Minimize the Influence of Drug-Polymer Interaction on Drug Release from Enteric Coated Extended Release Matrix Tablet

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Objectives

To develop formulation strategies to minimize the unexpected slow release due to drug-polymer interaction and to reduce pH dependent release behavior.

Background

H161 is a weak basic drug with HCl salt and is slightly soluble in pH 1 to 6. Extended release tablet was proposed in order to achieve once-a-day dosing. An enteric coated matrix tablet was designed to have about 10-14 hours release in vivo. The rate-controlling polymer HPMC and other excipients were blended with the drug to form the core tablets. The core tablets were then coated with Eudragit L100-55 enteric coating system.

During the dissolution tests, we found unexpected drug release profile when comparing the drug release rate in pH 6.0 buffer alone and in 0.1N HCl solution for 2 hours followed by pH 6.0 buffer (Figure 1). The drug release is much slower when the tablet was in 0.1N HCl first. And the drug release rate increased as the second stage buffer pH ranged from 6.0 to 6.8 (Figure 2). It seems that the unusual release behavior is resulted from the drug-enteric polymer interaction.

Several investigators have elucidated the possible roles and mechanisms of drug-polymer interactions which are relevant for drug release kinetics, product stability and polymorphic transformation of drugs [1-7].

The slow drug release profile and its sensitive pH dependence may contribute to in vivo variability. Therefore we investigated the mechanisms of the retarded drug release and developed strategies to minimize the pH dependent release behavior.

Materials

H161 – API (Huahai Pharmaceuticals), hydroxypropyl methylcellulose (HPMC) - Methocel K100LV, K4M, K100M (Dow), lactose monohydrate - (DMV-Fonterra), magnesium stearate (MgSt) - (Macron), methacrylic acid copolymer, Type C (Eudragit L 100-55) based coating system - Acryl EZE White (Colorcon), polyvinyl alcohol (PVA) based coating system – Opadry II White (Colorcon), and hypromellose phthalate - HPMCP 55 (Shin-Etsu)

Methods

Single layer core tablets were prepared by direct compression of a blend of drug, HPMC and other excipients using a rotary tablet press. The core tablet was optionally coated with PVA based Opadry II at 3% and 8% weight gain (sub-coating). The core tablets or sub-coated tablets were then coated by Acryl EZE at 6% wt gain or HPMCP 55 hydro-alcoholic coating solution at 8% wt gain. All coatings were carried out using Vector LDC5 coating pan.

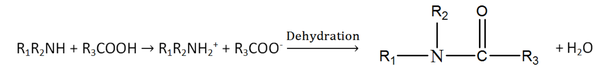
The bilayer tablet was prepared by a single punch tablet press. The top layer formulation was the same as the single layer tablet and the bottom layer contained a blend of HPMC and other excipients. The bilayer tablet was subsequently coated by Acryl EZE at 6% wt gain.

Dissolution tests were conducted by Distek dissolution device equipped with online automatic UV detection system. USP apparatus 2 at 150 rpm was employed. Either single stage in 900 ml pH 6.0 phosphate buffer or 2-stage dissolution test in 750 ml 0.1N HCl solution for 2 hours and then in 900 ml pH 6.0 to pH 6.8 phosphate buffer for 16 or 20 hours was performed.

Results and Discussion

During the second buffer stage in dissolution tests, we observed a swellable balloon like film covering the core tablet when a retarded release behavior happened. The film was eventually dissolved during dissolution. Based on the chemical reactivity [8] of functional groups in the drug and Eudragit L100-55, we propose that the slowly soluble film was drug - Eudragit L100-55 amide formed by neutralization and dehydration of the secondary amine group (simplified as R_1R_2NH) and carboxyl group in Eudragit carbon chain (simplified as R_3COOH).

The slow dissolving behavior of the drug-polymer complex can be regarded as a modification of Eudragit L100-55 function groups to increase its pH trigger point to above 6.

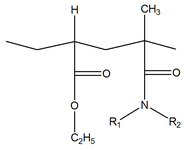


In order to prevent or minimize the drug-enteric polymer film interaction, three approaches were investigated.

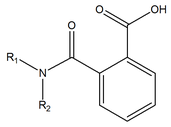
First we tried to prevent direct contact between the drug and the enteric polymer film. Soluble Opadry II separating layer was applied at 3% and 8% wt gain levels. The enteric tablet with even 8% Opadry II sub-coat failed to show any improvement of drug release rate. Actually, the drug release was even slower with higher sub-coat (shown in Figure 3). The higher coating level sub-coat may have improved the enteric film strength by smoothing tablet edges. Therefore, it seems the soluble separating coating cannot prevent the drug-polymer interaction effectively.

