Investigation of a Venlafaxine HCl (37.5 mg) Extended Release Formulation Using Hypromellose (HPMC) Matrices

ABSTRACT SUMMARY

The aim of this work was to investigate the influence of a barrier membrane coating on venlafaxine HCl (a highly soluble drug) release from a HPMC extended release formulation. A reduction in the initial burst effect, a commonly observed phenomenon with highly soluble drugs and hydrophilic matrices, was achieved.

HPMC is commonly used in the formulation of extended release (ER) matrix systems. The rate of drug release is mediated by a hydrated gel layer on the surface of the matrix and critical factors affecting the rate of release include polymer type and concentration, drug solubility, choice of fillers, tablet size and polymer/drug ratio.[1] The high water solubility of drugs (eg venlafaxine HCl has a solubility of 572 mg/mL), leads to an initial burst release from HPMC matrices. Therefore, the aim of this work was to investigate the influence of Surelease®, aqueous ethylcellulose dispersion, on the initial burst release from an HPMC (METHOCEL™, premium cellulose ethers) matrix formulation containing venlafaxine HCl.

INTRODUCTION

Venlafaxine HCl (Cadila Healthcare, India) was blended with Starch 1500®, partially pregelatinized maize starch, (Colorcon, India) in the ratio of 1:2 in a polyethylene bag. The blend was then granulated in a laboratory scale top-spray fluid bed, (Aeromatic–Fielder AG Switzerland) to a 12% weight gain using Surelease E-7-19040 (diluted to 15% solids using purified water prior to use). Formulation containing 42% w/w of the dried granules, 30% w/w METHOCEL™ K15MCR (Colorcon, India), 27% w/w microcrystalline cellulose (Avicel PH102, FMC), 0.50% w/w fumed silica (Aerosil 200, Degussa) and 0.50% w/w magnesium stearate (Vasa Pharma, India) was prepared. The granules, polymer and filler were blended for 10 minutes followed by the addition of glidant and lubricant, and blended for further 5 minutes.

300 mg tablets containing 37.5 mg drug were compressed on an instrumented 8 station rotary tablet press (Rimek, India) fitted with 10 mm standard concave tooling at 20 rpm, and a compression force of 15kN. A tap density tester (Pathak Industrial Works, India) was used to measure the bulk and the tap density of the powder. Tablet mechanical strength was determined using an automated tablet tester (Pharmatest Incorp.) and friability tester (Electrolab, India). The compressed tablets were coated with Surelease E-7-19040 to a 4% weight gain using an O'Hara Labcoat - I (12 inch pan diameter). Coating process parameters are shown in table 1.

Samples of coated tablets were packaged in HDPE bottles (50 tablets per bottle, without dessicant). The bottles were induction sealed (foil) and stored for 3 months at accelerated conditions of 40ºC/75%RH. Dissolution testing was performed in a USP apparatus II, Paddles (Electrolab, India) at 100rpm. The

dissolution medium was 900mL of distilled water. Samples were withdrawn over a 24-hour period and analysed at a wavelength of 224.6 nm using a double beam spectrophotometer (Shimadzu, Japan) fitted with 1mm cells (with and without granulation) and those coated with Surelease were evaluated. Samples that were stored for 3 months at accelerated conditions of 40ºC/75%RH were also evaluated for drug release.

Table 1. Coating Parameters Used to Coat the Matrices

Pan Charge (gms)	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)	2.0
Coating Solids Content (%)	15
Weight Gain (%)	4

RESULTS AND DISCUSSION

All blends showed good flow characteristics and produced robust compressed tablets with breaking force of 6-7 kp and friability of 0.1%. Drug release profiles from different formulations are shown in figure 1. Drug release from the compressed granules is rapid and no significant retardation due to granulation was observed. The METHOCEL™ matrix formulation produced an extended release profile characterized by an initial burst (~60% within 1 hour) and complete release within 8 hours. Combination of both granulation of the drug with Surelease and incorporation into METHOCEL™ matrix resulted in a slower release profiles, with a reduced initial burst effect (~30% release within 1 hour) and complete drug release within 12 hours.

