Eliminating Burst Release of Highly Soluble Drug from Hydrophilic Matrix Tablets using Venlafaxine HCl as a Model Drug

Manish Rane and Ali Rajabi-Siahboomi
Colorcon, Inc. Harleysville, PA, 19438
www.colorcon.com

AAPS
Poster Reprint 2015

Purpose

The purpose of this work was to investigate formulation approaches to eliminate burst release of a highly water soluble model drug venlafaxine hydrochloride (HCl) from a hydrophilic matrix tablet. High viscosity hypromellose polymer at 4000 and 200,000 mPa·s were incorporated in tablets at a lower than usual level of 20% w/w to allow the investigation of subtle changes in the burst release. It is generally recommended to apply suitable film coat to impart mechanical strength, assist packaging, enhance appearance, and support product stability, while improving patient compliance. In this study, the effect of low viscosity non-ionic or ionic polymers in combination with high viscosity polymers within hydrophilic matrix tablets were evaluated.

Methods

Preparation of Hydrophilic Matrix Tablets of Venlafaxine HCl

Extended release matrix tablets of venlafaxine HCl (37.5 mg strength) were prepared using METHOCEL™ K4M Premium CR Cellulose Ethers or METHOCEL™ K200M Premium CR (International Flavors and Fragrances Inc., USA) as the release controlling matrix former at 20% w/w and 30% w/w concentration, as shown in Tables 1 and 2 respectively. Formulations were also prepared to contain lower viscosity (LV) ionic polymers such as sodium alginate, sodium carboxymethylcellulose (sodium CMC) or non-ionic low viscosity hypromellose (METHOCEL E15LV), methylcellulose (METHOCEL A15LV), polyethylene oxide (POLYOX™ WSR N-80 NF LEO) or hydroxypropyl cellulose (HPC-LV). Starch 1500® partially pregelatinized maize starch, was also evaluated in place of LV polymers, since it has been previously shown to synergistically improve gel strength of hydrophilic matrix tablet resulting in further retardation of release of soluble drug.[1] API was pre-blended with LV polymers for intimate mixing, screened and mixed again before being added to the rest of the formulation. The tablets were manufactured by direct compression (GlobePharma Manual Press) using 9.5 mm standard concave tablet tooling at 2500 psi pressure and dwell time of 2 seconds. For all formulations, the target tablet weight was 300 mg with 12.5 % w/w drug content.

Based on the screening results for different LV polymers and their effect on reduction or elimination of burst release of venlafaxine in first and second hour time points, formulations containing LV ionic polymers such as sodium alginate and sodium CMC were also prepared by wet granulation (WG). The API and LV polymer were pre-blended, granulated with distilled water (~ 20% w/w) and dried at 60° C for 2 hours (conventional tray drier); granules were then passed through 30# ASTM sieve, blended with other tablet excipients and compressed into 300 mg tablets (GlobePharma Manual Press).

Table 1: Composition of ER Venlafaxine HCl Hydrophilic Matrix Tablets with METHOCEL K4M Premium CR

Formula no.	1	3	5	7	8	11	12	15	17	7A*	8A*
Ingredients	% w/w										
Venlafaxine HCl	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
METHOCEL K4M Premium CR	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	30.0	20.0	20.0
METHOCEL E15LV	------	10.0	------	------	------	------	------	------	------	------	------
METHOCEL A15LV	------	------	10.0	------	------	------	------	------	------	------	------
Sodium Alginate LV	------	------	------	10.0	------	------	------	------	------	10.0	------
Sodium CMC LV	------	------	------	------	10.0	------	------	------	------	------	10.0
POLYOX WSR N-80 NF LEO	------	------	------	------	------	10.0	------	------	------	------	------
HPC-LV	------	------	------	------	------	------	10.0	------	------	------	------
Starch 1500	------	------	------	------	------	------	------	10.0	------	------	------
MCC : Starch 1500 (2 : 1 mixture)	66.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5
Colloidal Silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

7A and 8A* formulations are wet granulated*

Table 2: Composition of ER Venlafaxine HCl Hydrophilic Matrix Tablets with METHOCEL K200M Premium CR

