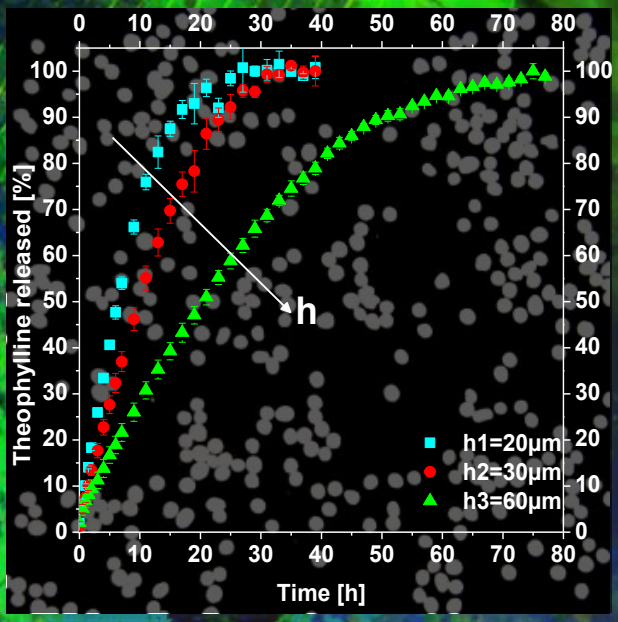
Extended release of theophylline from ethylcellulose coated pellets: preparation and characterization



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Extended release of theophylline from ethylcellulose coated pellets:preparation and characterization - M. Margherita Cafaro

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Extended release of theophylline from ethylcellulose coated pellets: preparation and characterization

Master's Thesis in Chemical Engineering

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To my crazy family

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Sommario

Una parte ricerca farmacologica è da anni dedicata allo studio di forme farmaceutiche a rilascio controllato. Uno dei metodi di preparazione di questi sistemi è quello dell'uso di un rivestimento prevalentemente di natura polimerica, involucro che per le forme farmaceutiche destinate alla via orale può avere anche altre funzioni, come ad esempio il camuffamento del cattivo sapore degli ingredienti della formulazione. Per anni sono state utilizzate, per produrre i rivestimenti, soluzioni organiche con polimeri opportunamente selezionati; attualmente la ricerca scientifica è sempre più orientata all'uso di rivestimenti ottenibili da dispersioni acquose per ragioni ambientali, di sicurezza e tossicità. Questo nuovo approccio formulativo è campo di sfida poiché molti studi preparativi e di caratterizzazione non sono stati ancora pienamente sviluppati e approfonditi. Lo scopo di questo lavoro di tesi è stato valutare le cinetiche ed i meccanismi di rilascio di principio attivo da una forma farmaceutica solida rivestita con una dispersione acquosa di etilcellulosa commerciale, il Surelease. Allo scopo di ottenere un rilascio controllato del farmaco, il Surelease è stato utilizzato per ricoprire una piattaforma di dosaggio micrometrica (pellet) strutturata a geometria sferica e costituita da tre strati: un core inerte di cellulosa microcristallina, uno strato di principio attivo composto da un farmaco modello, la Teofillina, e un polimero utilizzato come plastificante, l' idrossipropil metilcellulosa (HPMC), ed in superficie il rivestimento polimerico di etilcellulosa. Le sferette ricoperte sono state preparate utilizzando un letto fluido. La preparazione, in particolare, è stata suddivisa in due fasi differenti: durante la prima fase il core inerte è irrorato con la soluzione di Teofillina e HPMC; durante la seconda fase ha luogo il rivestimento di etilcellulosa, sempre adoperando la stessa apparecchiatura. Allo scopo di investigare l'influenza dello

