Drug Release Stability of Propranolol Hydrochloride ER Multiparticulates using Ethylcellulose Dispersions

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Introduction

Ethylcellulose aqueous dispersions are commonly used as barrier membrane coatings to develop sustained release (SR) multiparticulates (MP) formulations. In this study, the storage stability of multiparticulates formulations of a freely soluble model drug, propranolol hydrochloride (HCl), was evaluated using a fully formulated aqueous ethylcellulose dispersion (Surelease®) and an ethylcellulose dispersion that requires the addition of plasticizer (Aquacoat® ECD). Both MP formulations were exposed to different lengths of curing duration and the effect of accelerated stability conditions on drug release performance was evaluated.

Methods

Drug Layering and Sustained Release Coating – Propranolol HCl was layered onto sugar spheres (850 – 1000 µm) (Suglets®, PF011 Colorcon Inc., USA) using an HPMC-based Opadry® (Colorcon Inc., USA) as binder with 70:30 w/w drug/binder ratio in a fluid bed coater (Bosch Hüttlin Unilab). The MPs were then barrier membrane (BM) coated using either Surelease or Aquacoat ECD (Colorcon Inc., USA) in a fluid bed coater equipped with Wurster configuration (Glatt GPCG-2). The process parameters for drug layering and subsequent coating with the aqueous ethylcellulose dispersions are highlighted in Table 2. Before coating, a water-soluble plasticizer, triethyl citrate (TEC, Vertellus, USA) at 24% w/w with respect to the polymer, was added to Aquacoat ECD. The ethylcellulose aqueous dispersions were coated to a 10% w/w theoretical weight gain (WG). A top-coat (using the same Opadry) at 1% w/w WG was applied over the barrier membrane coatings.

Curing and Stability Evaluation: Each batch of coated MPs was split into three equal parts, with two parts subjected to post coating curing for 2 and 24 hours in a 60°C oven. After curing, 25 g of MPs was packed into 75 cc HDPE bottles, which were induction sealed and stored at accelerated stability conditions (40ºC / 75% RH). Samples were pulled at specified intervals and tested for drug release performance.

Drug Release Testing: The drug release from MPs was determined spectrophotometrically at 289 nm using USP Apparatus II (paddles), 1000 mL DI water at 37°C. The dissolution results generated were compared using the f_2 factor; where a value between 50 and 100 indicates that the two dissolution profiles are similar.[1]

Table 1. Batch Preparation Overview

Formulation Stages	Component	Solids (%w/w)	Weight Gain (%w/w)
Drug Layering	Propranolol HCl	15	7
Barrier Membrane Coating	Surelease	15	10
Top-coat	Opadry	10	1

Table 2. Drug Layering and Aqueous Ethylcellulose Dispersion Coating Parameters

Process Parameter	Drug Layering	Ethylcellulose Coating
Equipment	Huttlin Fluid Bed	Glatt CPCG-2
Batch size (kg)	4 – 6 kg	2.0
Intel temperature	57 – 58	53 – 65
Product temperature	45 – 50	41 – 46
Outlet temperature	41 – 46	38 – 44
Atomizing air (bar)	1.5	2.0
Air volume (CMH)/(m^3/hr)	325	120 – 130
Nozzle size (mm)	1.2	1.2
Fluid delivery rate (g/min)	12 – 24	10 – 14

Results

Stability Evaluation of Surelease Coated MP – Figures 1a to 1c show the drug release profiles of Surelease coated propranolol HCl multiparticulates that were uncured, cured for 2 and 24 hours and then exposed to accelerated stability condition (40°C and 75% RH) up to 6 months.

Surelease coated propranolol MPs demonstrated stable and consistent drug release behavior for uncured (f_2 > 71), 2hrs cured (f_2 > 70) and 24hrs cured (f_2 > 70).

