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Drug nanoparticle formation from drug/HPMC/SDS ternary ground mixtures

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Drug nanoparticle formation from a ternary ground mixture consisting of a poorly water-soluble drug, hydroxypropylmethylcellulose (HPMC), and sodium dodecyl sulfate (SDS) was investigated. Flurbiprofen, which did not show nanoparticle formation by co-grinding with polyvinylpyrrolidone (PVP) and SDS, was used as a model drug. Flurbiprofen, HPMC and SDS were mixed at the weight ratio of 1 : 3 : 1 and ground for 30 min in a vibrational rod mill. The drug nanoparticle formation was observed after the ternary ground mixture (GM) was dispersed into distilled water. Molecular interactions both between flurbiprofen and HPMC and between polymer and surfactant were found to be important factors for the nanoparticle formation. The GM was stable for 2 months at the storage condition of 40 °C and RH 22%. Mean particle size of the dispersed particles was still less than 350 nm after storage at 25 °C for 1 month. It was found that the drug/HPMC/SDS ternary grinding method was applicable not only for flurbiprofen but also for other hydrophobic drugs, such as tolbutamide, probucol, phenytoin and griseofulvin. The drug nanoparticles were also obtained using other cellulose derivatives, indicating that these pharmaceutical excipients were alternative to PVP for the grinding-induced drug nanoparticle formation.

1. Introduction

Dissolution rate enhancement of poorly water-soluble drugs is a crucial issue to improve their solubility and bioavailability. Numerous attempts have been made to improve the dissolution behavior including the use of solid dispersions of drugs with polymers (Leuner et al. 2000; Valizadeh et al. 2004), semi-solid dispersions with surfactants (Soliman et al. 2000) and inclusion complexes with cyclodextrins (Brewster et al. 2002; Uekama 2004). Particle size reduction is also an effective way to increase both solubility and dissolution rate of drug (Liversidge et al. 1995; El-Shabouri 2002; Merisko-Liversidge et al. 2003). For particle size reduction, mechanochemical methods such as co-grinding of drugs with additives is a promising way to obtain a dispersed system (Sugimoto et al. 1998; Yamada et al. 1999). The mechanical stress brings about distortion of particles, amorphization, polymorphic transformation and molecular interaction between drug and carrier. Several studies have revealed grinding-induced particle size reduction and enhanced dissolution rate (Sugimoto et al. 1998; Otsuka et al. 1998 Yamada et al. 1999).

For effective size reduction of drug particles, water-soluble polymers, surfactants and cellulose derivatives have been used as additives to inhibit particle agglomeration and to improve the physicochemical properties of the drug (Leuner et al. 2000; Suzuki et al. 2001a). Polyvinylpyrrolidone (PVP) is a commonly used water-soluble polymer in a variety of pharmaceutical formulations due to its low toxicity and chemical stability. Improved stability and dissolution properties of hydrophobic drugs prepared with PVP have been demonstrated for several kinds of drugs (Franco et al. 2001; Yagi et al. 2002; Berggren et al. 2004). Sodium dodecyl sulphate (SDS) has been used as an emulsifying agent in pharmaceutical formulations. Because of its intrinsic toxicity problems, SDS is often used in combination with other excipients to obtain enhanced solubility and dispersion stability of the drug particles (Merisko-Liversidge et al. 1996). Grinding-induced drug-PVP and drug-SDS binary systems may be applicable for the size reduction of drugs, though the obtained particles are easily agglomerated after storage of the suspension. Size reduction of particles to submicron order is an effective way to enhance the dissolution rate (Suzuki et al. 2001b; Vihola et al. 2002), however, preparation of a stable nanosuspension has been slightly reported.

