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Encapsulation of lipophilic drugs within enteric microparticles by a novel coacervation method

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Abstract

Enteric microparticles were prepared by a novel microencapsulation method in order to improve the oral bioavailability of lipophilic drugs. This method involved the addition of an aqueous polymer solution to an organic enteric polymer solution containing lipophilic drugs. In contrast to classical coacervation microencapsulation methods, the drugs were initially also dissolved and not dispersed in the organic polymer solution. The hydrophilic polymer (hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and Poloxamer 407) was dissolved in the aqueous phase and acted as a stabilizer for the coacervate droplets, preventing their coalescence and leading to the formation of enteric microparticles. The size of the enteric microparticles decreased with higher concentrations of the hydrophilic polymers, a higher pH of the aqueous polymer solution, a higher content of carboxyl groups of the enteric polymer and with better polymer solvents. Amide-containing lipophilic drugs, such as carbamazepine, lidocaine and cyclosporine A, were successfully encapsulated in the enteric microparticles in a non-crystalline state and were physically stable for 5 months. The high solubility of carbamazepine in the enteric polymer (>30%, w/w), a high partition coefficient between polymer-rich/-poor regions and strong drug/polymer interactions contributed to the high drug encapsulation efficiency (90%, w/w). In contrast, carboxyl-containing drugs (indomethacin, ibuprofen) and hydroxyl-containing drug (17β-estradiol hemihydrate) crystallized inside or outside the polymeric matrix due to their low solubility in the enteric polymer.

Keywords: Coacervation; Enteric polymer; Lipophilic drugs; Microencapsulation

1. Introduction

Various formulation strategies have been investigated to improve the solubility/rate of dissolution and hence the oral bioavailability of lipophilic drugs. These strategies include a reduction of drug particle size, the use of different polymorphic/amorphic drug forms, complexation (e.g., cyclodextrins), the use of cosolvents, solubilization by surfactants and the formation of solid drug solutions/dispersions (Pinnamaneni et al., 2002).

Lipophilic drugs have also been encapsulated in various polymeric carriers in the form of nano-/microparticles (Arangoa et al., 2001; Roger et al., 2003; Leroux et al., 1995). Enteric polymers, which are practically insoluble in water and below a pH of 5.5–7.0, are promising carriers for a variety of reasons. They protect the gastric mucosa from drug irritation and prevent drug degradation in the stomach by enzymes or acidic fluids (Amorim and Ferreira, 2001), they can deliver the drug to a particular region of the intestine or colon (Lamprecht et al., 2004), they can enhance the bioavailability by increasing the wettability and dissolution rate of the drug (Nazzal et al., 2002) and they can stabilize the drug within the polymeric matrix (Leroux et al., 1996; De Jaeghere et al., 2000, 2001).

Various methods for the preparation of solid dispersions or nano-/microparticles using enteric polymers have been developed including solvent evaporation (Nazzal et al., 2002), coprecipitation (Kislalioglu et al., 1991), emulsification–evaporation (Lee et al., 1999; Alavi et al., 2002), emulsification–diffusion (De Jaeghere et al., 2000, 2001) and salting-out method (Leroux et al., 1995, 1996). Each approach has its benefits and drawbacks (Galindo-Rodriguez, 2004).

Solvent evaporation is a common method to prepare solid solutions/dispersions by dissolving drug and carrier in a solvent and then evaporating the solvent. The resulting solid mass is

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ground and sieved. The limitations of this method have been reviewed previously (Serajuddin, 1999). Scale-up and physical/chemical instabilities are major problems.

Coprecipitation has been studied extensively as a means of increasing the dissolution rate of lipophilic drugs such as griseofulvin, ketoprofen, sulphathiazide, spirinolactone, tolbutamide and nifedipine (Lerk, 1987). Coprecipitates are prepared by transferring a solution of drug/polymer in a water-miscible solvent into an aqueous solution containing a stabilizer. The coprecipitates are formed instantaneously by rapid solvent diffusion. The use of low polymer solution concentrations is necessary to obtain small particles and to avoid large aggregates (Fessi et al., 1989).

For the emulsification–evaporation method, a drug/polymer solution in a water-immiscible solvent (e.g., dichloromethane) is emulsified into an aqueous solution containing an emulsifier. The subsequent evaporation of the solvent from the O/W-emulsion results in the formation of nano-/microparticles. The emulsification–diffusion method is similar to the emulsification–evaporation method, but it uses a partially water-soluble solvent (e.g., benzyl alcohol). A large amount of water is needed to induce diffusion of the solvent from the O/W-emulsion to form nano-/microparticles (De Jaeghere et al., 2001).

In the salting-out process, an organic solution of drug/polymer is emulsified into an aqueous phase containing an electrolyte (e.g., $MgCl_2$) and a stabilizer (e.g., polyvinyl alcohol). Sufficient water is subsequently added to the O/W-emulsion to induce the diffusion of the organic solvent, leading to polymer precipitation and formation of nano-/microparticles. A complicated purification stage is necessary to eliminate the high amounts of emulsifying agent and electrolyte (Leroux et al., 1996; Galindo-Rodriguez et al., 2004).

Spray drying of drug/polymer solutions is another alternative to prepare nano-/microparticles in order to improve the dissolution rate and the oral bioavailability of lipophilic drugs (De Jaeghere et al., 2000, 2001; Paradkar et al., 2004; Dollo et al., 2003).

Coacervation has been used to coat acid- or enzyme-sensitive compounds with enteric polymers. In the simple coacervation process, a non-solvent for the polymer was added to a polymer solution containing dispersed drug particles to induce the formation of the coacervate droplets. For example, a cellulose acetate phthalate solution in acetone containing a dispersed enzyme powder is emulsified into liquid paraffin with a suitable emulsifier. Acetone is evaporated by raising the temperature to 25 °C, and the filtered microcapsules are washed with benzene to remove residual liquid paraffin (Deasy, 1984). Another cellulose derivative enteric polymer, HPMCP, is dissolved in methylene chloride into which the enzyme particles are dispersed. This suspension is then emulsified into ethylene glycol to form an O/W-emulsion. Stirring is maintained until the methylene chloride has evaporated, producing the coating by phase separation of the polymer. The microcapsules are obtained after removal from the ethylene glycol and washing with water (Deasy, 1984). Due to the complicated process and the use of toxic solvent (e.g., methylene chloride), a simple and toxic solvent-free coacervation method is desired.