Figure 1a. Drug Release from Propranolol HCl ER MPs Coated with Surelease: Uncured

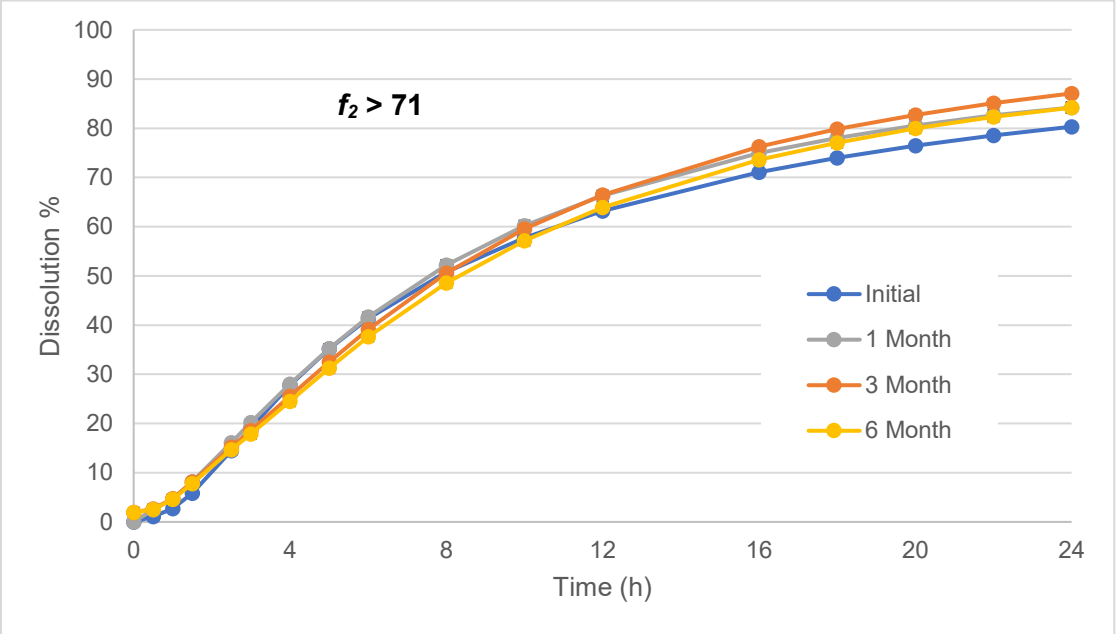


Figure 1b. Drug Release from Propranolol HCl ER MPs Coated with Surelease: 2 h Curing