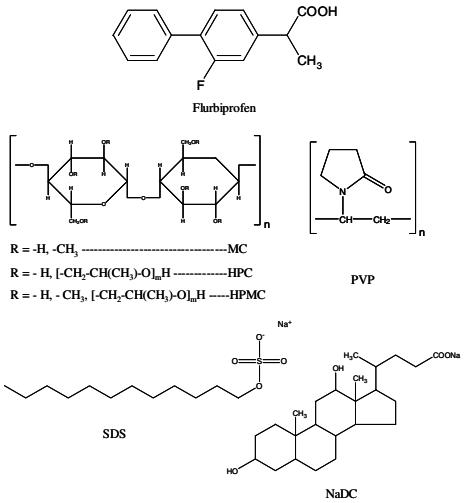
Ternary ground mixtures of N-5159 with PVP and SDS showed colloidal nanoparticle formation in distilled water (Itoh et al. 2003). Optimum composition for the drug/PVP/SDS ternary system, physicochemical properties and stability were also investigated for phenytoin, probucol and griseofulvin as model drugs (Pongpeerapat et al. 2004). The ternary system has been shown to be applicable for many kinds of hydrophobic drugs except for flurbiprofen and tolbutamide (Pongpeerapat et al. 2004). To apply the grinding-induced micronization procedure to flurbiprofen, tolbutamide and other hydrophobic drugs,

different kinds of drug/polymer/surfactant systems should be investigated instead of drug/PVP/SDS ternary systems. In this study, we used a drug/hydroxypropylmethylcellulose (HPMC)/SDS ternary system to investigate the grinding-induced drug nanoparticle formation. Flurbiprofen, which did not show nanoparticle formation by co-grinding with PVP and SDS, was used as a model drug to prepare nanoparticles by co-grinding. The effect of the ternary components on drug nanoparticle formation was investigated using cellulose derivatives such as methylcellulose (MC) and hydroxypropylcellulose (HPC).

2. Investigation, results and discussion

2.1. Physicochemical properties of flurbiprofen/HPMC/SDS ternary ground mixture

Co-grinding of a hydrophobic drug with polyvinylpyrrolidone K17 (PVP) and sodium dodecyl sulphate (SDS) at a weight ratio of 1 : 3 : 1 has been firstly introduced to prepare drug nanoparticles by Itoh et al. (2003). The drug/PVP/SDS ternary grinding method was found to be effective for many kinds of hydrophobic drugs, however, not for flurbiprofen (Pongpeerapat et al. 2004). To prepare flurbiprofen nanoparticles by ternary grinding and to prepare stable drug nanoparticles, hydroxypropylmethylcellulose (HPMC) was used as the hydrophilic polymer instead of PVP.



Physicochemical properties of the flurbiprofen/HPMC/SDS ternary GM at a weight ratio of 1 : 3 : 1 were investigated by PXRD measurement and IR spectroscopy. Fig. 1 shows PXRD patterns of flurbiprofen/HPMC/SDS ternary PM and GM. The PM shows characteristic X-ray diffraction peaks of both flurbiprofen crystals and SDS crystals (Fig. 1 (3)). The ternary GM exhibited crystalline SDS peaks, while X-ray diffraction peaks of flurbiprofen were hardly observed because of a decrease in crystallinity by the mechanical stress during grinding. Since the small particles surrounded by the additives do not clearly show the diffraction peaks in the X-ray diffractogram, the solid state of flurbiprofen in the GM might be amorphous and/or fine crystallites.

The molecular interaction between flurbiprofen and HPMC or SDS was investigated by FT-IR spectroscopy (Fig. 2). In flurbiprofen/SDS binary GM, a C=O stretching band of flurbiprofen was observed at 1701 cm^{-1}, which was the same position than in intact crystals. In the case of flurbiprofen/HPMC binary GM, however, the position of the C=O stretching band completely shifted to higher a wave number, 1734 cm^{-1}, indicating that flurbiprofen interacted with HPMC through hydrogen bonding. From the comparison of the IR spectra of ternary PM and GM, the peak shift of C=O stretching band was observed as a small shoulder at 1728 cm^{-1} after grinding. As flurbiprofen did not interact with SDS as shown in Fig. 2 (3), the small shoulder would be attributed to the interaction between flurbiprofen and HPMC molecules.