Aggregation of microparticles during coacervation preparation is troublesome problem commonly encountered in simple and complex coacervation. The rapid rise in apparent viscosity of the polymer-rich region causes undesirable cohesion and aggregation of microparticles. This could be reduced by using a shock-preventing agent (e.g., carboxymethylcellulose, sodium carboxymethylstarch and pectic acid) or cationic surfactants during the isolation and drying stages of complex coacervation. The surfactant is strongly adsorbed at the interface of the coacervate and its surrounding medium, reducing the interfacial tension and leading to reduced tendency of the particles to aggregate (Deasy, 1984). Poly(1-vinyl-2-pyrrolidone) is used as a stabilizer to form heparin/gelatin microcapsules by a complex coacervation using a spray-drying technique (Mei and Burgess, 1997).

The objective of this study was to develop a coacervation method to formulate enteric microparticles for lipophilic drugs to potentially improve their oral bioavailability. An aqueous phase containing various hydrophilic polymers as stabilizers was added into an organic drug/enteric polymer solution. The parameters influencing the formation of enteric microparticles such as polymer type, concentration and pH of aqueous phase, type of enteric polymer, type of organic solvent and the mechanism of encapsulation of lipophilic drugs were investigated.

2. Materials and methods

2.1. Materials

Drugs: micronized carbamazepine (CBZ), ibuprofen (BASF AG, Ludwigshafen, Germany), indomethacin, cyclosporine A (Fluka Chemie AG, Buchs, Switzerland), lidocaine base (Sigma–Aldrich Chemie GmbH, Steinheim, Germany), 17β-estradiol hemihydrate (Schering AG, Berlin, Germany).

Enteric polymers: Eudragit® L100-55 (poly(methacrylic acid-co-ethyl acrylate) 1:1), Eudragit® L100 (poly(methacrylic acid-co-methyl methacrylate) 1:1), Eudragit® S100 (poly-(methacrylic acid-co-methyl methacrylate) 1:2), (Degussa AG, Darmstadt, Germany), hydroxypropyl methylcellulose phthalate (HPMCP HP-55S), hydroxypropyl methylcellulose acetate succinate (HPMCAS AS-MF) (Shin-Etsu Chemical Co., Tokyo, Japan), cellulose acetate phthalate (CAP) (Eastman Chemical Co., Kingsport, USA). Water-soluble polymers: hydroxypropyl methylcellulose (HPMC, Methocel® K15M) (Colorcon Ltd., Orpington, UK), hydroxypropyl cellulose (HPC, Klucel HF), hydroxyethyl cellulose (HEC, Natrosol 250 HX) (Hercules Inc., Wilmington, USA), polyvinyl alcohol (PVA, Mowiol 40–88) (Clariant GmbH, Frankfurt, Germany), Poloxamer 407 (Lutrol® F127) (BASF AG, Ludwigshafen, Germany).

Solvents: acetone (Carl Roth GmbH, Karlsruhe, Germany), ethanol 96% (v/v), isopropanol (Sigma–Aldrich Chemie GmbH, Steinheim, Germany).

2.2. Preparation of enteric microparticles

The aqueous polymer phase was prepared by dissolving HPMC, Poloxamer 407, HPC, HEC or PVA in water, or HPMC in pH 7.4 phosphate buffer (KH_2PO_4 50 mM, NaOH 39.1 mM)

or in 0.1N HCl (pH 1.2). The organic polymer phase was prepared by dissolving the enteric polymers Eudragit® L100-55, Eudragit® L100, Eudragit® S100 or HPMCP HP-55S, HPMCAS-MF in ethanol (96%, v/v), or cellulose acetate phthalate in acetone/ethanol (1:1, v/v) or Eudragit® L100-55 in isopropanol or acetone.

The enteric microparticles were formed by dropping 15 g aqueous polymer solution into 10 g organic phase containing the enteric polymer (20% (w/w), based on polymer solution) with/without drug (carbamazepine, lidocaine, cyclosporine A, indomethacin, ibuprofen, 17β-estradiol hemihydrate) (10–20% (w/w), based on polymer and drug) under magnetic stirring (Janke & Kunkel GmbH & Co. KG, Staufen, Germany) at 800 rpm for 5 min. The viscous microparticle suspension was diluted with 50 ml water and stirred for 5 min. The microparticles were then observed and photographed with a polarized light microscope (Carl Zeiss Jena GmbH, Jena, Germany), collected by centrifugation (3000 rpm, 10 min) (Biofuge 22R, Heraeus Sepatech GmbH, Osterode, Germany), vacuum-dried (12 h) (Heraeus Holding GmbH, Hanau, Germany) and stored in desiccators.

2.3. Phase separation of enteric polymer and precipitation of drugs

The phase separation of enteric polymer solutions and precipitation of drugs upon addition of the aqueous phase to the organic polymer/drug phase were evaluated by the addition of 1% (w/w) HPMC aqueous solution to 10 g ethanolic solutions containing 20% (w/w) enteric polymers (Eudragit® L100-55, Eudragit® L100, Eudragit® S100, HPMCAS, HPMCP), or 20% (w/w) Eudragit® L100-55 in 8 g isopropanol or acetone, or 8 g ethanol containing 10–30% (w/w) drug (carbamazepine, indomethacin, ibuprofen) (based on enteric polymer and drug) under magnetic stirring at 800 rpm. The phase separation and precipitation point was the volume at which the solution became turbid.