Formula no.	2	4	6	9	10	13	14	16	18	9A*	10A*
Ingredients	% w/w										
Venlafaxine HCl	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
METHOCEL K200M Premium CR	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	30.0	20.0	20.0
METHOCELE15LV	------	10.0	------	------	------	------	------	------	------	------	------
METHOCEL A15LV	------	------	10.0	------	------	------	------	------	------	------	------
Sodium Alginate LV	------	------	------	10.0	------	------	------	------	------	10.0	------
Sodium CMC LV	------	------	------	------	10.0	------	------	------	------	------	10.0
POLYOX WSR N-80 NF LEO	------	------	------	------	------	10.0	------	------	------	------	------
HPC-LV	------	------	------	------	------	------	10.0	------	------	------	------
Starch 1500	------	------	------	------	------	------	------	10.0	------	------	------
MCC : Starch 1500 (2 : 1 mixture)	66.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5	56.5
Colloidal Silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

9A and 10A* formulations are wet granulated*

Dissolution Testing

Drug release testing was conducted using USP Apparatus II (50 rpm) with sinkers in 900 mL of deionized water, 37° C for 12 hours.[2] The amount of venlafaxine released was determined spectro-photometrically at 224 nm, using in-line detection system. Drug release profiles were evaluated for burst release at 1 and 2 hour time points. Drug release profiles were also compared for similarity factor (f_2)[3] where applicable.

Results

Effect of High Viscosity METHOCEL Type and Concentration

Venlafaxine released in first 6 hours from formulations containing different viscosity grades and levels of METHOCEL, are shown in Table 3. The release profile remained similar at 20% and 30% concentration within METHOCEL viscosity range of ~ 4000 mPa·s and ~200,000 mPa·s. Increasing either the concentration or the viscosity grade of METHOCEL did not result in reduced high drug release (burst release) within first 2 hours. In earlier studies, venlafaxine showed similar drug release when METHOCEL K100M CR (viscosity of 100,000 mPa·s) was used at 30% concentration.[4]

Table 3: Concentration of Venlafaxine Released in First Six Hours from Formulations Containing Different Polymer Viscosity Grades and Concentrations, Manufactured by Direct Compression

Formula no.	1	2	17	18
HV Polymer	20% K4M CR	20% K200M CR	30% K4M CR	30% K200M CR
Time (min)	Mean % Cumulative Venlafaxine Released			
15	15.4	14.8	16.1	13.0
30	23.0	21.9	22.3	19.0
45	28.5	26.9	26.9	23.6
60	32.9	31.0	30.8	27.7
90	40.2	37.9	37.5	34.5
120	46.2	43.9	43.3	40.1
180	56.1	53.8	53.1	49.1
240	64.1	61.8	60.9	56.5
360	76.0	73.8	72.4	67.3*

Standard deviation for mean cumulative release all time points was between ±0.0% to ±5%

**Standard deviation was between ±5.1% to ±6.0%*

Effect of Addition of Low Viscosity Non-ionic Polymers

Prior to final blending with other materials and tablet compression, LV polymers were mixed with venlafaxine HCl. Table 3 shows that the burst release of a highly soluble drug such as venlafaxine HCl was not reduced when using a higher viscosity grade of METHOCEL (K200M vs K4M) or higher concentration of the polymer (30% vs 20% w/w). Hence, it was postulated that use of a LV polymer in combination with high viscosity METHOCEL, might help in rapid hydration of the matrix and thereby reduce the burst release.

Table 4 shows the release of venlafaxine in first 6 hours of dissolution from formulations containing 10% w/w LV non-ionic polymers such as METHOCEL E15 LV (hypromellose), METHOCEL A15 LV (methylcellulose), POLYOX WSR N-80 (polyethylene oxide), HPC-LV (hydroxypropylcellulose) and excipient Starch 1500 (partially pregelatinized starch). None of these ingredients showed a reduction of burst release during the first 2 hours. The release profiles were similar to those with inclusion of high viscosity polymers alone. An illustrative release profile is shown in Figure 1 that compares effect of 10% METHOCEL A15LV with formulations not containing low viscosity polymers on release of venlafaxine.