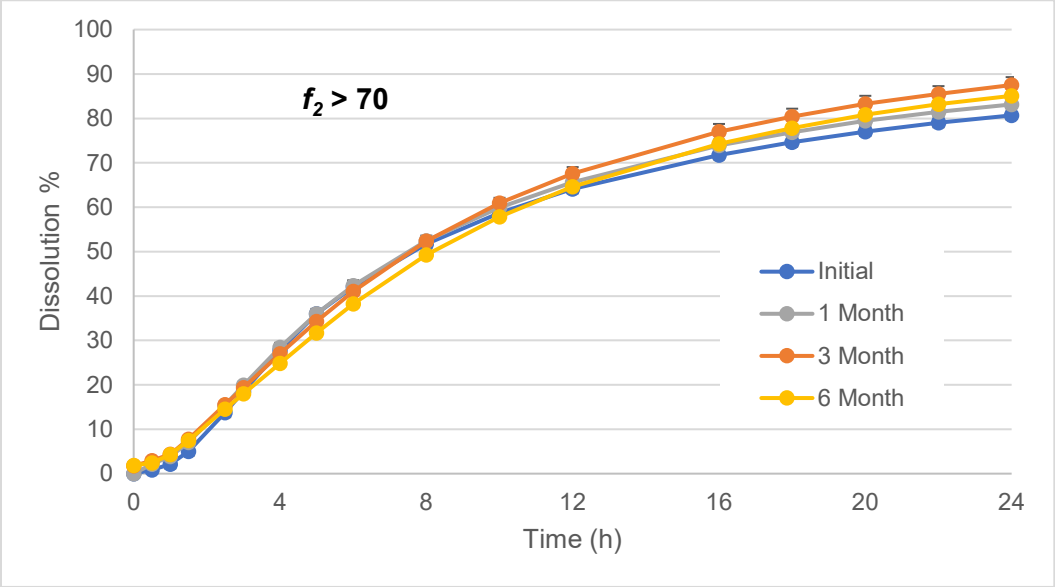
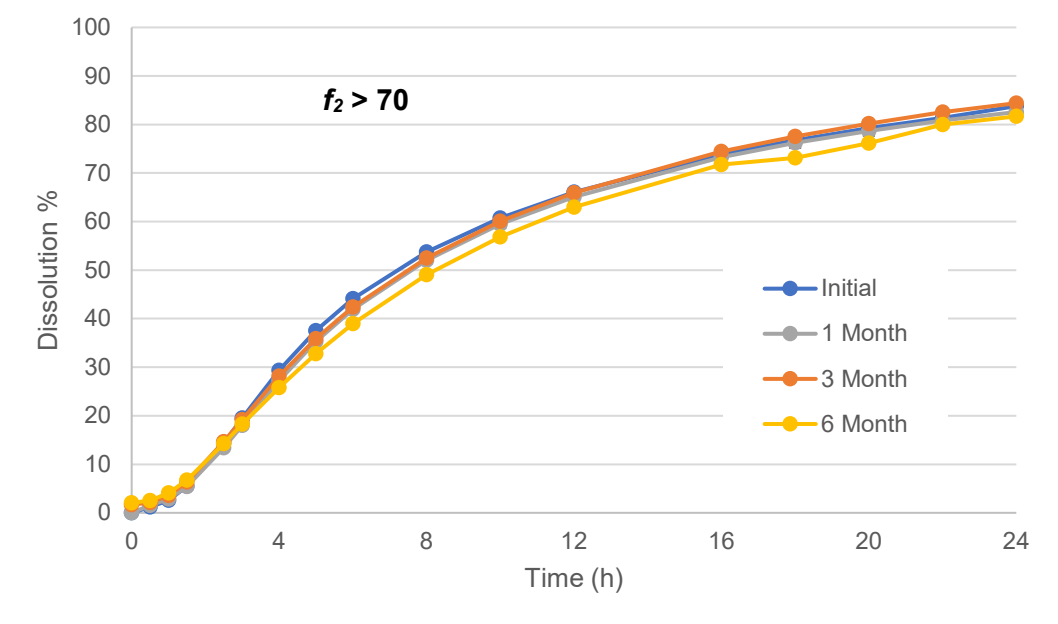


Figure 1c. Drug Release from Propranolol HCl ER MPs Coated with Surelease: 24 h Curing



Stability Evaluation of Aquacoat ECD Coated MP – Figures 2a to 2c show the drug release profiles of Aquacoat ECD coated propranolol multiparticulates that were uncured, cured for 2 and 24 hours, and then exposed to accelerated stability conditions (40°C and 75% RH) up to 6 months.

Stable drug release performance was observed from Aquacoat ECD dispersions after 2 h of curing (f_2 >50, Figure 2b). Additional curing up to 24 hours further ensures the consistency of the drug release (f_2 value >72) from Aquacoat ECD coated multiparticulates (Figure 2c). Drug release slows down from 0 hours to 2 hours to 24 hours curing, indicating coalescence of the EC particles during curing process. It was demonstrated that Aquacoat film show that porosity decreases with increasing curing duration.[2] The uncured film appears porous, and the 2 HR cured MPs produce good film density and 24-hour cured multiparticulates show a dense film. Current work demonstrates, Aquacoat requires curing but once cured, the release profile was found to be consistence and reproduceable on long term stability

Figure 2a. Drug Release from Propranolol HCl ER MPs Coated with Aquacoat ECD: Uncured