2.4. Determination of the coacervation region and of the amount of enteric polymer and drug in polymer-rich/-poor regions

Phase diagrams were generated to investigate the coacervation condition. HPMC (1%, w/w) in water was added dropwise into an ethanolic solution (10 g) of Eudragit® L100-55 or HPMCP (10%, 15%, 20%, 25%, 30% and 40% (w/w), based on polymer and ethanol) with/without carbamazepine (20% (w/w), based on drug and polymer) under magnetic stirring at 800 rpm. The phase separation and precipitation of the polymer were identified at different stages with a polarized light microscope (Carl Zeiss Jena GmbH, Jena, Germany). The composition of the mixtures used to generate the phase diagrams was calculated based on the weight ratio of 1% (w/w) HPMC aqueous solution, ethanol (96%, v/v) and enteric polymer and/or carbamazepine.

The amount of enteric polymer (Eudragit® L100-55) and drugs (carbamazepine, ibuprofen) in the polymer-rich and -poor regions was determined. One percent (w/w) HPMC aqueous solution was dropped into 10 g ethanolic solution of Eudragit®

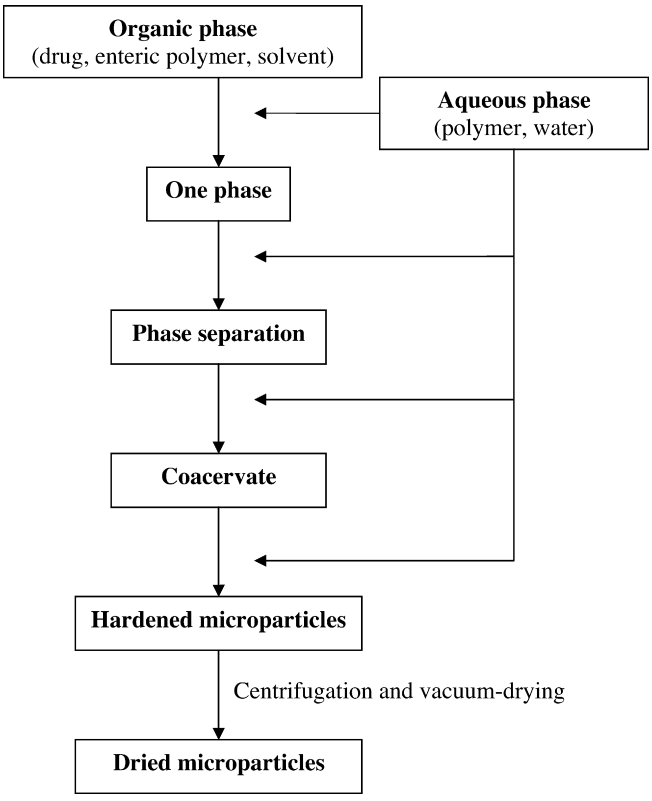


Fig. 1. Diagram of the coacervation method used to prepare the enteric microparticles.

L100-55 (20%, w/w) containing carbamazepine or ibuprofen (20% (w/w), based on drug and polymer). A 4 g sample was withdrawn at water/ethanol ratios (w/w) of 0.9, 1.2, 1.9, 3.3 and 5.9, photographed with a polarized light microscope and then centrifuged at 13,000 rpm (Biofuge 13/Haemo, Heraeus Instruments, Osterode, Germany) for 20 min. The content of Eudragit® L100-55 in the polymer-rich/-poor regions was determined gravimetrically by oven-drying 1 g samples

Table 1
Effect of aqueous polymer phase on the formation of Eudragit® L100-55 microparticles

Aqueous phase (%, w/w)	Viscosity (mPa s)	Miscible with EtOH/H_2O (80/20 v/v)[a]	Particle formation[b]
Water	–	+	–
$CaCl_2$ (1) and Tween 20 (0.25)	–	+	–
HPMC (0.75)	156 ± 8	+	+
HPMC (1)	410 ± 8	+	+
HPMC (1.5)	1528 ± 32	+	+
Poloxamer 407 (2)	3 ± 4	+	–
Poloxamer 407 (5)	3 ± 4	+	+
Poloxamer 407 (10)	8 ± 8	+	Solution
HPC (1)	285 ± 8	+	–
HPC (3)	6420 ± 484	+	+
HEC (1)	492 ± 12	–	–
HEC (3)	9855 ± 161	–	–
PVA (10)	1577 ± 33	–	–

[a] +: Miscible; –: not miscible.
[b] +: Particle formation; –: no particle formation.

at 105 °C to a constant weight. The amount of drug (carbamazepine, ibuprofen) in the two regions was quantified by dissolving 0.1 g samples in 100 g 1N NaOH solution, followed by UV-spectrophotometric analysis (carbamazepine: $\lambda = 287$ nm; ibuprofen: $\lambda = 221$ nm; UV-2101 PC, Shimadzu Scientific Instrument, Columbia, MD, USA).

2.5. Compatibility of drugs and enteric polymer

Drug-loaded polymeric films were prepared by casting ethanolic 20% (w/w) Eudragit® L100-55 solutions containing drugs (carbamazepine, lidocaine, cyclosporine A, ibuprofen, indomethacin, estradiol; 10–30% (w/w) based on polymer and drug) on Teflon plates, followed by drying for 48 h at room temperature and 24 h vacuum-drying. The dried films were removed from the Teflon plates and stored for 24 h in a desiccator until a constant weight was reached. A transparent film qualitatively indicated good compatibility of the drug with the polymer. The freshly prepared films and films stored at room temperature for 1.5 years were observed under a polarized light microscope (Carl Zeiss Jena GmbH, Jena, Germany) to investigate possible crystallization of the drugs in the films. A non-crystalline state was identified by the absence of birefringence of drug crystals.

2.6. Viscosity of the aqueous polymer phase

The viscosity of the aqueous polymer phase was determined with a rotational viscometer (Rheostress RS 100, HAAKE Mess-Technik GmbH, Karlsruhe, Germany) in a controlled rate mode ($D = 30\ s^{-1}$) at 25 °C utilizing a plate-cone-geometry (20 mm/4°, 60 mm/1°) ($n = 3$).