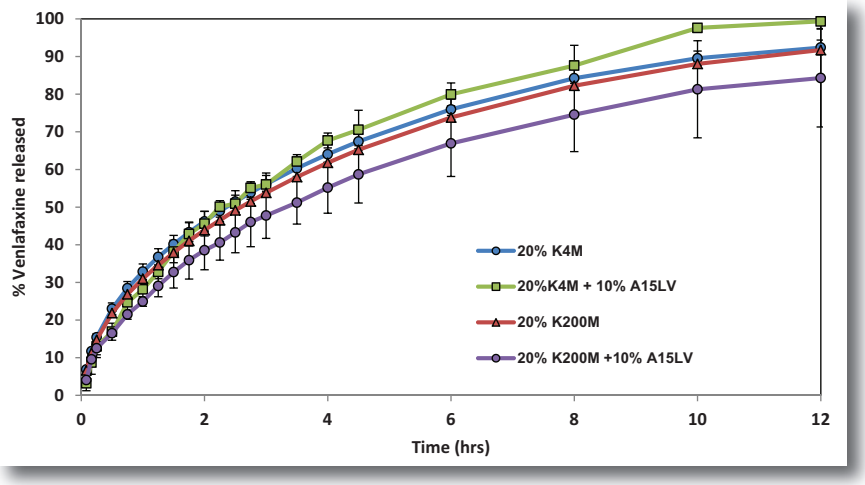
Table 4: Release Profile of Venlafaxine in First Six Hours from Formulations Containing Low Viscosity Non-Ionic Polymers or Excipient (Starch 1500) Manufactured by Direct Compression

Formula no.	3	4	5	6	11	12	13	14	15	16
HV Polymer	*20% K4M CR*	*20% K200M CR*	*20% K4M CR*	*20% K200M CR*	*20% K4M CR*	*20% K4M CR*	*20% K200M CR*	*20% K200M CR*	*20% K4M CR*	*20% K200M CR*
LV (Non-ionic) Polymer	*10% E15LV*	*10% E15LV*	*10% A15LV*	*10% A15LV*	*10% N-80*	*10% HPC-LV*	*10% N-80*	*10% HPC-LV*	*10% Starch 1500*	*10% Starch 1500*
Time (min)	Mean % Cumulative Venlafaxine Released									
15	15.2	11.6	13.0	12.5	12.9	16.0	14.3	15.2	17.4	12.6
30	22.2	16.1	16.9	16.5	19.5	22.7	22.2	21.6	24.4	18.8
45	27.6	22.2	24.7	21.5	24.4	27.2	27.9	26.3	29.2	23.3
60	32.2	26.0	28.2	24.9	28.5	30.8	32.6	30.1	32.9	27.0
90	40.0	35.1	38.2	32.7	35.5	36.8	40.5	36.4	39.1	33.1
120	46.5	41.6	45.6*	38.5*	41.6	41.8	47.0	41.6	44.2	38.2
180	57.3	52.2*	56.0	47.7*	52.1	50.5	57.8	50.3	52.7	46.6
240	66.1	60.2*	67.7	55.1*	61.0	57.9	66.3	57.4	59.6	53.2
360	79.0	73.2*	80.0	66.9*	74.1	69.4	78.3	68.0	70.8	63.5

Standard deviation for mean cumulative release all time points was between ±0.0% to ±5%

**Standard deviation was between ±5.1% to ±9%*

Figure 1: Comparison of Venlafaxine Release Profiles from Formulations Containing None or 10% Low Viscosity Non-Ionic Polymer (METHOCEL A15LV)