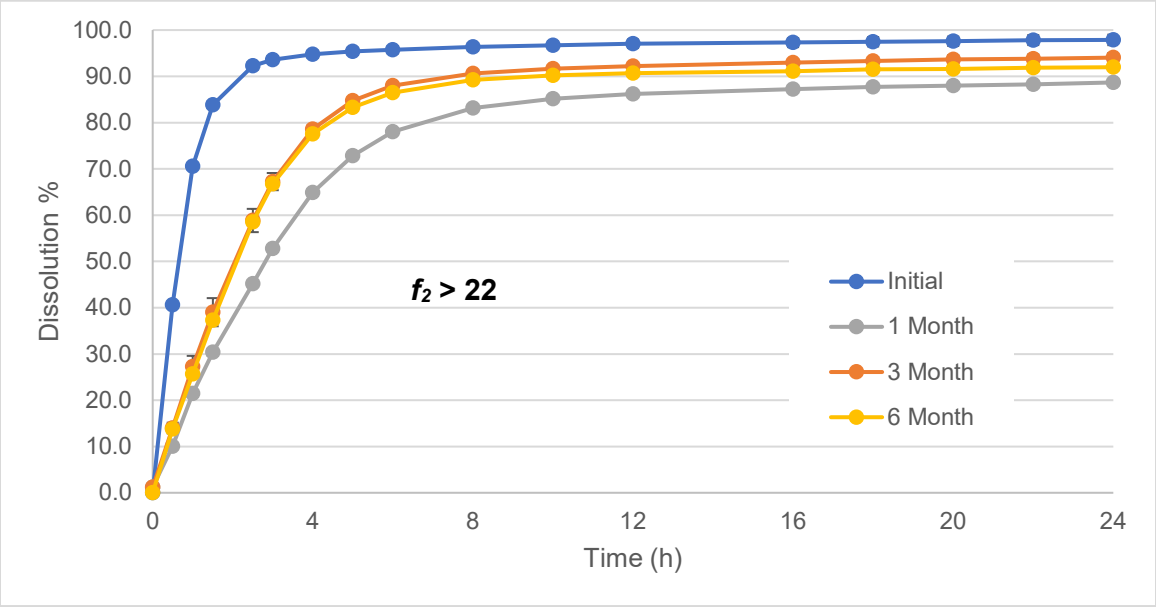


Figure 2b. Drug Release from Propranolol HCl ER MPs Coated with Aquacoat ECD: 2 h Curing

