Modulation of Drug Release from Hypromellose (HPMC) Matrices: Suppression of the Initial Burst Effect

OBJECTIVES

Hypromellose (HPMC) is widely used in extended release (ER) matrix systems. An initial burst effect in the release of highly water-soluble drugs from such matrices is a common occurrence. The purpose of this study was to modulate drug release of a highly water-soluble active from HPMC matrices using an aqueous ethylcellulose dispersion (Surelease®). The intent was to achieve an extended drug release profile without the typical initial burst effect.

Venlafaxine HCl, a serotonin and norepinephrine reuptake inhibitor (SNRI) and a weak inhibitor of dopamine reuptake, was chosen as the model drug due to its high water solubility (572 mg /mL).[1]

METHODOLOGY

Venlafaxine HCl (Cadila Healthcare, India) was blended with Starch 1500®, partially pregelatinized maize starch, in a ratio of 1:2. This blend was then granulated using Surelease E-7-19040, diluted to 15% solids and top sprayed in an Aeromatic Strea-1, Fluid Bed Laboratory Unit (Aeromatic – Fielder AG Switzerland). Process parameters are listed in Table 1.

Table 1. Granulation Process Parameters

Powder Charge (g)	112.5
Inlet Temperature (ºC)	55
Exhaust Temperature (ºC)	30
Atomization Air Pressure (bar)	1.5
Quantity of Granulation Fluid (g)	90
Spray Rate (g/min)	8

Venlafaxine HCl: Starch 1500 (1:2) granules 42% w/w, METHOCEL™ K15M CR 30% w/w, and microcrystalline cellulose (Avicel PH102) 27% w/w, were blended for 10 minutes. Fumed silica (Aerosil 200) 0.5% w/w was added as a glidant and magnesium stearate 0.5% w/w as a lubricant, then blended for a further 5 minutes. The matrix formulation is listed in Table 2. 300 mg tablets were compressed using 10 mm standard concave tooling.

Table 2. Venlafaxine HCl Matrix Formulation (mg/tablet)

Material	**mg**
Venlafaxine HCl: Starch 1500 (1:2) granules	126
METHOCEL™ K15M CR (Colorcon, India)	90
MCC (Avicel PH102, FMC, USA)	81
Magnesium Stearate (Vasa Pharma, India)	1.5
Fumed Silica (Aerosil 200, Degussa, DE)	1.5

For comparative evaluation of drug release, matrices were also prepared without the drug granulation step. Avicel PH102 quantity was adjusted to compensate for Surelease in the absence of the granulation step. The matrix formulation is listed in Table 3. Matrices of both formulations were then coated with Surelease to a 4% weight gain (coating process parameters are shown in Table 4) using an O'Hara Labcoat-I (12-inch pan diameter) and evaluated for drug release.

Table 3. Venlafaxine HCl Matrix Formulation - Without the Granulation Step (mg/tablet)

Material	**mg**
Venlafaxine HCl	37.5
Starch 1500	75
METHOCEL™ K 15M CR (Colorcon, India)	90
MCC (Avicel PH102, FMC , USA)	94.5
Magnesium Stearate (Vasa Pharma, India)	1.5
Fumed Silica (Aerosil 200, Degussa, DE)	1.5

Table 4. Surelease Coating Process Parameters

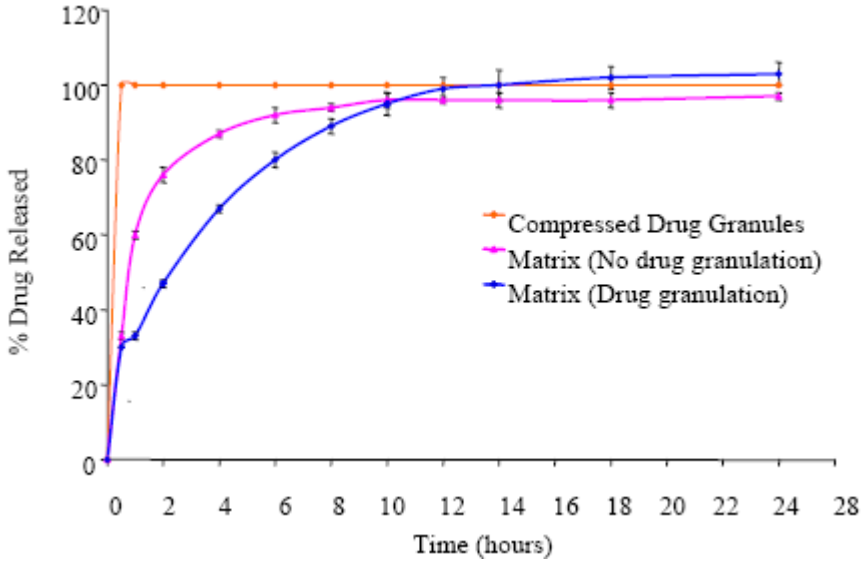
Pan Charge (g)	600
Air Volume (cfm)	150
Inlet Air Temperature (C)	50
Exhaust Air Temperature (C)	42
Product Temperature (C)	40
Fluid Delivery Rate (g/min)	7
Pan Speed (rpm)	8
Atomization Air Pressure (bar)	1.5
Pattern Air Pressure (bar)	2
Coating Solids Content (%)	15
Weight Gain (%)	4

Drug release was also determined from compressed drug granules. Dissolution testing was performed in 900 mL distilled water (37 ±0.5ºC), in a USP apparatus II, paddles (Electrolab, India) at 100rpm. Samples were withdrawn over 24 hours and analyzed at a wavelength of 224.6 nm using a double beam spectrophotometer (Shimadzu, Japan) fitted with 1mm cells. For stability determinations, coated tablets were packaged in foil-sealed 100 cc HDPE containers, without desiccant and stored at 40ºC/75% RH for 3 months.