Effect of Addition of Low Viscosity Ionic Polymers

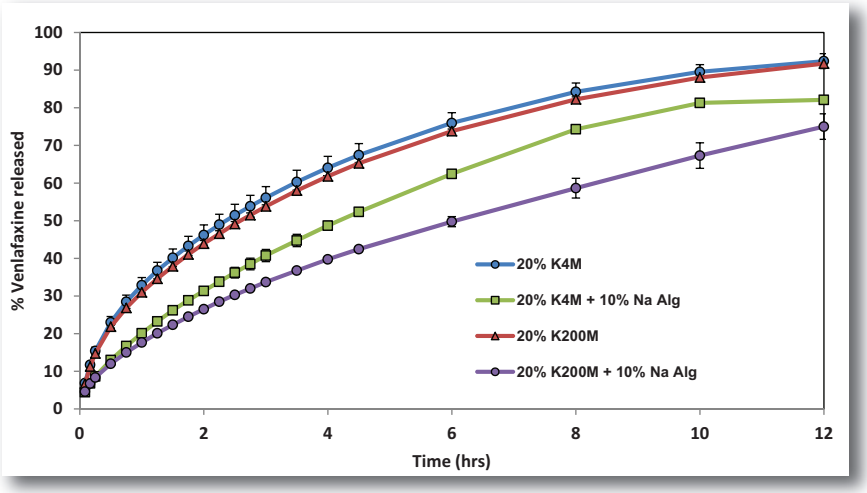
The amount of venlafaxine released in first 6 hours from formulations containing LV ionic polymers such as sodium alginate and sodium CMC, is shown in Table 5. The burst release of drug was reduced in the first two hours of dissolution profiles, and METHOCEL K200M further reduced the drug release profile. Drug release from matrix formulations containing METHOCEL K200M and both ionic polymers showed similar pseudo-zero order drug release. An illustrative release profile, as shown in Figure 2, compares the effect of 10% LV sodium alginate on release of venlafaxine.

Table 5: Release Profile of Venlafaxine in First Six Hours from Formulations Containing Low Viscosity Ionic Polymers Manufactured by Direct Compression

Formula no.	7	8	9	10
HV Polymer	*20% K4M CR*	*20% K4M CR*	*20% K200M CR*	*20% K200M CR*
LV (Ionic) Polymer	*10% Na Alginate*	*10% Na CMC*	*10% Na Alginate*	*10% Na CMC*
Time (min)	Mean % Cumulative Venlafaxine Released			
15	8.7	8.2	11.1	7.9
30	13.0	12.6	15.7	11.6
45	16.7	16.5	19.1	14.6
60	20.1	20.1	22.0	17.4
90	26.2	27.1	27.0	22.5
120	31.4	33.7	31.4	27.3
180	40.8	46.2	39.5	36.8
240	48.7	56.3	47.6	45.6
360	62.5	71.6	63.1	60.9

Standard deviation for mean cumulative release all time points was less than ±3%

Figure 2: Comparison of Venlafaxine Release Profiles from Formulations Containing Either None or 10% Low Viscosity Ionic Polymer (Na Alginate)



Effect of Manufacturing Process on Formulations Containing Ionic Low Viscosity Polymers

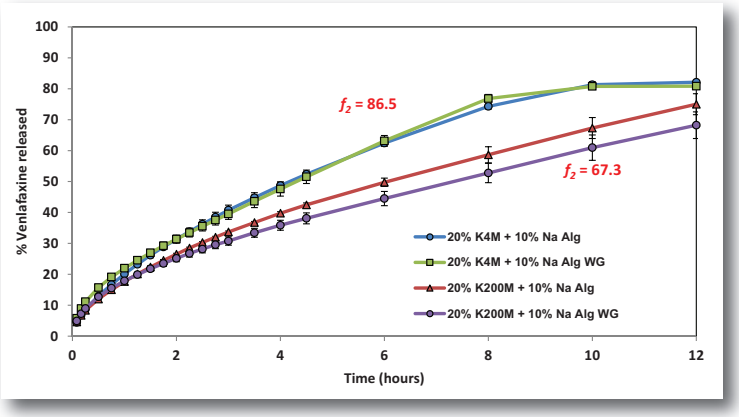
Concept for use of ionic polymers such as sodium CMC, along with HCl salt of weakly basic drugs such as metformin HCl, has been described earlier;[5] granulation of metformin HCl with sodium CMC resulted in creation of a weak base having relatively lower solubility due to acid-base reaction, with a biphasic controlled release formulation. Granulation seemed to be critical in order to activate the acid-base reaction. Similarly, we performed aqueous granulation of venlafaxine HCl with either sodium alginate or sodium CMC, and incorporated dried and sized granules in METHOCEL matrix. The release profile obtained was similar to the release profile obtained from similar composition of tablets obtained by direct compression. Table 6 gives the release profile of venlafaxine in first 6 hours from formulations containing ionic polymers and manufactured using wet (aqueous) granulation. Burst release was reduced in the first 2 hours; however, there was no significant improvement in further suppression of burst release when manufacturing method was changed. An illustrative release profile, shown in figure 3, compares the effect of manufacturing method on the release of venlafaxine from formulations containing 10% low viscosity sodium alginate.