2.7. Solubility of carbamazepine and ibuprofen in water/ethanol mixtures

0.5 g drug (carbamazepine or ibuprofen) was placed into a 10 ml glass tube filled with 5 ml water/ethanol (ratios of 0.05, 0.32, 1.27, 1.90 and 5.07, w/w), which was shaken overnight at room temperature. The concentration of drug in the clear supernatant was measured UV-spectrophotometrically after proper dilution with water ($n = 3$).

2.8. Yield of enteric microparticles and encapsulation efficiency of carbamazepine

Fifteen grams of a 1% (w/w) HPMC solution in 0.1N HCl or pH 7.4 phosphate buffer was added dropwise into an ethanolic solution containing 20% (w/w) Eudragit® L100-55 or HPMCP HP-55S. The microparticle suspensions were diluted with 50 ml water and centrifuged (3000 rpm, 10 min) (Biofuge 13/Haemo, Heraeus Instruments, Osterode, Germany). The enteric microparticles were then vacuum-dried. The yield of the enteric microparticles was calculated as the weight ratio of the amount of microparticles to the amount of polymer used.

The carbamazepine loading was determined by dissolving 10 mg microparticles in 100 ml pH 6.8 phosphate buffer followed by UV-spectrophotometric assay at 287 nm (Shimadzu

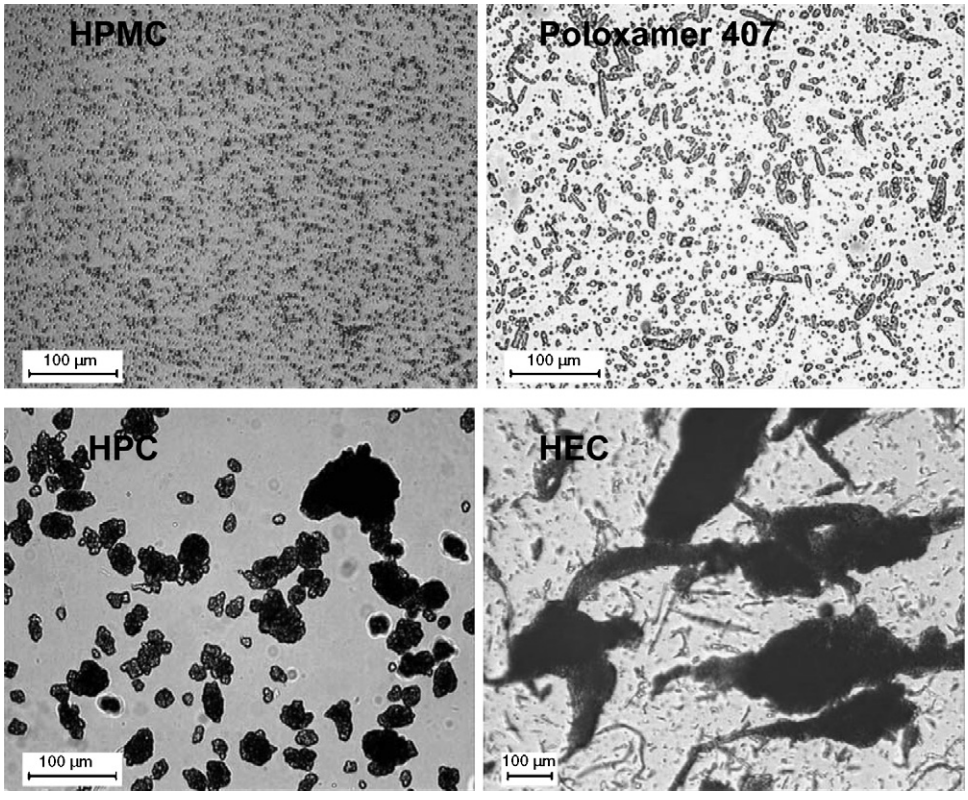


Fig. 2. Photographs of Eudragit L100-55 microparticles/precipitates formed with different aqueous polymer phases: 1% (w/w) HPMC, 5% Poloxamer 407, 3% HPC and 3% HEC.

Scientific Instrument, Columbia, MD, USA) ($n = 3$). The enteric polymeric carrier did not interfere at this wavelength. The drug encapsulation efficiency was the ratio of the actual drug loading to the theoretical loading expressed in percent.

2.9. Particle size analysis

The size of the microparticles was measured by laser diffractometry (LS 230, Beckman Coulter GmbH, Krefeld, Germany) and calculated on the basis of the volume distribution.