Figure 1. Drug Release from Granules, METHOCEL™ Matrix and Granules in the METHOCEL™ Matrix

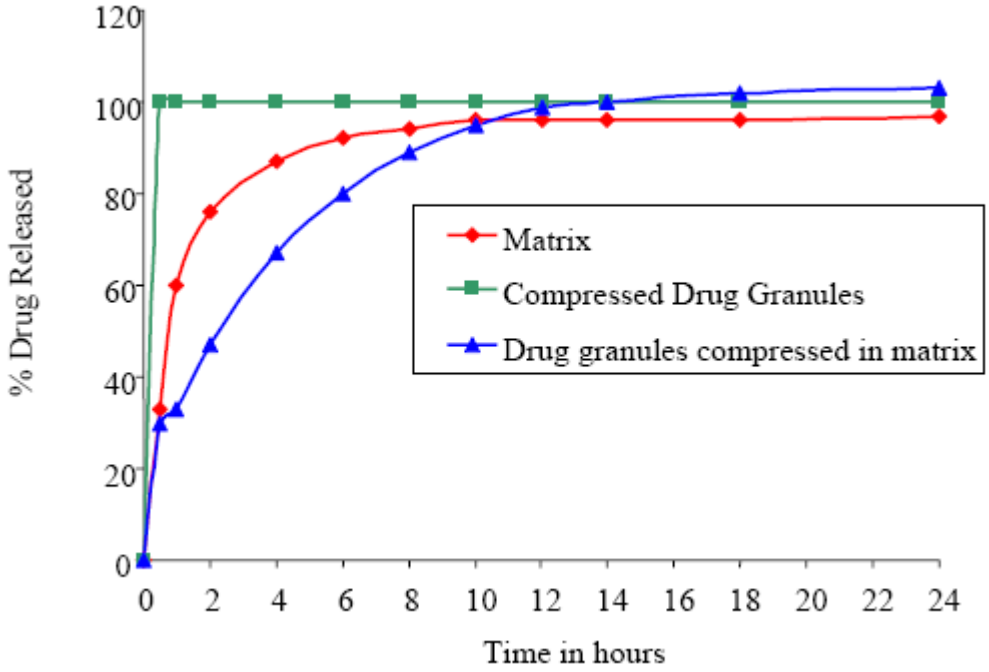
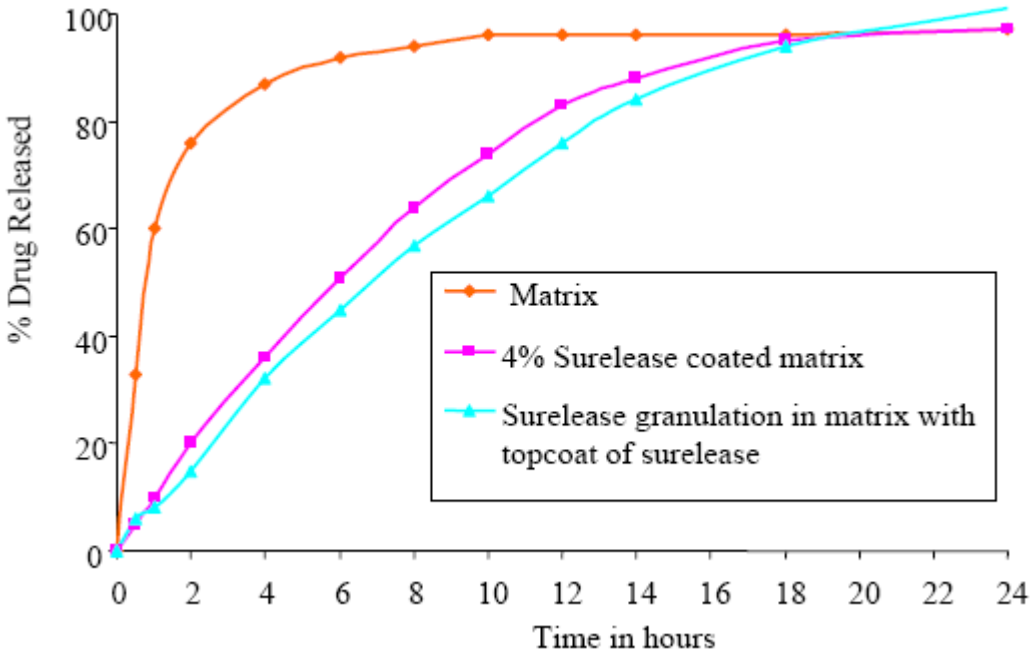


Figure 2 shows a significant retardation of drug release from matrices coated with 4% Surelease weight gain. These results show that application of Surelease as the binder during granulation of the drug, caused a significant retardation of the release profiles from the matrix formulation. In addition, application of a 4% Surelease coat onto the matrix further retarded the drug release, and prevented the initial burst effect of the matrix.

This initial burst was inhibited by the insoluble but permeable film of Surelease over the matrix tablet. The barrier coating complements the hydrophilic matrix, preventing rapid drug dissolution and release from the surface of the matrix and thus retarding drug release at the initial stage of dissolution. Further, ethylcellulose in the granulating fluid (Surelease) may form part of solid bridges between drug-drug, and drug-Starch 1500 particles on drying. This will increase the particle size and reduce the surface area of the drug particles, and decrease the dissolution rate of the drug within the matrix. Moreover, the drug particles may be coated with insoluble ethylcellulose film, in which case drug is released via diffusion through the film.[2] The incorporation of these granules into an HPMC matrix formulation results in slower drug release, compared to a formulation in which the drug is directly mixed and compressed in a HPMC matrix (Figure 2).