Table 6: Release Profile of Venlafaxine in First Six Hours from Formulations Containing Low Viscosity Ionic Polymers Manufactured by Wet (Aqueous) Granulation

Formula no.	7A	8A	9A	10A
HV Polymer	*20% K4M CR*	*20% K4M CR*	*20% K200M CR*	*20% K200M CR*
LV (Ionic) Polymer	*10% Na Alginate*	*10% Na CMC*	*10% Na Alginate*	*10% Na CMC*
Time (minutes)	Mean % Cumulative Venlafaxine Released			
15	8.4	7.4	9.0	8.1
30	12.0	11.0	12.7	11.3
45	15.0	13.9	15.5	13.8
60	17.7	16.3	17.9	16.1
90	22.4	20.7	21.8	19.9
120	26.5	24.5	25.2	23.3
180	33.7	31.2	31.0	29.2
240	39.8	37.0	35.9	35.0
360	49.8	47.5	44.5	45.5

Standard deviation for mean cumulative release all time points was less than ±3%

Figure 3: Comparison of Venlafaxine Release Profiles from Formulations Containing 10% Low Viscosity Ionic Polymer (Na Alginate) Manufactured by Direct Compression and Wet Granulation



Conclusions

Low viscosity ionic polymers, such as sodium alginate and sodium CMC along with high viscosity METHOCEL polymer reduced the burst release of highly soluble drug venlafaxine HCl, within first two hours of dissolution. However LV non-ionic polymers such as METHOCEL E15LV, METHOCEL A15LV, POLYOX WSR N-80, HPC-LV and Starch 1500 excipient, did not reduce burst release. This formulation approach would be beneficial for formulators who attempt to reduce burst effects of hydrophilic matrices containing highly soluble drugs. Film coating of hydrophilic matrix tablets would help in patient compliance by helping in easy identification and swallowability[6], without affecting the drug release profiles.[7]

References

1. Levina M and Rajabi-Siahboomi A, The influence of excipients on drug release from hydroxypropyl methylcellulose matrices, J Pharm Sci, 93(11), 2004, 2746–2754.
2. USFDA dissolution methods database (http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm) accessed on April 16th, 2015.
3. Moore J and Flanner H, Mathematical comparison of dissolution profiles, Pharm Tech, 20, 1996, 64–74.
4. Dias V, Gothoskar A and Rajabi-Siahboomi A, Investigation of venlafaxine HCl (37.5 mg) extended release formulation using hypromellose (HPMC) matrices, Controlled Release Society Annual Meeting, July 2006.
5. Timmins P, Dennis A and Vyas K, Biphasic controlled release delivery system for high solubility pharmaceuticals and method, US Patent no. 6,475,521 (filed in Sept 1999).
6. Wilson C, O' Mahony B, Farrell T, Friend, B and Taylor D, Modern tablet film coatings and influence on ease of swallowing, AAPS Annual Meeting and Exposition, October 2006.
7. Patel P, Missaghi S, Tiwari S, Farrell T and Rajabi-Siahboomi R, Investigation of the effect of variable surface area-to-volume ratios and film coating on drug release from hypromellose matrices, AAPS Annual Meeting and Exposition, November 2009.