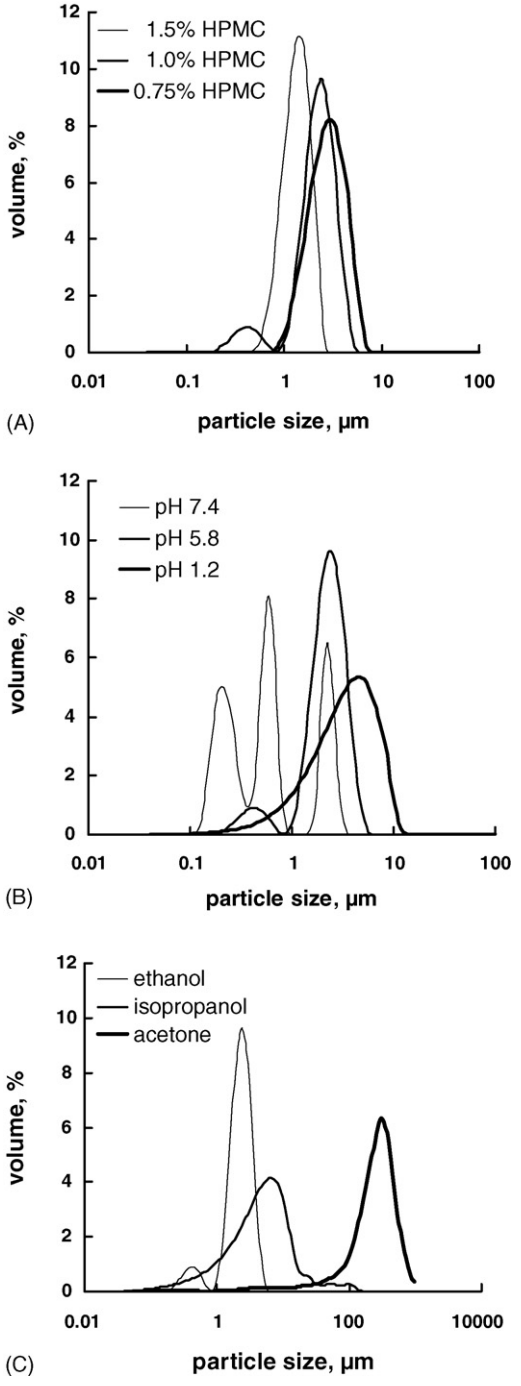


Fig. 3. Effect of (A) HPMC concentration in water, (B) pH of the HPMC (1%, w/w) solution and (C) type of organic solvent on the size distribution of Eudragit® L100-55 microparticles.

2.10. Scanning electron microscopy

The microparticles were spread and fixed on a sample holder with a double-sided tape and were then coated for 230 s with gold–palladium (SCD 040, Bal-Tec GmbH, Witten, Germany) under an argon atmosphere. The surface morphology of the microparticles was examined with a scanning electron microscope (SEM) (S-4000, Hitachi High-Technologies Europe GmbH, Krefeld, Germany) using secondary electron imaging at 10 kV.

3. Results and discussion

Enteric microparticles were prepared by a coacervation method, whereby an aqueous polymer solution was added to an organic enteric polymer solution (Fig. 1). Water was a non-solvent for the enteric polymer causing phase separation and formation of coacervate droplets, which hardened into microparticles upon further addition of the aqueous polymer solution. The hydrophilic polymer in the aqueous phase acted as a stabilizer for the coacervate droplets, preventing coalescence. The effect of the following parameters on the formation of enteric microparticles was investigated: type, concentration and pH of aqueous polymer solution, type of enteric polymer and organic solvent and type of lipophilic drug.

3.1. Formation of drug-free enteric microparticles

The order of mixing of the organic enteric and aqueous polymer solutions was very important for the successful preparation of the microparticles. Large polymer precipitates formed when the organic enteric polymer solution was added into the aqueous polymer solution. In this case, a small amount of the enteric polymer solution was in contact with a large excess of aqueous polymer solution (non-solvent), resulting in a rapid organic solvent diffusion and polymer concentration/precipitation because of the complete miscibility of the polymer solvent (ethanol) and the aqueous phase. The use of water-immiscible organic solvents would allow the formation of microparticles by emulsification of the polymer solution in the aqueous phase (solvent evaporation method) (Lee et al., 1999; Alavi et al., 2002). However, unwanted toxic organic solvents such as dichloromethane (ICH class 2) are used in the solvent evaporation method. In this study, the goal was to form microparticles with less toxic organic solvents such as ethanol, isopropanol or acetone (ICH class 3).

Next, the order of addition was reversed; the aqueous phase was added to the enteric polymer solution. The choice of aqueous phase strongly affected the successful microparticle formation. For example, the addition of only water or an aqueous solution of 1% (w/v) $CaCl_2$ and 0.25% (w/v) Tween 20 (surfactant) (Zaghloul et al., 2001) to the ethanolic Eudragit® L100-55 solution resulted in the formation of aggregates at room temperature. The coacervate droplets were not stable towards coalescence and aggregated. Various hydrophilic polymers were investigated as polymeric stabilizers for the coacervate droplets and the formation of hardened microparticles (Table 1). Microparticles were successfully formed with HPMC, 3% (w/w) HPC and 5% (w/w)

Table 2
Effect of enteric polymer (20%, w/w) and pH of HPMC solution (1%, w/w) on the formation of enteric microparticles

Enteric polymer	Solvent	COOH No.[a]	Microparticle formation[b]		
			pH 1.2	Water	pH 7.4
Eudragit® L100-55	96% Ethanol	537	+	+	+
	Isopropanol		+	+	+
	Acetone		+	+	+
Eudragit® L100	96% Ethanol	537	+	+	+
Eudragit® S100	96% Ethanol	349	–	–	+
HPMCP HP-55S	80% Ethanol	181–235	–	–	+
HPMCAS-MF	80% Ethanol	99–138	–	–	+
CAP	Acetone/ethanol 1:1	238	–	–	–

[a] Number of carboxyl groups per 100,000 Da.
[b] +: Particle formation; –: no particle formation.

Poloxamer 407 solutions (Table 1, Fig. 2). Large aggregates formed with HEC, PVA and 2% (w/w) Poloxamer 407. The organic phase was completely miscible with 10% (w/w) Poloxamer 407, no coacervation or polymer precipitation occurred.

The hydrophilic polymer had to be soluble in the newly formed ethanol/water mixture in order to stabilize the coacervate droplets. HPMC, HPC and Poloxamer 407 were soluble, while HEC and PVA were insoluble thus not acting as polymeric stabilizers and leading to aggregates.

HPMC was most effective in forming Eudragit® L100-55 microparticles by acting as a stabilizer and thickening agent to prevent coalescence of the coacervate droplets. The particle size decreased with increasing HPMC concentration due to an increased stabilizing and thickening effect (Fig. 3A).

The effect of pH of the HPMC solution and the type of enteric polymer on the formation of enteric microparticles were evaluated by adding a 1% (w/w) HPMC solution (HPMC dissolved in 0.1N HCl, water or phosphate buffer pH 7.4) to different enteric polymer solutions (Table 2). Eudragit® L100-55 and L100 formed particles at all pH-values. In contrast, cellulose acetate phthalate (CAP) did not form microparticles. Microparticles were also obtained with Eudragit® S100, HPMCP HP-55S and HPMCAS at pH 7.4, but lumps formed at pH 1.2 or in water (Table 2).

