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Research paper

Preparation, characterization and photostability assessment of curcumin microencapsulated within methacrylic copolymers

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ABSTRACT

Microencapsulated curcumin (CUR) was obtained by coevaporation with polymethacrylate polymers (blends at various percent ratios of Eudragit® RS100 and RL100 resins). The suspensions were freeze-dried to produce free flowing microparticles, which were sieved in the 420–90 μm range. They were characterized in the solid state for micromeritic properties and drug loading, and by FT-IR, powder X-ray diffractometry and differential scanning calorimetry for physical state. Encapsulation efficiency largely varied from 35 to 95%, mainly depending on the copolymer composition and to a less extent from drug-to-polymer ratio. Solid-state characterization confirmed the chemical stability of CUR in microparticles, and suggested that the drug was in a microcrystalline form within the polymer matrix; microscopy analysis confirmed the latter statement. In vitro release and dissolution profile of neat and encapsulated CUR were assessed in simulated gastric and intestinal fluids: from these studies, it was however found that the microencapsulation of CUR in these polymers did not improve the solubility of this very poorly soluble compound in simulated gastric and intestinal aqueous media.

Interestingly, photostability experiments showed that the dispersion of CUR in the polymer matrix effectively protects the drug from light-induced chemical degradation, with an effect dependent on the drug-to-polymer ratio.

1. Introduction

Curcumin (diferuloymethane; CUR) is the most active component of Curcuma longa (or turmeric), belonging to the family *Zingiberaceae*. Apart its use as a food additive and pigment, centuries of traditional use in Chinese and Indian medicine has suggested a plethora of potential therapeutic applications. In the last decades, many scientific studies have validated various pharmacological effects, such as antioxidant, anti-inflammatory, antibacterial, and, more recently, anticancer activity [1]. This opened the way to a wide therapeutic potential for this natural compound, and CUR has been recommended to various extent in arthritis, diabetes, cardiovascular diseases, liver fibrosis, gall stone formation, neurological diseases, tumors, and inflammatory bowel disease [2,3]. Such a plethora of apparently different clinical conditions is related to the range of molecular targets of CUR, that include transcription factors, inflammatory cytokines, enzymes and the epigenetic modulation which modulate histone deacetylases, histone acetyltransferases, DNA methyltransferase I and miRNAs [4,5].

Unfortunately, oral bioavailability of CUR is very limited (about 60%) [6], mainly because of its very low solubility in aqueous media

Abbreviations: CUR, curcumin; DSC, differential scanning calorimetry; ERL, Eudragit® RL100; ERS, Eudragit® RS100; FT-IR, Fourier-transform infrared spectrophotometry; PDI, Polydispersity Index; PXRD, powder X-ray diffractometry; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; UV, visible-ultraviolet spectrophotometry.

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and incomplete absorption in the gastro-intestinal tract [7].

To overcome such drawbacks, different technological approaches have been explored, including encapsulation of CUR in colloidal polymeric and lipid-based delivery systems, such as liposomes, nanoparticles and microspheres [8–12]. Many of these strategies have shown to improve the solubility and bioavailability of CUR, although its biological activity has not always been positively affected, thus raising an intriguing hypothesis about the effects of encapsulation inside delivery systems on the metabolism and pharmacodynamics of CUR and its active metabolites [13]. However, dispersion of CUR in polymeric or lipid micro- or nanomatrices remains a potentially valid strategy to improve the solubility and absorption of this compound after oral administration [8,14,15].

We are conducting a wide research project aimed at producing microcarriers, made using Eudragit® Retard polymers, for the oral delivery of naturally occurring active compounds [16]. Eudragit® RS100 (ERS) and RL100 (ERL) resins are copolymers of poly(-ethylacrylate, methyl-methacrylate and chlorotrimethyl-ammonioethyl methacrylate), containing an amount of quaternary ammonium groups between 4.5–6.8% and 8.8–12% for ERS and ERL, respectively. Both are insoluble at physiological pH values and capable of swelling [17], thus being valid candidates for the dispersions of bioactive compounds [18–20]. These polymers are usually employed for the coating of solid oral dosage forms; however, recent studies supported the use of these polymers for producing controlled release micro- and nanosystems of pharmaceutical interest [21–27].