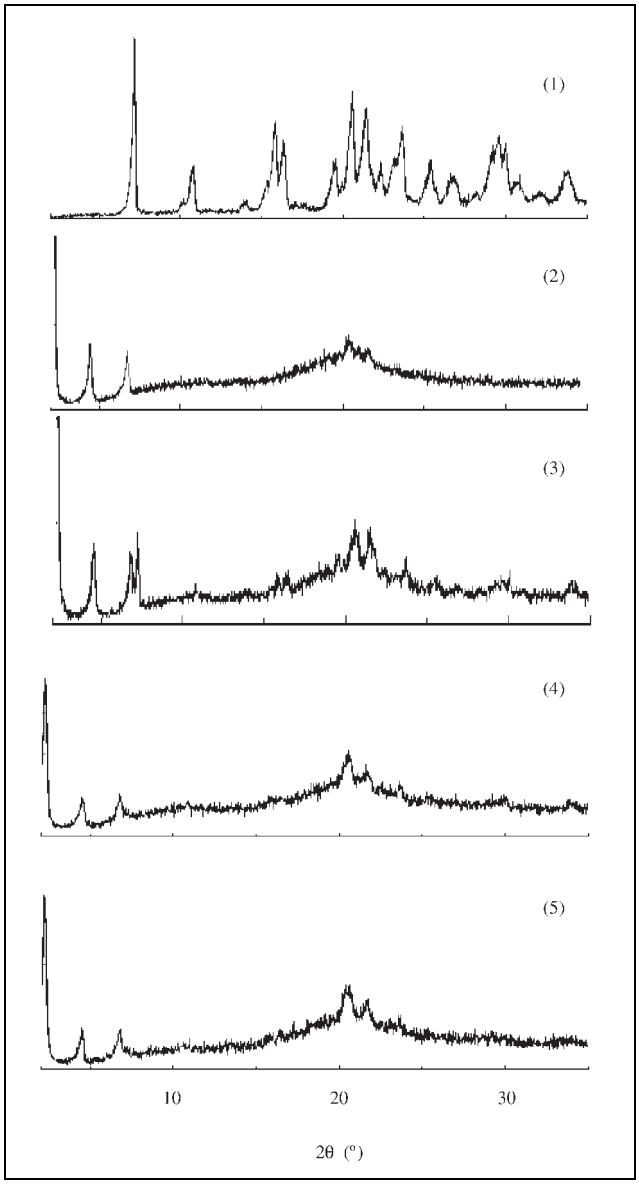


Fig. 1: PXRD patterns of flurbiprofen/HPMC/SDS systems: (1) Flurbiprofen intact; (2) HPMC/SDS GM (weight ratio 3 : 1); (3) Flurbiprofen/HPMC/SDS PM (weight ratio 1 : 3 : 1); (4) Flurbiprofen/HPMC/SDS GM (weight ratio 1 : 3 : 1); (5) Flurbiprofen/HPMC/SDS GM after storage at 40 °C, RH 22% for 2 months

2.2. Flurbiprofen nanoparticle formation and stability study

Fig. 3 shows the particle size distribution of flurbiprofen/HPMC/SDS GM dispersion in distilled water. Volumetric particle size of flurbiprofen nanoparticles was determined at 346 nm. After storage for 4 h, the distribution was not changed, showing the high stability of the nanoparticles formed. The effect of HPMC and SDS on flurbiprofen nanoparticle formation was investigated to estimate the

