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Effect of Different Fillers on Low Dose Extended Release Hydrophilic Matrix Tablets

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Purpose

Extended release (ER) hydrophilic matrix formulation is a popular technology that provides improved therapeutic benefit and patient acceptability for reduced dosing frequency. Designing ER formulations for low dose drugs, based on the desired extended release profile, may require a high amount of polymer and filler. The choice of filler, in combination with the polymer, may affect drug release profiles. Therefore, it is important to understand the influence of fillers on ER matrix formulations.[1]

Starch excipients are widely used as fillers in solid oral dosage forms. Starch 1500®, partially pregelatinized maize starch, has been shown to improve the gel strength of hydrophilic matrices through synergistic interactions with hypromellose (HPMC).[2] A next-generation starch product, StarTab®, has been designed for direct compression with improved powder flow and tablet compressibility.[3] The use of StarTab in ER matrix formulations has not yet been evaluated. The purpose of this work was to investigate the effect of modified starch products on low dose extended release hydrophilic matrix tablets containing water-soluble or water-insoluble model drugs.

Methods

The compositions of two low dose model drugs, venlafaxine HCl (soluble) and naproxen (insoluble), in hydrophilic matrices, are shown in Tables 1 and 2. METHOCEL™ K100M DC2 (IFF.) was selected to formulate venlafaxine HCl, and METHOCEL™ K100 LV DC2 and METHOCEL™ K4M DC2 (IFF.) to formulate naproxen. All formulations were prepared with StarTab (Colorcon) or Starch 1500 (Colorcon) as fillers. Formulation blends were weighed, mixed for 10 minutes, then lubricated with 0.5% magnesium stearate (passed through 60# mesh screen) for an additional minute. Tablets with a target weight of300 mg were compressed on a manual tablet press (GlobePharma) at 3000 psi and 2 second dwell time, using 9.5 mm round standard concave tooling. Dissolution testing was performed using USP Apparatus II (paddles) at 100 rpm in 900 mL of deionized water (venlafaxine HCl) or phosphate buffer pH 7.4 (naproxen) at 37°C. Venlafaxine HCl and naproxen were analyzed spectrophotometrically at 225 nm and 332 nm, respectively.

Table 1. Composition of Venlafaxine HCl Extended Release Formulations

Ingredients	F1	F2
	%w/w	
Venlafaxine HCl	5.0	5.0
METHOCEL K100M DC2	30.0	30.0
StarTab	64.5	-
Starch 1500	-	64.5
Magnesium stearate	0.5	0.5
Total	**100.0**	**100.0**

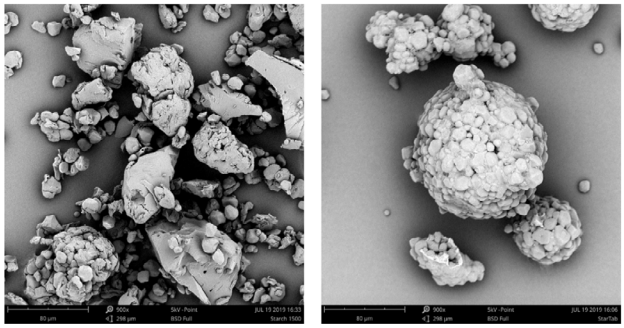
Table 2. Composition of Naproxen Extended Release Formulations

Ingredients	F3	F4	F5	F6
	%w/w			
Naproxen	5.0	5.0	5.0	5.0
METHOCEL K100LV DC2	30.0	30.0	-	-
METHOCEL K4M DC2	-	-	30.0	30.0
StarTab	64.5	-	64.5	-
Starch 1500	-	64.5	-	64.5
Magnesium stearate	0.5	0.5	0.5	0.5
Total	**100.0**	**100.0**	**100.0**	**100.0**

Results

Both Starch 1500 and StarTab are partially pregelatinized (modified) starch, having different particle morphologies. Starch 1500 is composed of irregularly shaped particles, and StarTab possesses spherical particles. Figure 1 depicts the particle morphology of Starch 1500 and StarTab.

Figure 1. SEM images of (A) Starch 1500 and (B) StarTab at 900x magnification level



(A) (B)

Drug Release Profiles of Water-Soluble and Water-Insoluble Model Drugs

All formulations demonstrated the extended release of the model drugs for up to 12 hours. In the case of highly soluble drug venlafaxine HCl, the inclusion of Starch 1500 or StarTab showed similar drug release profiles (~100% at 12 hours) (Figure 2). In comparison, for the water-insoluble drug naproxen, the inclusion of Starch 1500 led to a slower drug release profile while the use of StarTab resulted in faster drug release (Figure 3).

