SWELLABLE ANTI-TUBERCULAR DRUG-POLYELECTROLITE MATRICES: CHARACTERIZATION AND DELIVERY PROPERTIES

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INTRODUCTION
Rifampicin (RIF) and Isoniazid (INH) are administered in Fixed Dose Combination (FDC) solid formulations to improve patient compliance in the treatment of tuberculosis. In FDC, RIF bioavailability problems are frequent because of its acid decomposition, catalyzed by INH. RIF degradation is proportional to INH concentration in acidic media. These problems could be overcome by developing an FDC in which the delivery of the drugs is site-specific and segregated, with RIF released in stomach and INH in small intestine (1). The aim of this work is to obtain and characterize swellable drug-polyelectrolyte matricial systems of RIF and ISO for a further development of a bi-layer tablet that sequentially release RIF and INH.

MATERIALS AND METHODS
Alginic acid (AA), carboxymethylcellulose (CM), RIF and INH were used to obtain solid acid-base complexes. The solid powders were characterized by FT-IR, DSC-TG and powder X-Ray diffraction. The flow properties were also evaluated. Matrices prepared by compression of the complexes were subjected to measurements of solvent up-take and release kinetics in simulated gastric and intestinal fluid. RIF stability in the dissolution media was determined.

RESULTS
The AA-ISO and CM-RIF material were easily prepared as particulate materials. Characterization through FT-infrared spectroscopy, powder X-ray diffraction and DSC indicates the ionic nature of the interaction between the carboxylic groups of the polyelectrolytes and the basic group of the drugs. The complexes were granulated using ethanol to obtain powders with improved flow properties. Fluid uptake from CM-RIF matrix was fast reaching quickly a plateau; water diffuses promptly through the matrix pores to completely wet it in a few minutes. On the other hand, sorption rate of AA-ISO matrix was slow and decreased with time as a consequence of the development of a continuous hydrogel layer on matrix surface. Experimental results indicate that delivery rate from matrices is a function of its composition. When the CM-RIF matrix was immersed in the dissolution media to determine release rates, it takes solution quickly, swell, and finally disintegrate in a very short period of time. RIF release in acidic media approached 100% as a consequence of the fast exchange between the H+ or Na+ of the dissolution medium and RIFH+. This behavior was previously observed for CM-model basic drugs matrices (2). In contrast, ISO release from matrices of AA–ISO exhibited a slow delivery rate, by a diffusion mechanism, in simulated gastric fluid followed by a complete release in simulated intestinal fluid. The mechanism is different of previously developed AA- complexes (3). RIF stability in simulated gastric medium was improved in the matricial system in relation to RIF/INH acid solutions as a result of the slower INH concentration in the dissolution medium.

CONCLUSIONS
The release rate of RIF and INH could be modulated by acid-base complexation with different polyelectrolytes. The in vitro release behavior is reasonably satisfactory to continue with the formulation step of a bi-layer tablet that sequentially release RIF and INH.

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