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Structure and properties of ibuprofen–hydroxypropyl methylcellulose nanocomposite gel

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ABSTRACT

From a mixture of a methanol solution of ibuprofen (IB) and an aqueous solution of hydroxypropyl methylcellulose (HPMC), clear, uniform sol was obtained at the methanol/water proportion 7/3. When sol was brought to dryness, nanocomposite gel was obtained with amorphous IB particles of 20–50 nm dispersed in HPMC matrix. Simultaneous and quick nano-hybridization and amorphization are based on: (i) re-precipitation of IB in the restricted space of HPMC network, and (ii) recombination of hydrogen bonds from those within IB crystal to those between IB and HPMC. Associated change in the properties including dissolution into aqueous medium was discussed briefly in view of application feasibility to pharmaceutical processing.

1. Introduction

Increase in the release rate and apparent solubility of sparingly soluble drugs is one of the major challenges of pharmaceutics and pharmacology. In the case of solid state, comminution of the drugs is conventionally performed in an attempt to particle size reduction, phase transformation or amorphization [1]. When a drug is ground with excipients, solid dispersion is obtained to enhance the release rate as well [2–6]. Rogers et al. combined similar technique with spray drying and succeeded in enhancing dissolution and suggested a new drug particle engineering [7]. Watanabe et al. succeeded in the substantial increase in the release rate of indomethacin, an anti-inflammatory drug, by co-grinding with silica nanoparticles [8–10] or polyvinylpyrrolidone [10]. They basically attributed the enhancement to drug amorphization. In view of stabilization of drug crystals by intra-crystalline hydrogen bonds and based on the simultaneous observation of chemical shifts in IR spectra, amorphization of the drug due to those works were associated with the recombination of hydrogen bonds from intra-crystalline ones to those between the drug and the excipient. These processes, relying upon the grinding operation, are, however, time consuming and inevitably associated with contamination from various parts of a grinding machine.

Drugs sparingly soluble in water are quite often highly soluble in organic solvents. Indeed, Rasenack et al. succeeded by mixing alcoholic solution of drugs with polymeric materials to control association and micronize the drugs down to a fraction of micrometer [11]. The products were better than those by conventional jet milling with an option of morphological control on top of its process merit of simplicity. However, the particle size reached was still in the range of several hundreds of nanometers and the drugs were in their crystalline states.

A number of efforts were paid to obtain drug–polymer nanocomposites to expect increased rate of drug release [12–15]. Many studies are conducted to increase solubility by combination with excipients [16,17]. For a wet process like spray drying, alcohol [18] or alcohol–water cosolvent [19] is used as a dispersing medium in drug manufacturing. These liquids also serve as solvents to promote dissolution and precipitation the drug. However, only a few studies were reported to make drug particles with their average particle size below 100 nm. An exception is an attempt with pulsed laser deposition to obtain indomethacin [20,21]. However, the method was unaffordable for practical fabrication because of its very low productivity.

We therefore try in the present study to obtain amorphous drug nanoparticles below 100 nm by using a sol–gel process. The objective of this study is to examine the existence of those nanoparticles in xerogel, obtained as a final hybridized product. We also try to check whether and to what extent recombination of the hydrogen bonds is involved, i.e., those within drug crystals among drug molecules and those between drug and matrix.

2. Experimental details

2.1. Sample preparation

We chose hydroxypropyl methylcellulose (HPMC, Shin-etsu Chemicals, Metolose 60SH-15) as a polymeric matrix due to its high hydrophilicity, chemical stability and popularity as an excipient.

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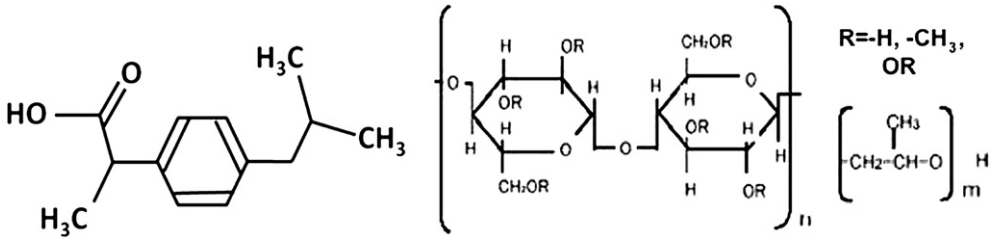

Fig. 1. Molecular structures of ibuprofen (IB, left) and hydroxypropyl methylcellulose (HPMC, right).

Ibuprofen (IB, TCI, Analytical grade, used as purchased), a popular anti-inflammatory drug, was used as a model drug. Molecular structures of IB and HPMC are shown in Fig. 1.

We systematically varied the proportion between the drug and the matrix, and between methanol and water to find out appropriate condition to obtain homogeneous, clear sol, being a key point of the present method. Before preparing IB–HPMC composites, we tested dissolution property of IB without HPMC in water–methanol mixtures. We put 0.1–1.0 g of IB into 10 ml of a series of mixed solvents, i.e., water:methanol = 5:5, 4:6, 3:7, 2:8, and 1:9 (v/v). More than 0.6 g of IB was dissolved in the mixed solvents of water:methanol = 3:7, 2:8, and 1:9. We then prepared IB–HPMC composites as follows. 0.72 g of IB was dissolved in 21 ml methanol. Separately, we put 2.88 g HPMC into 9 ml deionized water and kneaded until clear, highly viscous sol was obtained. This gives rise to the proportion, IB:HPMC = 2:8, and water:methanol 3:7. The sol remained clear and homogeneous as we put IB methanol solvent and mixed with HPMC aqueous sol. Note that HPMC is not completely soluble in pure methanol.