The second strategy utilized the double-layer core tablet concept. The drug was only on the first layer and the second layer contained swellable hydrophilic polymer HPMC. Thus the second layer will swell first when in contact with fluid. The swelling layer does not have drug, thus will not interact with the enteric polymer. At the same time, the swelling layer also facilitated the breaking or dissolving of enteric film. The drug can subsequently release freely from the broken or dissolved enteric film. The dissolution results demonstrated the concept (shown in Figure 4).

H161-Eudragit L 100-55 amide complex



H161 phthalamide



The drug release from the coated bilayer tablet was similar to the core tablet and no retarded release was observed.

It has been proposed the slowly soluble film likely resulted from the modification of Eudragit L100-55 function groups by H161-Eudragit L100-55 amide complex formation. Therefore, other types of enteric polymers with no carboxyl group directly attached to polymer chain may not suffer from the insolubility problem. We tried HPMCP 55 enteric coating with hydro-alcoholic coating solution at 8% wt gain. Again the drug release from the HPMCP coated tablet was similar to the core tablet and no retarded release was observed (Shown in Figure 5).

It is suspected that the weak basic drug may only react with the polymer degradation products or residual free phthalic acids present in HPMCP to form small molecule H161 phthalamide which was very likely soluble. Thus, no significant modification of HPMCP polymer function groups occurred.

Conclusions

- Unwanted retarded release in pH 6.0 phosphate buffer stage after an acid stage for 2 hours was observed for an Eudragit L100-55 coated ER tablet. The slow release was caused by a slowly soluble enteric film covering the tablet.
- Based on chemical reactivity of secondary amine group present in the drug, we proposed that drug-Eudragit L100-55 amide formed by neutralization and dehydration of amine group and carboxyl group in Eudragit carbon chain. The reaction was facilitated in acid medium and the complex was readily soluble in pH 6.8 or higher.
- The mechanisms of slow release can be regarded as a modification of Eudragit L100-55 function groups to increase pH trigger point to above 6.
- Our results showed the retarded release can be avoided either by a bilayer core tablet concept or by switching to other enteric polymers (such as HPMCP).

Figure 1. Drug release from core & Eudragit coated tablets 1-stage vs. 2-stage dissolution methods

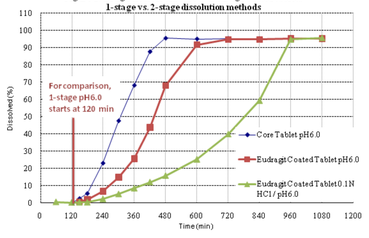


Figure 2. Drug release from Eudragit coated tablet in different buffer pHs

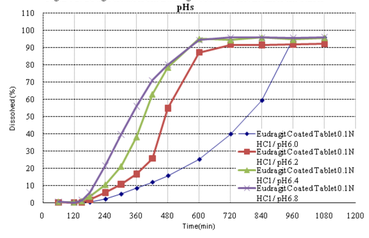


Figure 3. Effect of Opadry II sub-coat on drug release from Eudragit coated tablets

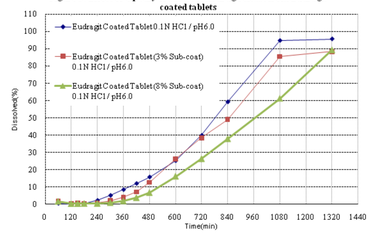


Figure 4. Drug release from Eudragit coated single layer and bilayer tablets

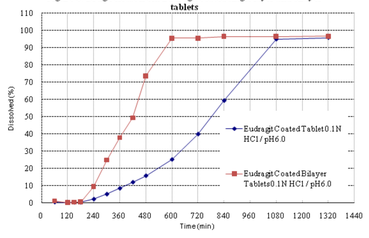
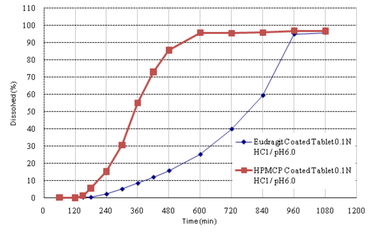


Figure 5. Drug release of Eudragit and HPMCP coated tablets



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