In this paper, the preparation and characterization of CUR-loaded ERL/ERS microparticles are reported. Microparticles were produced by a solvent displacement technique, starting from a co-solution of CUR and polymer(s) in organic solvents. The micromeritics and drug loading of microparticles were analyzed, as well as the chemical interactions of CUR with Eudragit® polymers in the solid-state. The dissolution profile and in vitro release pattern of neat and encapsulated CUR were assessed in simulated gastric fluid and in phosphate buffer (pH 6.8).

Furthermore, the photostability of CUR loaded in the microparticles was assessed in different media both under UV and visible irradiation. It is in fact known that several degradation products are formed upon light exposure of this compound, and CUR itself was found to act as photosensitizer via a singlet oxygen mechanism [28,29].

2. Materials and methods

2.1. Chemicals

CUR (*Curcuma longa* rhizome dry extract; total curcuminoids 95% min.) was produced by Vivatis Pharma GmbH (Hamburg, Germany) and was kindly gifted by Labomar srl (Istrana, Italy); ERL and ERS resins (Evonik Rohm GmbH) were kindly provided by Rofarma Italia srl (Gaggiano, Italy). HPLC solvents were from VWR and Labscan (Milan, Italy); the other reagents and solvents were purchased from Sigma-Aldrich Chimica srl (Milan, Italy). All of them were used as received.

2.2. Preparation of blank microparticles

To optimize the composition and properties of Eudragit microparticles, unloaded systems were initially produced using different variables. Concentrated solutions with the copolymer composition reported in Table 1 were prepared by dissolving 4 g total of each Eudragit® resin blend in 40 ml of ethanol, by overnight mechanical stirring at room temperature. An exact volume of these solutions (i.e., 5, 10 or 20 ml, corresponding to a final copolymer concentration of 1, 2 or 4%, w/v, respectively) (Table 2) was slowly dropped within 60 min into 50 ml distilled water containing 0.02% (w/v) Tween® 80, under mechanical stirring at 150 rpm and room temperature, to produce the microparticles. The mixture was then left under stirring for about 24 h to allow the evaporation of the solvent, after which it was frozen and lyophilized for 24 h (Edward Modulyo).

Table 1
Polymer composition of blank microparticles.

Code	ERL (%)	ERS (%)
A	100	–
B	70	30
C	50	50
D	30	70
E	10	90

2.2.1. Sieving and size distribution

The produced microparticle batches were passed through European Pharmacopoeia standard metallic sieves (841, 420, 210, 125, and 90 μm; corresponding to 20, 40, 70, 120, and 170 mesh, respectively) using a vibratory apparatus (Giuliani Tecnologie srl, Turin, Italy). Each portion was collected and weighed, to calculate the size distribution data gathered in Table 2, where d10, d50 and d90 are the mean particle size (in μm) determined at the 10th, 50th and 90th percentiles of undersized microparticles, respectively.

2.3. Preparation of CUR-loaded microparticles

Based on the behaviour of blank microparticles, selected compositions were individuated to be loaded with CUR (Table 3). The amount of drug needed to produce each chosen drug-to-polymer weight ratio (DPR) (namely 1:1, 1:5 and 1:10) was dissolved in 10 ml acetone and added to the volume of polymer ethanol solution required for each batch, as above described. The preparation, collection and sieving of CUR-loaded microparticles was carried out as described for the blank systems.

2.4. Preparation of the physical mixtures

For the sake of comparison of physico-chemical properties, physical mixtures having the same composition of microparticles were produced by simple mixing CUR and the required polymers in a porcelain mortar for 10 min. To attain an average diameter

Table 2
Cumulative size distribution of sieved blank microparticles (see Table 1 for the composition of copolymer blends).

Code	Polymer concentration (%, w/v)	Yield[a]	Cumulative size distribution (μm)		
			d10	d50	d90
A1	1	72.5	<90	330	675
B1	1	90.2	100	115	285
B2	2	81.5	115	335	705
B4	4	74.8	<90	120	525
C1	1	95.6	95	235	565
C4	4	60.0	<90	100	145
D4	4	79.8	110	195	440
E1	1	36.0	<90	<90	120
E2	2	32.8	<90	<90	320
E4	4	73.8	90	160	>841

[a] Percent of recovered microparticles in the pooled 841–90 μm sieve fractions, compared to the initial amount of polymers.