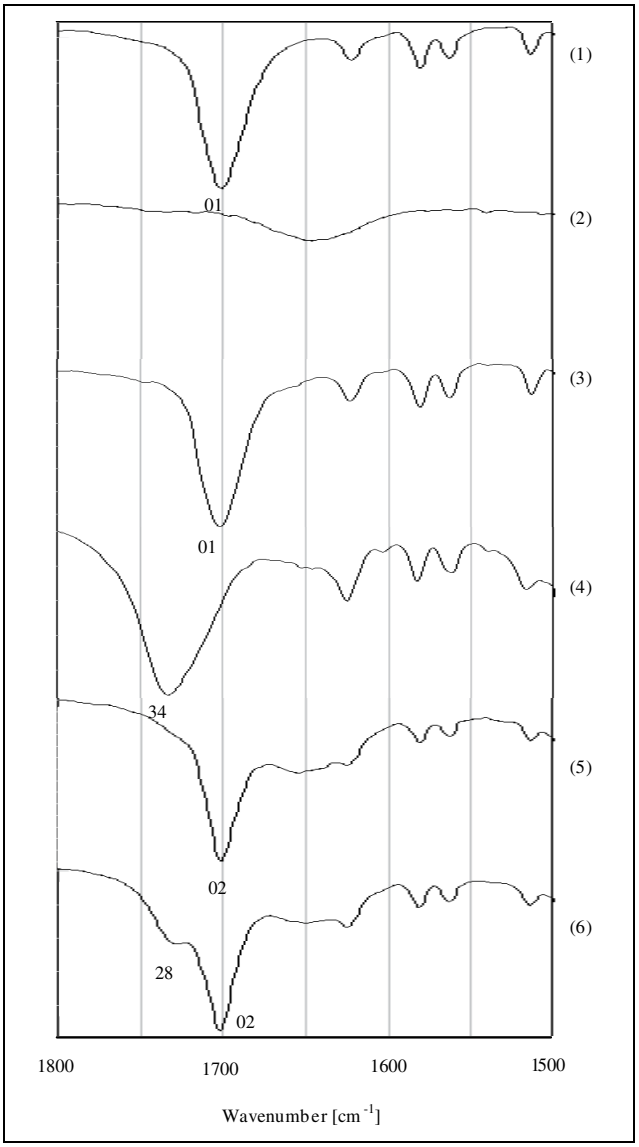


Fig. 2: IR spectra of flurbiprofen/HPMC/SDS systems:
(1) Flurbiprofen intact; (2) HPMC/SDS GM (weight ratio 3 : 1); (3) Flurbiprofen/SDS GM (weight ratio 1 : 1); (4) Flurbiprofen/HPMC GM (weight ratio 1 : 3); (5) Flurbiprofen/HPMC/SDS PM (weight ratio 1 : 3 : 1); (6) Flurbiprofen/HPMC/SDS GM (weight ratio 1 : 3 : 1)

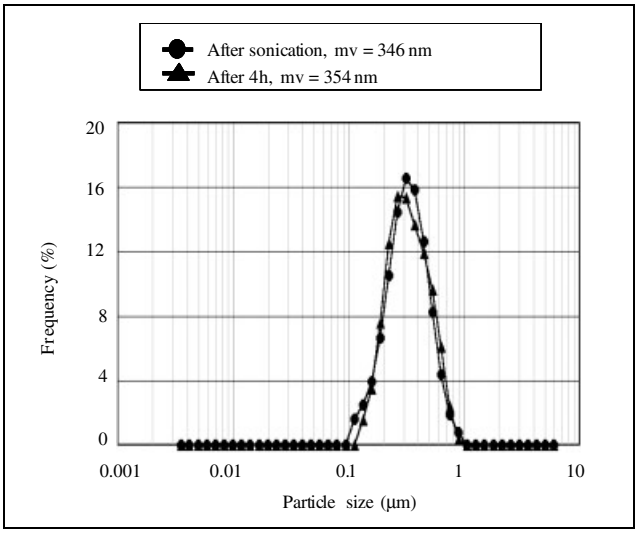


Fig. 3: Changes in particle size distribution pattern of flurbiprofen/HPMC/SDS GM dispersed in water

Table 1: Mean particle size of drug in the suspensions obtained from PM, binary and ternary GMs of flurbiprofen/HPMC/SDS systems

Composition (weight ratio)	Mean particle size (μm)
Flurbiprofen intact crystal	12.5
Flurbiprofen/HPMC/SDS 1 : 3 : 1, PM	15.1
Flurbiprofen/HPMC 1 : 3, GM	16.7
Flurbiprofen/SDS 1 : 1, GM	1.4
Flurbiprofen/HPMC/SDS 1 : 3 : 1, GM	0.3

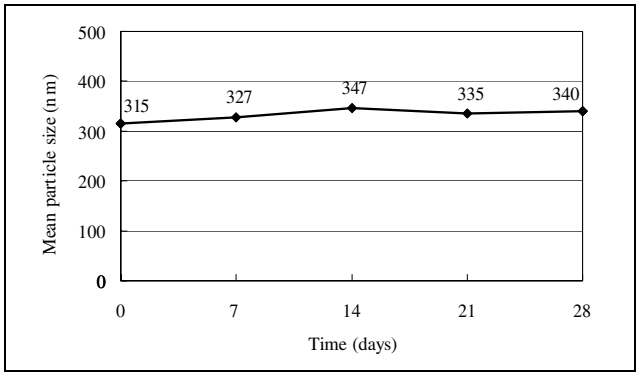


Fig. 4: Long-term stability of suspension obtained from flurbiprofen/HPMC/SDS GM

mechanism of the drug nanoparticle formation (Table 1). The mean particle size of flurbiprofen crystals was 12.5 μm. Flurbiprofen/HPMC binary GM showed no particle size reduction, even some molecular interaction between flurbiprofen and HPMC was observed in IR spectra as shown in Fig. 2. On the contrary, flurbiprofen/SDS binary GM effectively exhibited the reduction of drug particle size to ca. 1.5 μm.