The content of carboxyl groups of the enteric polymers strongly affected the formation and particle size of the enteric microparticles. The number of carboxyl groups in each polymer was calculated based on the molecular weight of one polymer unit containing one carboxyl group. For example, one methacrylic acid–ethyl acrylate unit of Eudragit® L100-55 (186 Da) contained one carboxyl group. Eudragit® L100-55 (high content of carboxyl groups) formed microparticles, even in low pH medium (Table 2) and required the addition of more aqueous HPMC solution for polymer phase separation than the other enteric polymers (Table 3). In contrast, large aggregates formed from enteric polymers with less carboxyl groups, such as Eudragit® S100, HPMCP HP-55S and HPMCAS-MF in pH 1.2 and in water. Microparticles formed in pH 7.4, where partial neutralization and thus stabilization occurred (Table 2).

The addition of HPMC-pH 7.4 solution to the enteric polymer (Eudragit® L100-55) solution led to a slower phase separation and polymer precipitation when compared to HPMC solutions in water or pH 1.2 (Table 3). The particle size decreased with increasing pH of the aqueous phase (Figs. 3B and 4). This was caused by the partial neutralization of the carboxyl groups of the enteric polymer at the higher pH, resulting in an electrostatically induced stabilizing effect of the microparticles. The lower microparticle yield at pH 7.4 (Eudragit® L100-55: 46.7%; HPMCP: 91.3%) when compared to 0.1N HCl (Eudragit® L100-55: 92.7%; HPMCP: 104%) was attributed to polymer dissolution and the formation of a colloidal polymer dispersion, which was difficult to collect by centrifugation.

Acetone, ethanol and isopropanol, which are ICH class 3 solvents (CDER) with a low risk to human health, were

Table 3
Amount of 1% (w/w) HPMC solution added to (a) 10 g Eudragit® L100-55 (20%, w/w) solution in different solvents, (b) different enteric polymers dissolved in ethanol (20%, w/w), or to (c) drug solutions in ethanol, which resulted in polymer phase separation/drug precipitation ($n = 3$)

Enteric polymer or drug solutions	HPMC solution (g)		
	pH 1.2	Water	pH 7.4
20% Eudragit® L100-55			
Ethanol	7.4	8.6	9.5
Isopropanol	–	6.9	–
Acetone	–	5.2	–
20% Enteric polymer in ethanol			
HPMCP 55S	–	4.3	–
HPMCAS	–	6.7	–
Eudragit® S100	–	4.5	–
Eudragit® L100	–	8.8	–
Drug in ethanol			
10% Carbamazepine	–	27.2	–
10% Indomethacin	–	13.1	–
10% Cyclosporine A	–	13.4	–
10% Ibuprofen	–	16.0	–
20% Ibuprofen	–	13.6	–
30% Ibuprofen	–	12.2	–

–: Not determined.