spessore di ricoprimento sulla cinetica di rilascio del principio attivo, sono stati prodotti tre diverse tipologie di lotti di sferette ricoperte; lo spessore è stato modificato variando la quantità di dispersione di etilcellulosa impiegata durante la seconda fase di preparazione, ottenendo ricoprimenti di 20, 30 e 60 μm. Le sferette micrometriche sono state caratterizzate con diversi metodi. La microscopia elettronica a scansione (SEM) è stata utilizzata per studiare la morfologia e per misurare lo spessore effettivo dello strato di ricopertura in Surelease. Le proprietà di rilascio di sistemi di dosaggio approntati sono state investigate ponendo in immersione in tampone fosfato a pH 6.8, a 37°C e sotto agitazione controllata, sia lotti di microsferette ricoperte che microsferette singole. I test di rilascio condotti sui lotti di microsferette sono stati condotti per avere informazioni sulla cinetica di rilascio complessiva; i test di rilascio da microsferette singole sono stati effettuati per investigare il comportamento "non di massa" e l'eventuale presenza di fenomeni di lag time. Per i lotti di microsferette prodotte con spessore pari a 30 μm (ricoprimento con spessore di valore intermedio) sono stati condotti test di rilascio variando anche l'osmolalità del mezzo di rilascio, attraverso la solubilizzazione di NaCl, al fine di valutare l'influenza della pressione osmotica sulla cinetica di rilascio. Test di rigonfiamento (swelling) di lotti di microsferette sono stati effettuati per investigare l'effetto dell'espansione dello strato polimerico di HPMC sul film di Surelease di ricopertura, in particolare, per osservare la possibile formazione di fratture. Parallelamente alla preparazione delle microsferette ricoperte, sono stati condotti studi di resistenza a trazione meccanica e di permeabilità ad acqua e teofillina di film di Surelease ottenuti mediante lo spray di dispersioni su supporto inerte posizionato su un tamburo rotante. I risultati sperimentali mostrano che il metodo utilizzato per la preparazione delle microsferette ricoperte finalizzate al rilascio controllato del farmaco fornisce buoni risultati: la ricopertura di etilcellulosa ritarda significativamente il rilascio del farmaco e, variando lo spessore del ricoprimento, è possibile variare il tempo necessario affinché tutto il farmaco inizialmente caricato nella formulazione passi nel bulk di dissoluzione. Il meccanismo di rilascio predominante per la formulazione preparata e caratterizzata sembra essere diffusivo, poiché il film di etilcellulosa appare intatto dopo l'esposizione al mezzo di rilascio.

Abstract

A section of pharmaceutical research is dedicated to the study of controlled release formulations. One technique adopted to prepare this remedies consist of using a polymeric coating, in case of oral administrations the coating can have more functions, for example it can be used for taste masking applications. For many years coatings were produced using organic solutions of the chosen polymer, but nowadays the research is switching on coating based on aqueous dispersions because of the environment, safety and toxicity. Aqueous based coatings are a new challenge for many reasons and they have to be studied and characterized. The aim of this thesis work is to understand the mechanism of the active substance release from a solid formulation coated with a commercial aqueous dispersion of ethylcellulose, called Surelease®. In order to design a controlled release formulation, Surelease® was used to coat a spherical micrometric formulation (pellet) made of three layers: an inert core of microcrystalline cellulose, a layer of active substance made by a model drug, theophylline, and polymer used as plasticizer, hydroxypropyl methylcellulose (HPMC), and a polymeric layer of ethylcellulose. Pellets were prepared using a fluid bed coater equipment. The preparation was divided in two steps: during the first step the inert core was sprayed with a solution of theophylline and HPMC and during the second one the drug layered pellets were coated with the aqueous dispersion of ethylcellulose. Three different batches were made with three different coating thicknesses in order to understand the influence of coating thickness on the release rate of theophylline; the thickness of the coating was changed modifying the amount of dispersion used during the second phase of preparation, the values of thicknesses investigated are 20, 30 and 60 μm. Pellets were characterized with different methods. Scanning electron microscopy

was used on whole pellets to study them morphology and it was used on pellets cross-section to evaluate the real coating thickness. Drug release experiments from a whole dose of pellets and from single pellets were performed using phosphate buffer pH 6.8, at 37°C, under stirring. Whole dose release tests were used to evaluate the drug release curve. Single pellets release tests were used to understand if every pellet has the same release behaviour; this test was also used to check if the system is characterized by lag time. Drug release experiments from a whole dose of the batch with coating thickness 30 µm were performed, changing the osmolality of the release medium to understand the influence of it on the release rate. Pellets swelling behavior was investigated to check the formation of eventual cracks and fracture in the film. In order to characterize the only layer of coating, Surelease® free standing film was prepared, with a modified fluid bed equipment, spraying the ethylcellulose dispersion onto a rotating drum. Free film cross-section was investigated by scanning electron microscopy. Mechanical properties were determined by tensile testing. Several permeability studies were performed to determine water and drug permeability coefficients.

It can be concluded, from the experimental data, that the technique used to prepare coated pellets intended for controlled release applications provided satisfying results: drug release rate over time is significantly delayed by the ethylcellulose layer; using different thickness of the coating the time needed to release the whole amount of drug in the formulation can be changed. The release mechanism predominant in this system seems to be drug diffusion.

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