These results indicated that the combined use of HPMC and SDS played an important role for the flurbiprofen nanoparticle formation, even the drug-SDS binary system showed some effectiveness for particle size reduction. Effect of storage conditions of GM on the powder properties was investigated. Powder X-ray diffraction pattern of the GM was not changed after storage at 40 °C, RH 22% for 2 months (Fig. 1 (5)) and particle size of the GM after dispersing in water was 370 nm, which was almost the same as that before the storage. Mean particle size of the dispersed GM was still less than 350 nm after storage of the GM suspension at 25 °C for 1 month as shown in Fig. 4. These results indicated that both flurbiprofen/HPMC/SDS ternary GM and flurbiprofen nanoparticles prepared by dispersing the GM into aqueous media were both stable under conventional storage conditions.

2.3. Application of the drug/HPMC/SDS ternary grinding method for other hydrophobic drugs

Drug nanoparticle formation by the drug/HPMC/SDS ternary grinding method was further investigated using other hydrophobic drugs to evaluate wide applicability of this method. Table 2 shows the mean particle sizes observed after dispersing drug/HPMC/SDS ternary GM in water. Tolbutamide demonstrated stable nanoparticle formation compared with that of the drug/PVP/SDS system (Pongpeerapat et al. 2004), where probucol, phenytoin and griseofulvin also showed drug nanoparticle formation by co-grinding with HPMC and SDS.

Molecular interaction between HPMC and SDS developed during the co-ground process with drug crystals seemed to

Table 2: Mean particle size of the micronized drug particles obtained from drug/polymer/SDS ternary GM* after dispersion into distilled water

	Mean particle size (nm)									
	Flurbiprofen		Tolbutamide		Probucol		Phenytoin		Griseofulvin	
	t = 0	t = 4 h	t = 0	t = 4 h	t = 0	t = 4 h	t = 0	t = 4 h	t = 0	t = 4 h
PVP/SDS	1622	>2000	461	>2000	83	96	136	137	133	144
HPMC/SDS	346	354	298	399	317	347	343 (139**)	353 (135**)	144	193

* drug : polymer : surfactant, 1 : 3 : 1 w/w, ground for 30 min
** Samples were ground for 60 min

play a key role for the effective size reduction. Alli et al. (1991) reported that ion-dipole interaction of SDS with the ethereal oxygen in HPMC contributed to the molecular interaction between HPMC and SDS not only in the aqueous solution but also in the solid state. Hydrophobic interaction between SDS molecules also produced in the process of HPMC/SDS aggregate formation in the aqueous solution. As HPMC has an intrinsic surface activity, the combined use of both HPMC and SDS may result in an effective size reduction of flurbiprofen crystals. Molecular interaction between flurbiprofen and HPMC would be another key interaction that influences the effective size reduction as shown in Fig. 2. In drug/PVP/SDS ternary GMs, molecular interaction between PVP and SDS, which has been reported by Li et al. (1998), also played an important role in drug nanoparticle formation (Pongpeerapat et al. 2004). However, a molecular interaction between flurbiprofen and PVP was not observed by IR spectroscopy in flurbiprofen/PVP/SDS ternary GMs. That would be the reason why flurbiprofen/PVP/SDS ternary GM did not show effective size reduction of the drug. As co-existence of HMPC and SDS during the grinding process with flurbiprofen crystals was required for effective particle size reduction and the binary system showed no nanoparticle formation, molecular interaction not only between flurbiprofen and HPMC but also between HPMC and SDS was supposed to be important for the nanoparticle formation.

2.4. Effect of ternary composition on drug nanoparticle formation

The effect of ternary components on drug nanoparticle formation was investigated using cellulose derivatives such as methylcellulose (MC) and hydroxypropylcellulose (HPC) instead of HPMC (Table 3). Effective size reduction to a submicron level was also observed with MC and HPC. The most effective size reduction was observed for the flurbiprofen or tolbutamide/HPC/SDS system. These results indicated that cellulose derivatives are promising candidates for a grinding-induced drug nanoparticle formation instead of PVP.