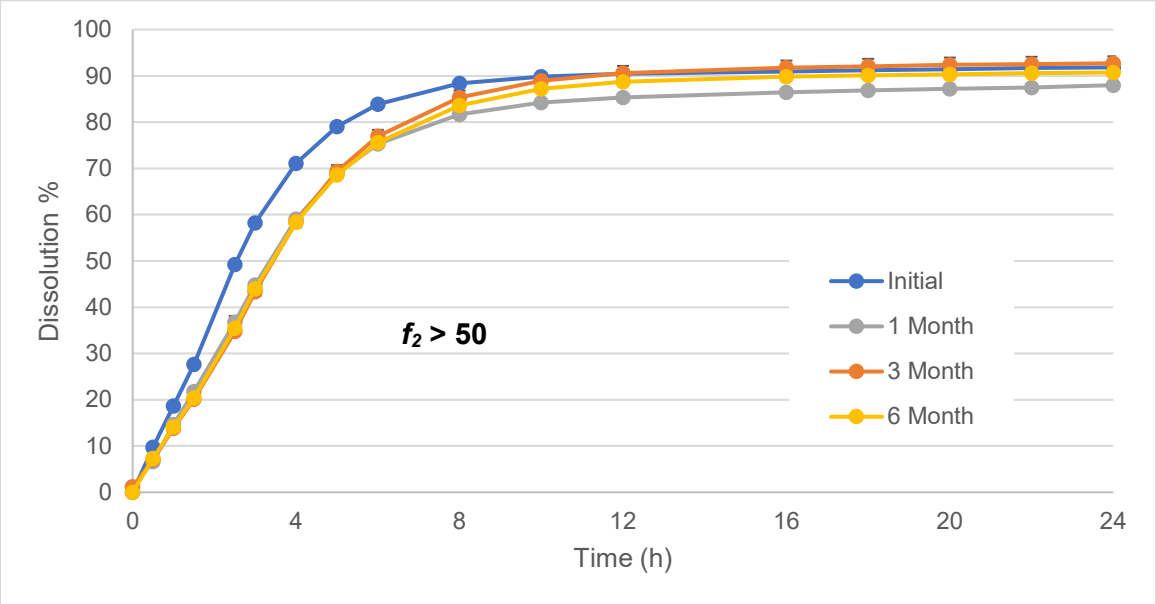
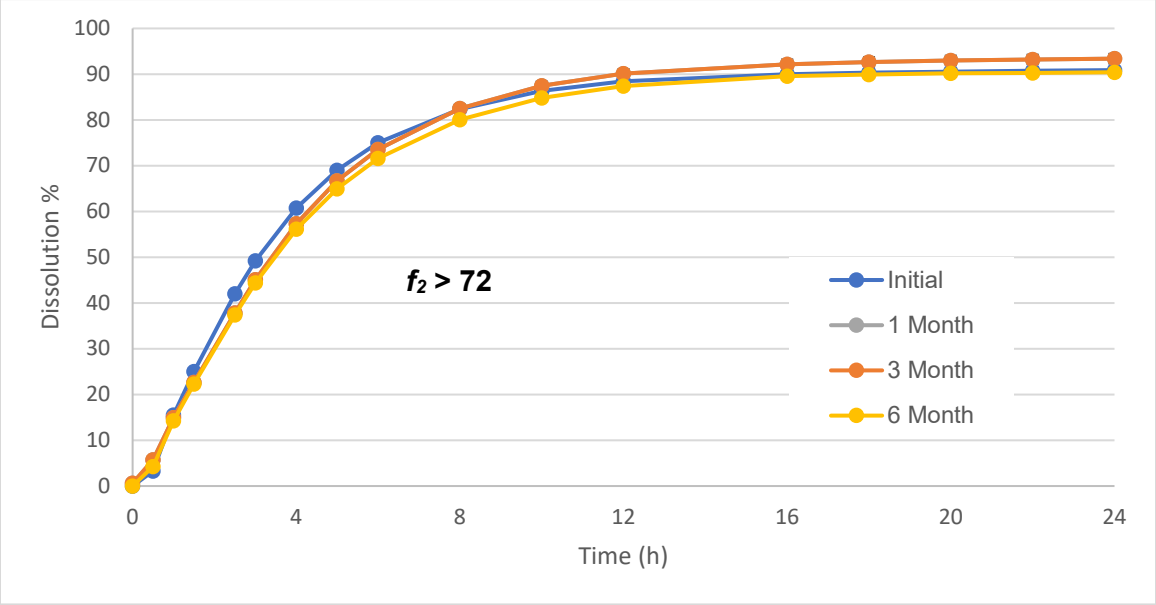


Figure 2c. Drug Release from Propranolol HCl ER MPs Coated with Aquacoat ECD: 24 h Curing



Conclusions

Both ethylcellulose aqueous dispersions demonstrated successful coating application to achieve sustained release for propranolol HCl multiparticulates. Application of ethylcellulose aqueous dispersions provided consistent drug release performance following storage at accelerated stability conditions. The results show the importance of optimized processing parameters and curing duration to achieve consistent drug release from sustained release MP systems.

References

1. Moore, J. W., and H. H. Flanner, 1996, "Mathematical Comparison of Dissolution Profiles," Pharmaceutical Technology, 20 (6):64-74.
2. Hoxha, K., Mehta, R., Ghimire, M. and Rajabi-Siahboomi, A. R, 2021, “Evaluation of Formulated Ethylcellulose Aqueous Dispersions to Develop Controlled Release Multiparticulate Formulation of Freely Soluble Drug, Propranolol Hydrochloride,” Controlled Release Society Annual Meeting.

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