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Development of a Controlled Release Coating System for Highly Soluble Drug-Matrix Tablets

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Introduction

Monolithic drug-polymer matrix tablets are the most commonly used controlled release technology for oral drug delivery. Their popularity can be attributed to a well established history of safe and efficacious use, well understood mechanisms, relative robustness and relatively simple and economical manufacturing. However the delivery of high loads of highly soluble drugs for periods extending beyond 10 hours is challenging when using matrix systems. Typically such highly soluble, highly loaded matrix tablet systems show a high initial burst (with up to 50 percent drug released within 3 hours) followed by a rapid non-linear decline in release rates, thus yielding relatively unsatisfactory results, except for drug candidates where such intermediate release kinetics are acceptable. This study highlights the development of an Aquarius™ SRX coating system, an ethylcellulose (EC) based coating system suitable for the application of swellable matrix cores loaded with highly soluble drugs. Venlafaxine HCl (aqueous solubility 1740 mg/ml, drug load 100 mg/ 300 mg tablet) and metformin HCl (aqueous solubility 728 mg/ml, drug load 500 mg/1000 mg tablet) were chosen as model drugs. The new coating system extends the utility of matrix systems to the controlled delivery of highly soluble actives over extended periods of time and according to a variety of pre- determined release rates.

Experimental methods

Venlafaxine matrix tablets were prepared by wet granulating the drug (33%), Klucel™ hydroxypropylcellulose HXF Pharm (36%) and microcrystalline cellulose 30.5%, followed by drying, milling, and lubrication with 0.5% magnesium stearate. The final powder blend was compressed on an instrumented rotary press using 3/8" standard concave tooling. Target tablet weight was 300 mg.

Metformin matrix tablets were prepared by wet granulating the drug (50%), Benecel™ hypromellose K100M CR (30%) and microcrystalline cellulose (19.5%) followed by drying, milling and lubrication with 0.5% magnesium stearate. The final powder blend was compressed on an instrumented rotary press using 0.750" X 0.343" capsule shaped tooling. Target tablet weight was 1000 mg.

Tablet coating of 1kg pan loads was performed in a 12 inch perforated pan (Vector Corporation, Marion, IA) with Aquarius SRX coating systems comprising EC and varying ratios of pore former to optimize retardation, ability to achieve complete drug release from the matrix tablets and ability to maintain integrity of the coating while expanding with the swelling matrix tablet. The amount of coating weight gained by the tablets was varied up to 10% weight gain. The Aquarius SRX coating systems were sprayed at 11% solids concentration from a solvent mixture comprising ethanol (80%) and water (20%). A spray rate of 11 g/min, and atomization pressure of 1.0 bar were used. Inlet temperatures were maintained between 57 and 59°C resulting in a bed temperature of 40°C. The pan rotation speed was 18 rpm.

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, November 8-12, 2009, Los Angeles, California.

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Dissolution Testing was performed with the USP apparatus I (Distek Dissolution System 2100 C,North Brunswick, NJ) at 100 rpm. The dissolution media (900 ml each) comprised of pH 6.8 buffer.

Materials

1 Klucel™ hydroxypropylcellulose HXF Pharm, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2 Benecel™ hypromellose K100M CR Pharm, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
3 Venlafaxine HCl, USP, marketed by RIA International, Whippany, NJ
4 Metformin HCl, USP, marketed by RIA International, Whippany, NJ
5 3. Avicel* PH-101 Microcrystalline cellulose, NF, marketed by FMC Corporation, Philadelphia, PA.
6 HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.

Results and Discussion

As shown in Figures 1 and 2, uncoated tablets yielded typical diffusion controlled drug release profiles with a pronounced burst effect and 80% drug released in 4 and 6 hours for metformin and venlafaxine respectively. This is followed by a rapid decline in release rate in the late time period. 100% release occurred at 9 and 12 hours for metformin and venlafaxine respectively. For both metformin and venlafaxine the Aquarius SRX coating system was able to eliminate burst effects completely and deliver near linear rates for extended periods at all coating weights tested. As seen in Figures 1 and 2, the rates were predictable and programmable by simple coating weight adjustments. For the coated 300 mg standard round, concave venlafaxine tablets, release was controlled by the osmotic pressure gradient generated by the diffusion of water into the highly soluble drug core and the expansion of the core against the porous coating, which remained intact throughout the dissolution experiment and controlled the swelling of the tablet (Figure 3). Characteristic of osmotically controlled devices, an initial lag time is seen in the profiles until a constant pressure gradient is established followed by linear release up to about 80% drug released.

