obtained by increasing the percentage of the drug in the coating layer. Solubilizers or other excipients may be added to the drug layering solution to further modulate the release. Color coating over drug layered matrices did not impact the release profile.

Release profiles from the matrices showed excellent reproducibility after 6 months at accelerated conditions (40ºC/75%RH).

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