Figure 2. Venlafaxine HCl Release from Methocel Matrix (Uncoated and Coated) with Surelease



The internal pressure as a result of swelling and relaxation of the matrix may cause micro rupturing of ethylcellulose film during the dissolution testing.[3] The Surelease film on the matrix tablets in this study was found to rupture after 90 minutes into the dissolution study. Axial relaxation of the matrix tablet caused the film to open along the circumference of both the tablet faces (Figure 3). Drug release profiles from the matrices showed excellent reproducibility after 3 months at accelerated conditions (40ºC/75%RH) with a similarity factor, f_2 of 72.33 (Figure 4)

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

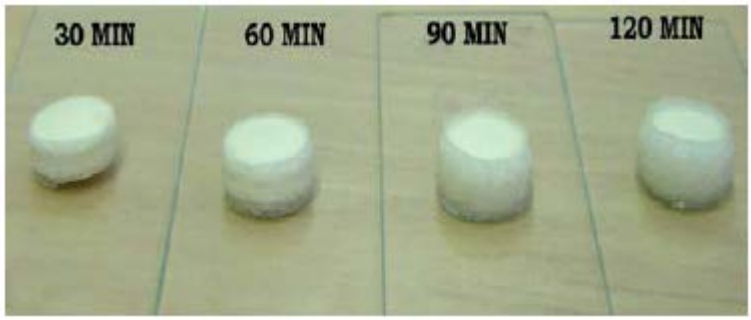
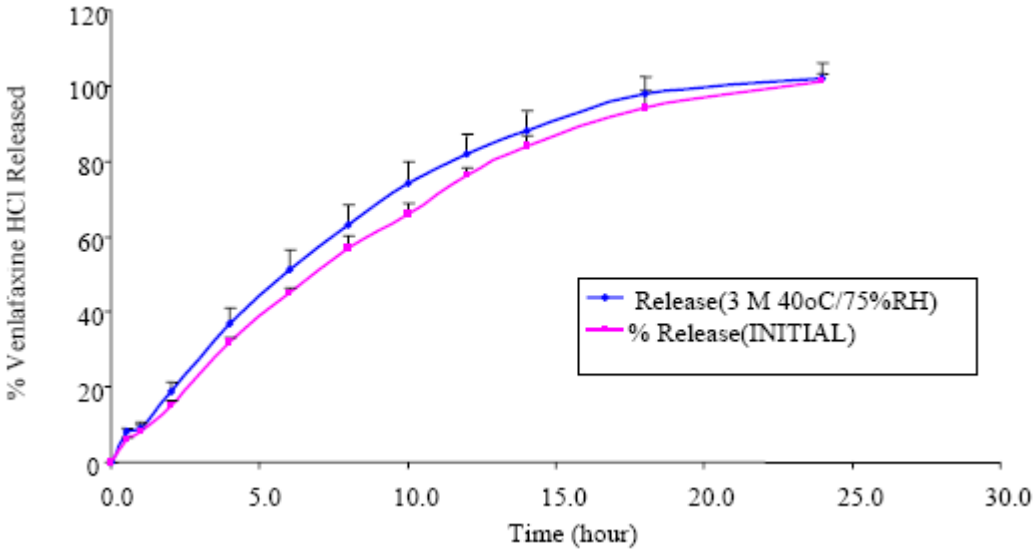


Figure 4. The Influence of Storage Conditions on Drug Release from Venlafaxine HCl Matrices Coated with Surelease



CONCLUSIONS

Single unit HPMC matrix formulations offer the advantages of simplicity and ease of manufacture. Application of a Surelease barrier membrane coating over the hydrophilic matrix prevented the initial burst effect commonly observed with highly soluble drugs. Combination of different ER technologies, such as hydrophilic matrices, granulation and use of barrier membranes offer formulation flexibility for the development of highly soluble drugs such as venlafaxine HCl.

Reprint of poster presented at CRS – July 2006. Viena D. Dias, Abhijit V. Gothoskar and Ali R. Rajabi-Siahboomi.

REFERENCES

1. Rajabi-Siahboomi, A. R., and Jordan, M.P. (2000), Slow release HPMC matrix systems, European Pharmaceutical Review 5: 21-23
2. Gothoskar, A.V., Oza, K.P. & Rajabi-Siahboomi, A.R., (2005) Study of Slow Release Matrix Formulation of a Highly Soluble Drug (Venlafaxine HCl), Proc. Int. Symp. Control. Rel. Bioac. Mater.
3. Aqueous polymeric coatings for Pharmaceutical Dosage forms.edited by James W. McGinty pp 78-79.

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