Table 3: Effect of cellulose derivatives on mean particle size of the micronized drug particles obtained from ternary GM* after dispersion into distiled water

	Mean particle size (nm)			
	Flurbiprofen		Tolbutamide	
	t = 0	t = 4 h	t = 0	t = 4 h
HPMC/SDS	346	354	298	399
HPC/SDS	298	310	251	301
MC/SDS	441	467	613	685

* drug : polymer : surfactant, 1 : 3 : 1 w/w/w, ground for 30 min

The effect of polymer hydrophobicity of the cellulose derivatives on the interaction with SDS has been investigated previously by titration microcalorimetry and the overall mechanism of interaction was found to be similar for all the cellulose derivatives (Singh et al. 1999). The polymer-SDS interaction was dominated by polymer-surfactant and surfactant-surfactant interactions, which depended on the SDS concentrations. In drug/polymer/SDS ternary GMs, the molecular interaction between cellulose derivative and SDS would not be different from cellulose derivatives used, even that between cellulose derivative and drug should be different.

2.5. Conclusion

We have demonstrated flurbiprofen nanoparticle formation by using drug/HPMC/SDS ternary GM. Since flurbiprofen/HPMC/SDS ternary GM and the drug suspension showed good stability, HPMC is a promising hydrophilic polymer for flurbiprofen nanoparticle formation. It was suggested that molecular interactions both between HPMC and SDS and between flurbiprofen and HPMC were important for particle size reduction. The drug/HPMC/SDS ternary grinding method was applicable not only to flurbiprofen but also to other hydrophobic drugs. Drug nanoparticles were also obtained with other cellulose derivatives, indicating that cellulose derivatives were pharmaceutical excipients alternative to PVP for grinding-induced drug nanoparticle formation.

3. Experimental

3.1. Materials

Flurbiprofen and probucol were supplied from Kaken Pharmaceutical Co., Ltd. (Japan) and Daiichi Pharmaceutical Co., Ltd. (Japan), respectively. Tolbutamide, phenytoin and griseofulvin were purchased from Wako Pure Chemical Industries, Ltd. (Japan).
Polyvinylpyrrolidone K17 (PVP) was obtained from ISP Technologies, Inc. (U.S.A.). Hydroxypropylmethylcellulose 2910 (HPMC) and methylcellulose (MC) were supplied from Shin-Etsu Chemical Co., Ltd. (Japan). Hydroxypropyl cellulose (HPC) was obtained from Nippon Soda Co., Ltd. (Japan). Sodium dodecyl sulphate (SDS) was purchased from Wako Pure Chemical Industries Ltd. (Japan). All chemicals were of reagent grade and used as received.

3.2. Methods

3.2.1. Preparation of physical mixture (PM)

Drug (250 mg) and 1.00 g of a ground mixture of HPMC/SDS (HPMC/SDS = 3/1 w/w) were physically mixed in a glass vial by a vortex mixer.

3.2.2. Preparation of ground mixture (GM)

Drug (0.500 g), HPMC (1.50 g) and SDS (0.500 g) were mixed and then ground at room temperature by a vibrational rod mill (CMT TI-200, Japan)

for 30 min. For the binary systems, drug (0.625 g) and HPMC (1.88 g) or drug (1.25 g) and SDS (1.25 g) were ground by the same method as described above. The GM suspension was obtained by dispersing the GM in distilled water.

3.2.3. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) measurements were performed on a Rigaku Miniflex powder X-ray diffractometer (Rigaku, Japan) under the following conditions: target, Cu; filter, Ni; voltage, 30 kV; current, 15 mA; scanning angle from 2 to 35° and scanning speed, 4°/min.

3.2.4. IR spectroscopy

Fourier transform infrared spectroscopy was carried out by the KBr disk method. IR spectra of the samples were measured on a JASCO 230 FT-IR spectrometer (JASCO corporation, Japan).

3.2.5. Particle size measurement

The volumetric particle size distribution for each suspension was determined by a dynamic light scattering method using Microtrac UPA (Nikkiso, Japan). The particle size distribution was measured after sonication and after storage at room temperature for 4 h.

3.2.6. Stability study

Stability studies of the GM suspensions were investigated by particle size analysis after storage at 25 °C for 7, 14, 21 and 28 days.

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