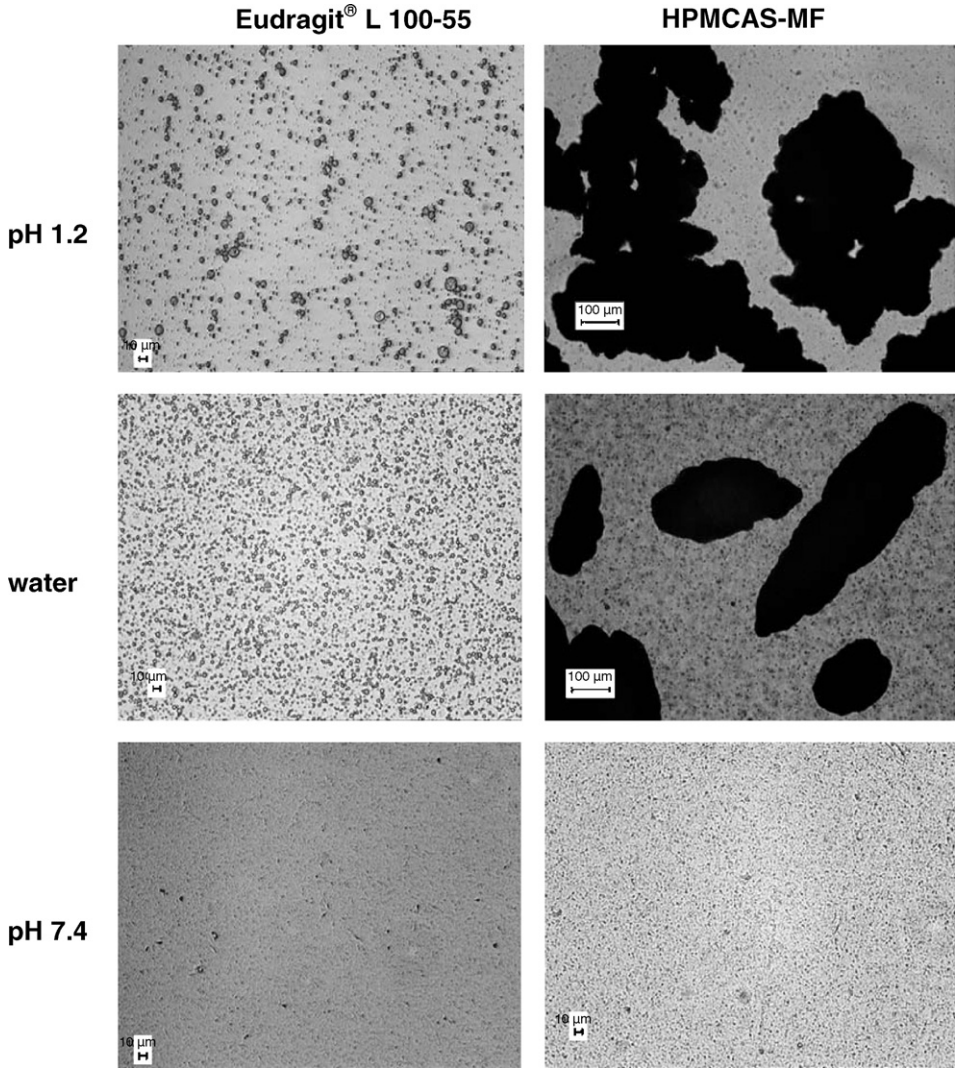


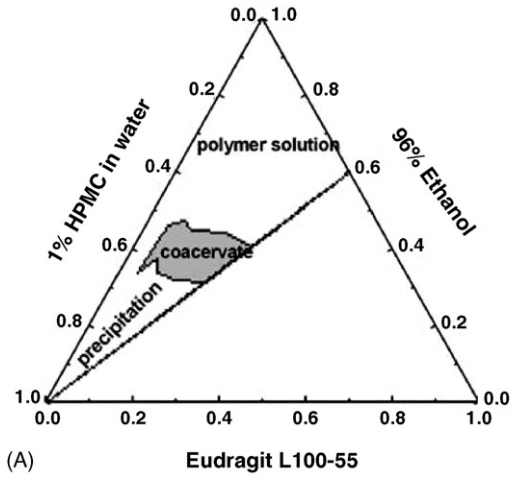
Fig. 4. Photographs of enteric microparticles/precipitates prepared with different enteric polymers (Eudragit® L100-55, HPMCAS-MF) and with aqueous HPMC solutions of different pH.

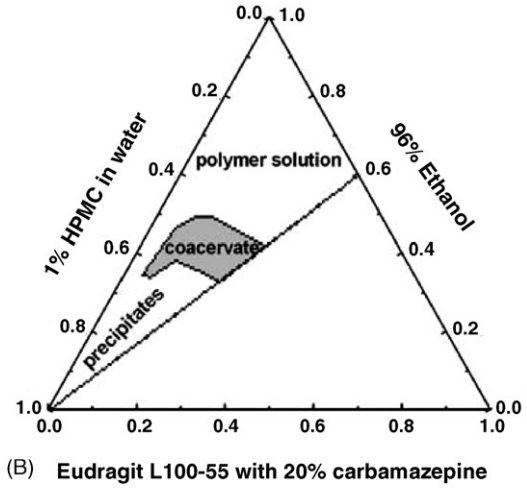
evaluated as organic solvents for the enteric polymers. The size of the enteric microparticles was strongly affected by the organic solvent and decreased in the following order: acetone > isopropanol > ethanol (Fig. 3C). The solvent quality for the enteric polymer was in order of ethanol > isopropanol > acetone, as indicated by the amount of aqueous phase needed to induce phase separation of the polymer (Table 3). Ethanol (strong hydrogen bond capability and high Hildebrand solubility parameter/26.0 $MPa^{1/2}$) is a good solvent for Eudragit® L100-55 thus forming small coacervate droplets and no precipitates (Barton, 1983). However, acetone (moderate hydrogen bond capability, Hildebrand solubility parameter/20.2 $MPa^{1/2}$) is a poor solvent for the enteric polymer (Galindo-Rodriguez et al., 2004) and resulted in a rapid phase separation and polymer precipitation and the formation of large particles upon addition of the aqueous polymer solution (Table 3).

The phase separation and subsequent precipitation of the enteric polymers were achieved by dropwise addition of 1% (w/w) HPMC aqueous solution to ethanolic solutions of the enteric polymers (Eudragit® L100-55, HPMCP) with/without carbamazepine (20%, w/w). A phase diagram of the enteric polymer–ethanol 96% (v/v) (solvent)–1% (w/w) HPMC aqueous solution (non-solvent) revealed the coacervation region (Fig. 5). Phase separation and polymer precipitation occurred over a narrow aqueous phase concentration range (phase separation: 32.4–48.7% 1% HPMC solution, 27.0–5.1% Eudragit® L100-55; precipitation: 47–62% 1% HPMC solution, Eudragit® L100-55, 21.2–3.8%) (Fig. 5A). The faster phase separation and precipitation of HPMCP than of Eudragit® L100-55 was attributed to the higher lipophilicity of HPMCP having less carboxyl groups (Fig. 5C versus A, Table 2).

3.2. Drug-loaded enteric micropartides

Various lipophilic drugs were dissolved in the organic Eudragit® L100-55 solution and tested for their influence on the





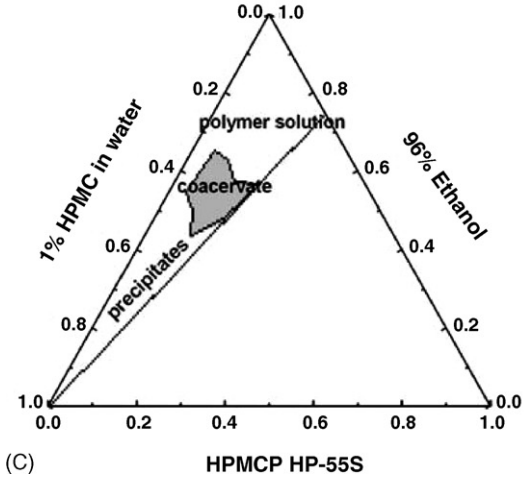


Fig. 5. Phase diagrams for the coacervation of (A) Eudragit® L100-55, (B) Eudragit® L100-55 with 20% (w/w) carbamazepine and (C) HPMCP in ethanol induced with 1% (w/w) HPMC aqueous solution.

formation of drug-loaded enteric microparticles and their encapsulation behavior. Carbamazepine, cyclosporine A, lidocaine and ibuprofen were successfully encapsulated in the enteric microparticles without crystals being visible in the external liquid phase (Fig. 6). The encapsulation efficiency of carbamazepine was 90%. Scanning electron micrographs revealed spherical carbamazepine- and cyclosporine A-loaded microparticles with smooth surfaces (Fig. 7). In contrast, indomethacin and estradiol crystallized outside the polymeric microparticles (Fig. 6).