Figure 2. Drug Release Profiles for Venlafaxine HCl Matrix Tablets (f_2 = 75.7)

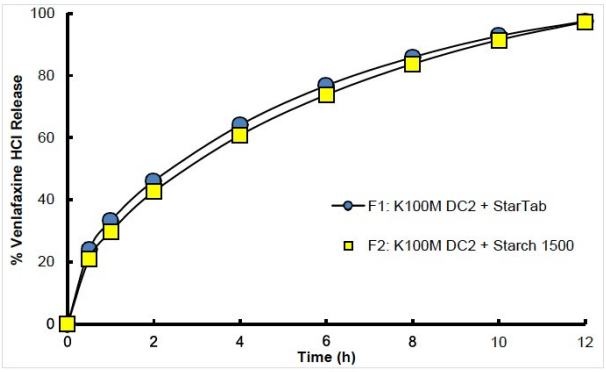
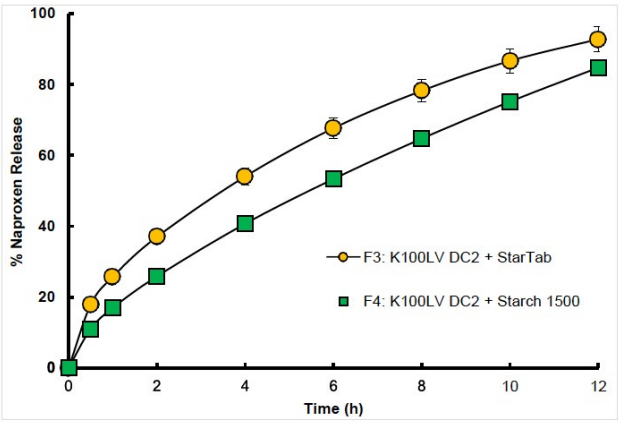


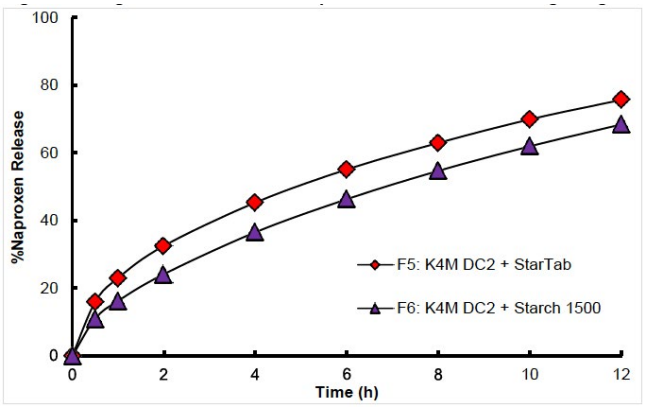
Figure 3. Drug Release Profiles for Naproxen Matrix Tablets (f_2 = 47.4)



Impact of Polymer Viscosity on Drug Release of Water Insoluble Model Drug

The drug release of ER naproxen matrices containing Starch 1500 and StarTab was further evaluated using a higher viscosity grade of hypromellose (METHOCEL™ K4M DC2). A higher viscosity grade of METHOCEL™ slowed down the drug release to less than ~80% in both starch formulations. However, the inclusion of StarTab still resulted in faster drug release compared to Starch 1500 (Figure 4). This data suggests that differences in the level of gelatinization between Starch 1500 and StarTab, with StarTab having lower gelatinization, can impact insoluble drug release from hydrophilic matrices. This may be explained by the mechanism of release for an insoluble drug, which is mainly through erosion. Higher gelatinized modified starch (such as Starch 1500) contributes to the structure of the hydrophilic matrix gel strength and undergoes slower erosion and therefore, slower drug release. Selecting the right combination of hypromellose viscosity grade and starch type could help in modulating the drug release profile of an insoluble drug in an ER tablet.

Figure 4. Drug Release Profiles of Naproxen Matrix Tablets using a Higher Viscosity Polymer (f_2 = 55.4)



Conclusions

Hydrophilic matrix tablets containing low dose drugs were successfully prepared to provide extended drug release. Inclusion of Starch 1500 and StarTab in a hydrophilic matrix formulation for a soluble model drug, venlafaxine HCl, provided similar release profiles. However, the release of an insoluble model drug, naproxen, was significantly faster with the inclusion of StarTab, as a result of lower gelatinization. Starch products are suitable fillers to be used in hydrophilic matrices to provide robustness to the formulation, manufacturing and in vivo performance.

References

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2. Levina M. and Rajabi-Siahboomi A. The influence of excipients on drug release from hydroxypropyl methylcellulose matrices. J Pharm Sci. 2004; 93(11), 2746-2754.
3. Tran-Dinh J., Roberts M., Rane M. and Rajabi-Siahboomi A. Compression profiles of a directly compressible starch using compaction simulation and high-speed tablet press. AAPS 2019, San Antonio, USA.

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