For the 1000 mg oblong metformin tablets, the coating was able to restrain swelling and remain intact for the first 2 hours at all coating weights, thus controlling the burst release. However axial splitting of the coating is visible after 4 hours of dissolution testing for 4 to 8% coating weight. Nonetheless drug release also remains linear for the metformin tablets. Based on the visual evidence, the operating mechanism is likely a combination of osmotically controlled drug release in the early time period followed by a gradual shift to gel diffusion controlled release as the sides of the tablets become increasingly exposed to the dissolution medium.

Conclusions

Optimized Aquarius™ SRX coating systems for swellable tablets have been developed. These controlled release coating systems expand with the swelling system to provide near linear release of highly soluble actives for periods up to 24 hours. Release rates were shown to be a function of membrane thickness. Moderate coating weights of 4 to 8% were found to be effective, thus ensuring short processing times.

Figure 1
Release profiles for Venlafaxine HCl tablets with varying amounts of Aquarius™ SRX coating system.

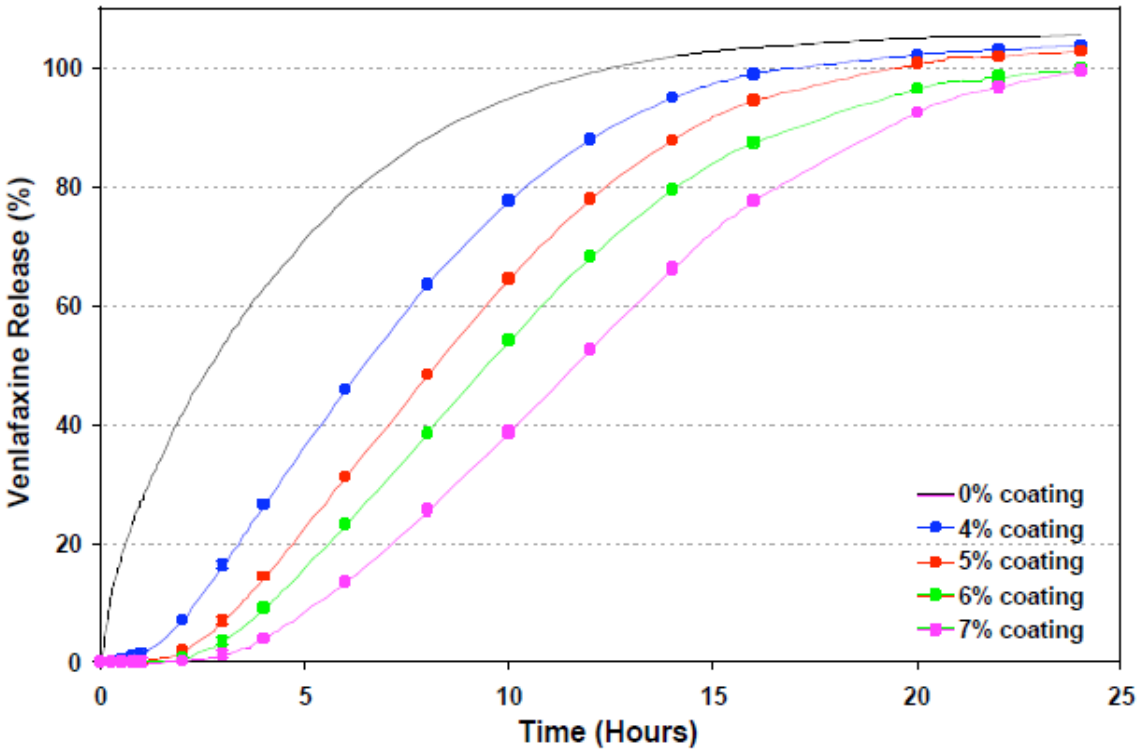

Figure 2
Dissolution profiles for metformin tablets coated with varying amounts of Aquarius SRX coating system.