We obtained a xerogel from the composite sol obtained above in the form of film of ca 100 μm thickness by casting with a stainless steel coater of an aperture 1.5 mm and dried at room temperature for more than 12 h. We also prepared xerogel granules of ca 700 μm after extrusion of half-dried gel through a PTFE punching board with 800 μm openings and dried at room temperature for 3 days. We also tried dry co-grinding for 6 h using planetary mill (Fritsch, Pulversitte 5) at rotation and revolution speeds 245 rpm and 196 rpm in an agate vessel, just for comparison.

2.2. Characterization

Change in the crystallinity was monitored by conventional X-ray diffractometry (Rigaku, RINT 2000). Physical states of sol were observed by optical microscope (OM) and transmission electron microscopy (FE-TEM, TECNAI F20, TECNAI, with 120 kV acceleration voltage). We exposed the film sample to the vapor above a 1 w/v% aqueous solution of OsO_4 for 2 h for better contrast in the micrograph.

Chemical states of IB and HPMC, including their interaction were examined by FT-IR spectroscopy (FT-IR, FTS60A, Varian). Spectrometry was done by conventional KBr method, except for that of film, where we prepared extra thin film for direct transmission spectra.

Dissolution test was performed on the samples using the JP 14 Type 2 (Paddle) method (Miyamoto Riken, PJ-12N). A composite sample containing 100 mg of IB was weighed out and placed into 1000 ml of deionized water. The concentration was deliberately chosen in excess of the solubility of IB, i.e. ca 20.6–26.4 mg/l in aqueous media at 35.0–40.0 °C [22]. To avoid floating of samples, we stirred the water–drug mixture at 300 rpm with an installed paddle for 5 s, during which the powdered IB moved quickly toward the center of the vortex. We then reduced the rotational speed swiftly to 50 rpm. We set the moment, at which the stirring speed was settled down to the constant value, 50 rpm, as the dissolution time zero. Bath temperature was set at 37.0 °C. About 5 ml samples were collected at 5, 10, 30 and 60 min through the cellulose hydrophilic membrane filter of 200 nm (Advantec, DISMIC-25cs). The concentration of IB in the collected solution samples was analyzed by UV–vis (JASCO, V-500) spectrometer using the intensity at 221 nm [23]. We confirmed that the absorption coefficient of HPMC was zero at this wavelength.

3. Experimental results

3.1. Crystallographical properties of IB

XRD profiles are shown in Fig. 2. While HPMC is non-crystalline from the beginning, as shown in Fig. 2(a), IB is well crystallized (Fig. 2(b)). In a simple physical mixture, structures of both ingredients remain intact (Fig. 2(c)). While IB remains partially crystalline after co-grinding with HPMC for 3 h (Fig. 2(d)), it turns into amorphous perfectly in a xerogel film, as shown in Fig. 2(e). Note that simple dissolution–re-precipitation in the mixed solvent used for our sol formation brought about no amorphization, as shown in Fig. 2(f). Instead, phase transformation took place, judging from the different diffraction peaks. Indeed, phase transformation of the drugs like phenytoin during recrystallization is well known [24]. It is, therefore, obvious, that the presence of HPMC is inevitable for IB amorphization in the present sol–gel process. Thus, complete amorphization of IB was achieved by very simple sol–gel procedure under the optimized condition indicated.

3.2. Observation of structural and molecular states

Microscopic observation of the xerogel is displayed in Fig. 3. It is interesting to note, that the film exhibits fragmentation into pieces of several tens of micrometer, as shown in Fig. 3(a). When we observe such a fragment under TEM, fine units of 20 nm–50 nm are recognized, as shown in Fig. 3(b). Similar nanoparticles are observed on the thin film directly exerted on the micro grid of TEM from diluted

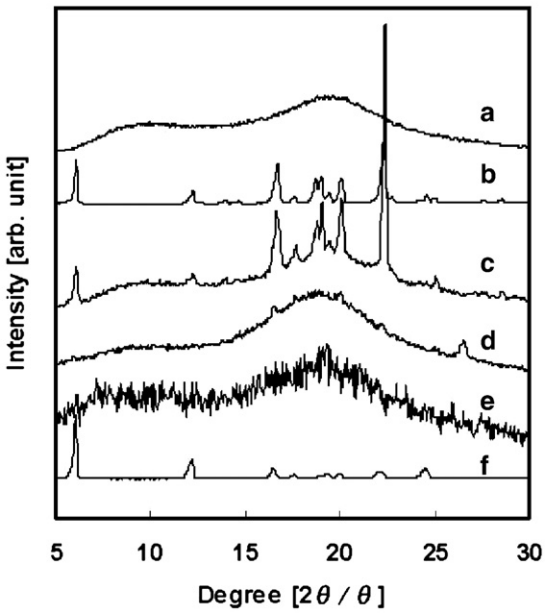

Fig. 2. XPD profiles of a) HPMC, b) IB intact, c) 20% physical mixture d) 20% mixture milled for 6 h, e) 20% xerogel film, f) IB recrystallized in water/methanol solvent.