RESULTS

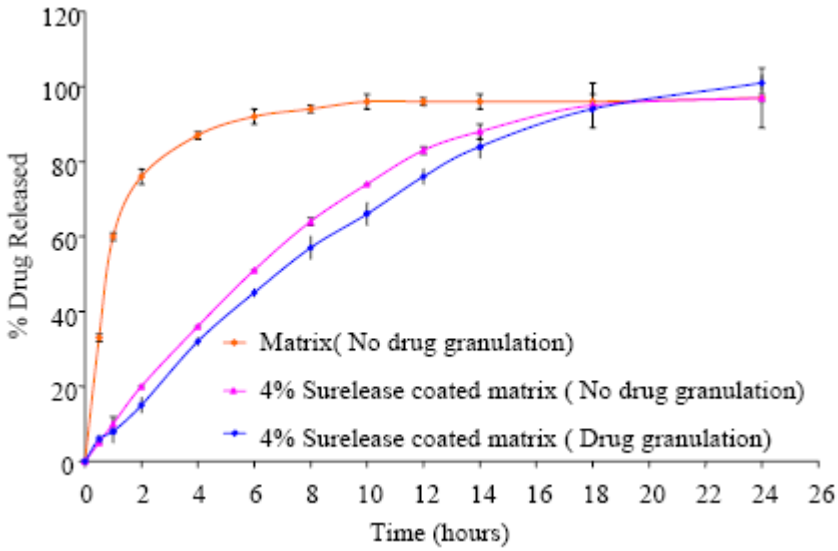
Robust physical properties were obtained for the compressed tablets of all formulations, with breaking forces of 6 -7 kp. Figure 1 shows that drug release from the matrix tablets is slower when a Surelease granulation step is introduced (30% release within 1-hour, complete release within 12 hours) as compared to that when there is no granulation step (60% within 1-hour, complete release within 8 hours). Drug release retardation may be due to the solid bridges between drug-drug and drug-Starch 1500 particles formed by the ethylcellulose in the granulation fluid. Increased particle size reduces the surface area of the drug particles, thereby decreasing the rate of dissolution of the drug.

Figure 1. Effect of Granulation on Drug Release



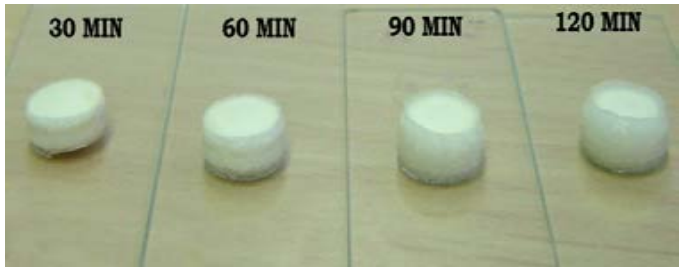
Additionally, drug particles coated with ethylcellulose film may be released via diffusion through the film.[2] Applying Surelease film over the matrix tablets (Figure 2) reduced the initial burst effect, and the drug release was extended over 18 hours. However, similar drug release profiles were obtained for matrices using granulated or ungranulated venlafaxine HCl.

Figure 2. Effect of Coating on Drug Release



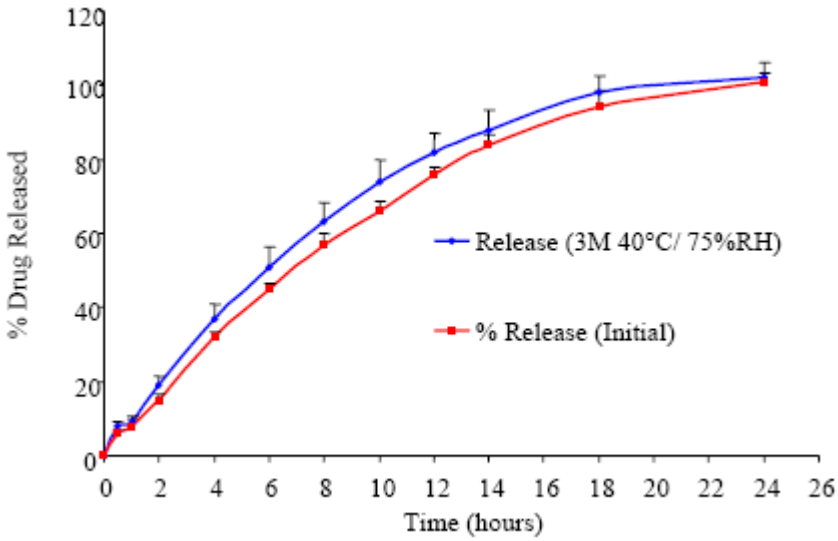
It has been shown that the internal pressure generated due to swelling and relaxation of the matrix may cause micro rupturing of the ethylcellulose film during the dissolution testing.[3] Here, the Surelease film on the matrix tablets also ruptured along the circumference of both the tablet faces after 90 minutes into the dissolution run (Figure 3).

Figure 3. Swelling and Rupture of Surelease Coated Matrices During the Dissolution Run



Drug release from coated matrices remained unchanged when stored at accelerated stability conditions (3 months at 40ºC/75% RH) with a similarity factor, f_2 of 72.33 (Figure 4).

Figure 4. Effect of Storage Conditions on Drug Release



CONCLUSIONS

Extended release formulations of venlafaxine HCl were prepared with good tablet physical characteristics. Drug release from HPMC matrices was fast and exhibited a burst effect. Applying Surelease film over the matrix tablets provided slower release profiles with a lack of initial burst, and the drug release was extended over 18 hours. Combinations of extended release technologies (barrier membrane and hydrophilic matrix) resulted in stable (3 months accelerated conditions) unique release profiles.

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