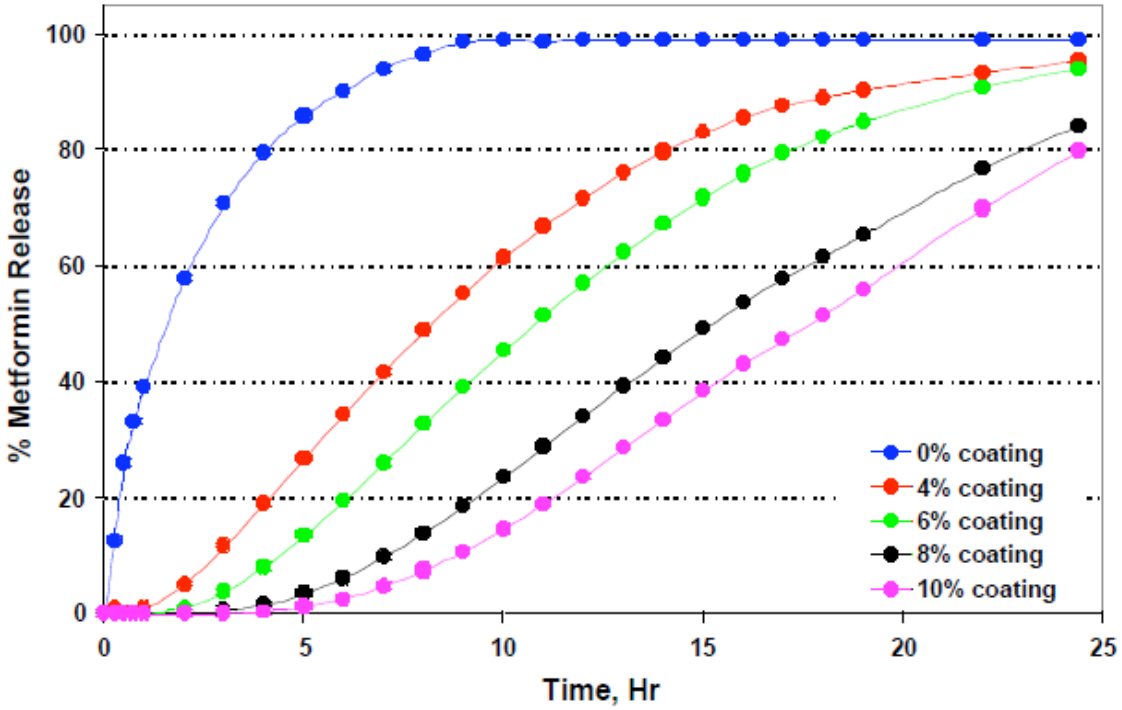

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Figure 3
Dimensional change for venlafaxine tablets at various dissolution time points.

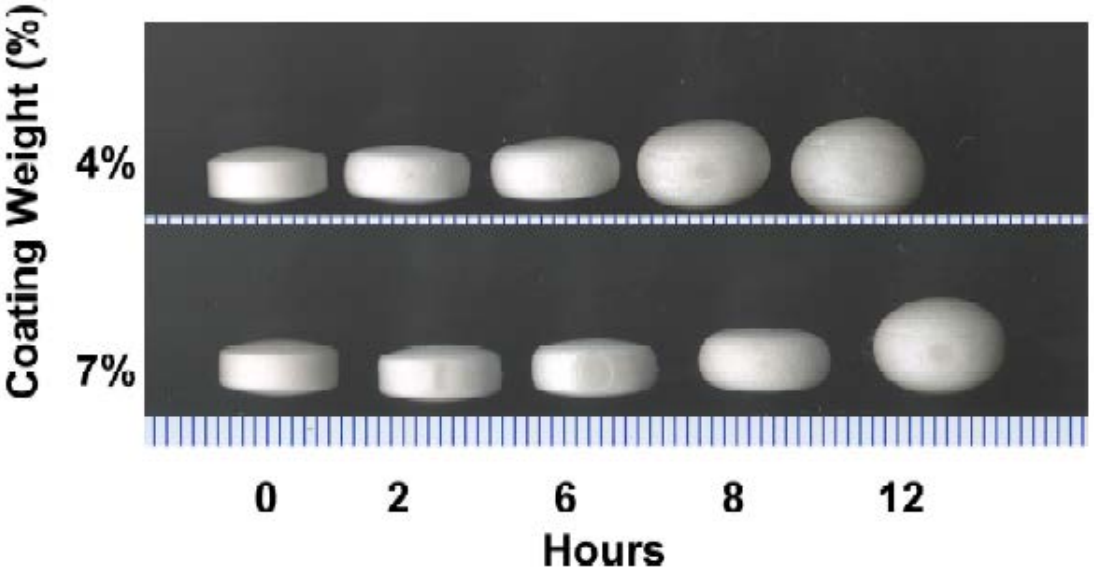
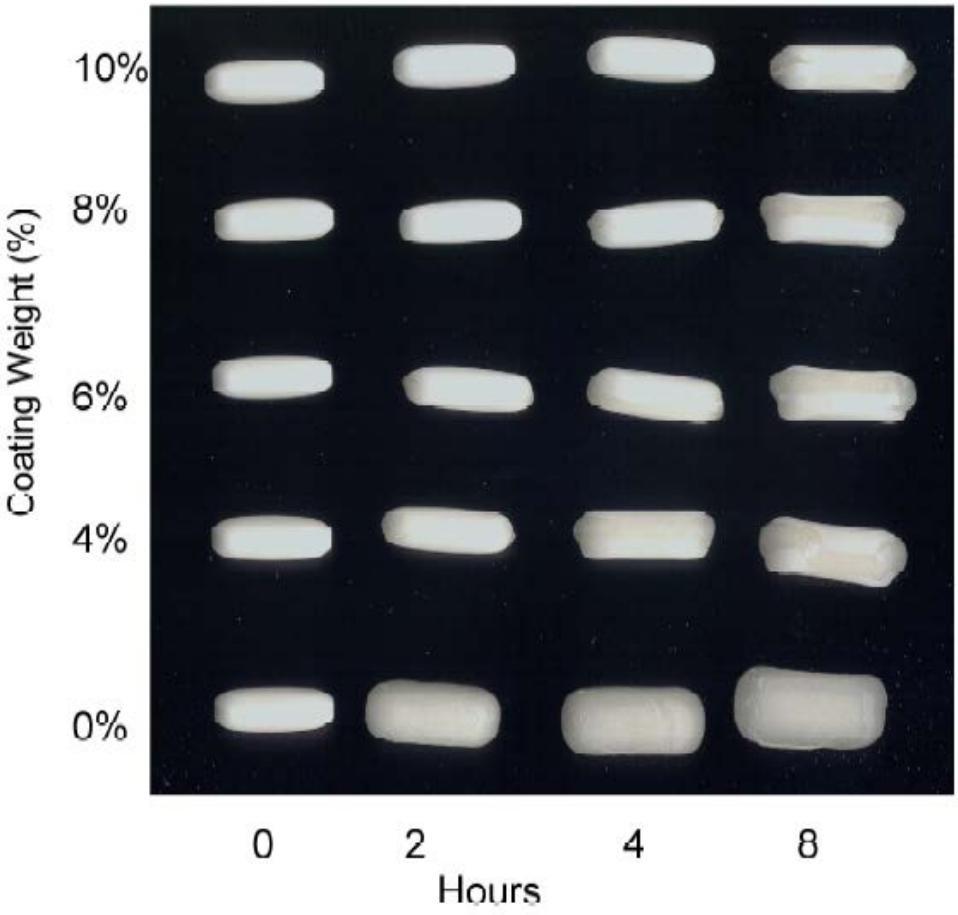


Figure 4
Dimensional change for coated and uncoated metformin tablets at various dissolution time points.



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