In contrast to classical coacervation microencapsulation methods, the drugs were initially dissolved and not dispersed in the polymer solution prior to addition of the non-solvent (aqueous polymer) phase. The aqueous HPMC solution, which induced coacervation of the enteric polymers, was also a non-solvent for the lipophilic drugs. Upon addition of the HPMC solution, Eudragit® L100-55 came out of solution before the drugs. This indicated a lower solubility of the polymer in the solvent/non-solvent mixture when compared to the drugs (Table 3, Fig. 8). Depending on the solubility of the drugs within the enteric polymers, they were either dissolved in the enteric microparticles or they crystallized inside or outside the polymeric matrix in the aqueous phase. A simple qualitative test for drug/polymer compatibility was the observation of cast drug-containing films. Clear films indicated drug dissolved in the polymer matrix, while turbid films indicated undissolved (crystallized or amorphous) drug. Carbamazepine, cyclosporine A and lidocaine (30% (w/w) loading) were soluble in Eudragit® L100-55 films (clear films). The drugs did not recrystallize during 1.5 years of storage. Ibuprofen formed transparent films up to 20% (w/w), but not at 30% (w/w) drug loading, while indomethacin and estradiol formed crystals already at 10% (w/w) drug loading, indicating a low drug/polymer compatibility (low drug solubility in the polymer). This explained their crystallization outside the enteric microparticles, as described above (Fig. 6).

The amounts of Eudragit® L100-55, carbamazepine or ibuprofen (20%, w/w) in both polymer-rich and -poor regions were determined during the coacervation process in order to investigate the mechanism of drug encapsulation within the enteric microparticles (Fig. 8). The enteric polymer formed coacervates prior to the drug precipitation. The drug preferentially stayed in the polymer-rich phase in the initial stage. With the addition of 1% (w/w) HPMC solution, the solubility of the drugs further decreased in the polymer-poor phase (Fig. 9), resulting in a partitioning of the drug into the polymer-rich phase. Carbamazepine with its high solubility in the enteric polymer was encapsulated in a non-crystalline state (possibly in a molecular state), while ibuprofen partially crystallized due to its limited solubility in the enteric polymeric matrix (Fig. 10). Interestingly, the particle size of carbamazepine microparticles was larger than of the one of ibuprofen particles.

In conclusion, enteric microparticles were prepared by a novel microencapsulation method. Various lipophilic drugs, such as carbamazepine, lidocaine and cyclosporine A, could be successfully encapsulated in the enteric microparticles in a non-crystalline state.

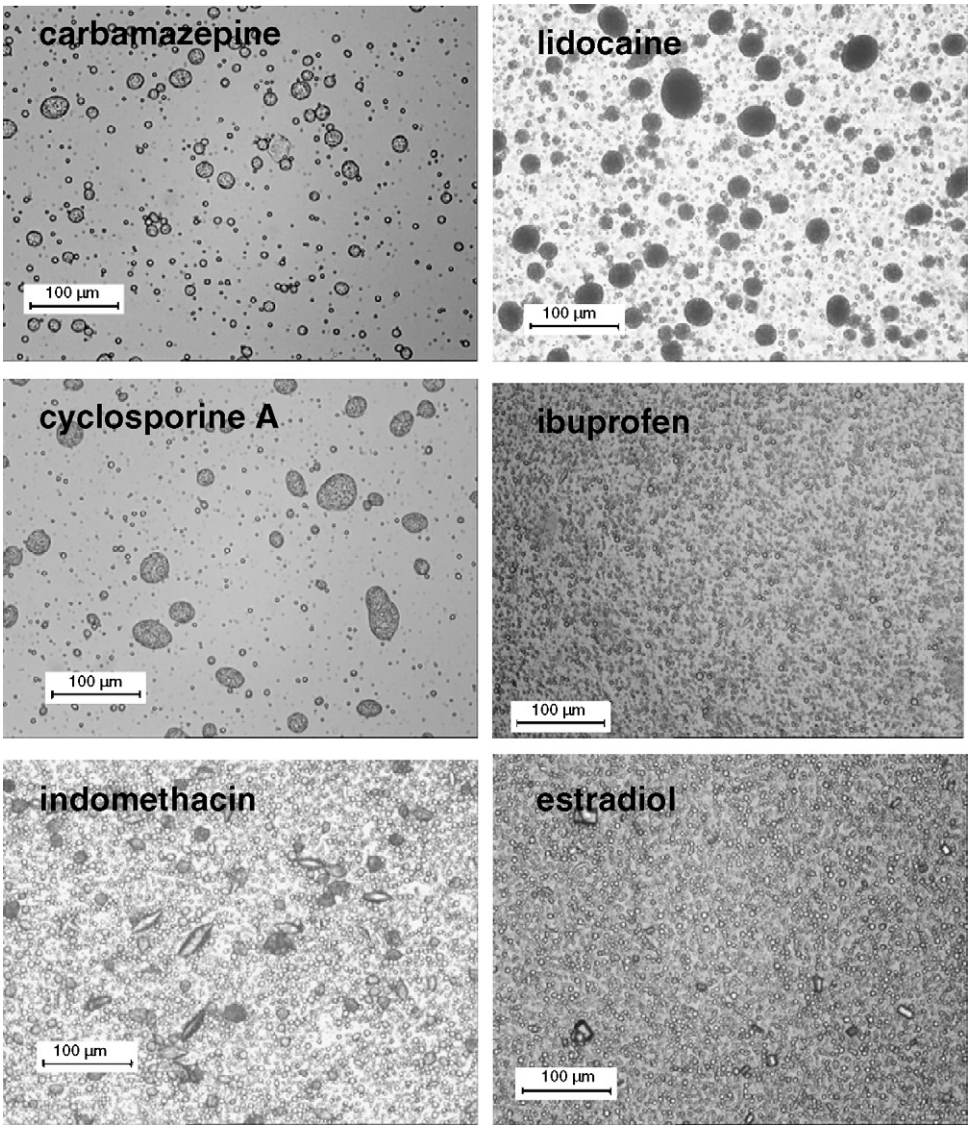


Fig. 6. Photographs of drug-loaded (10%, w/w) Eudragit® L100-55 microparticles.

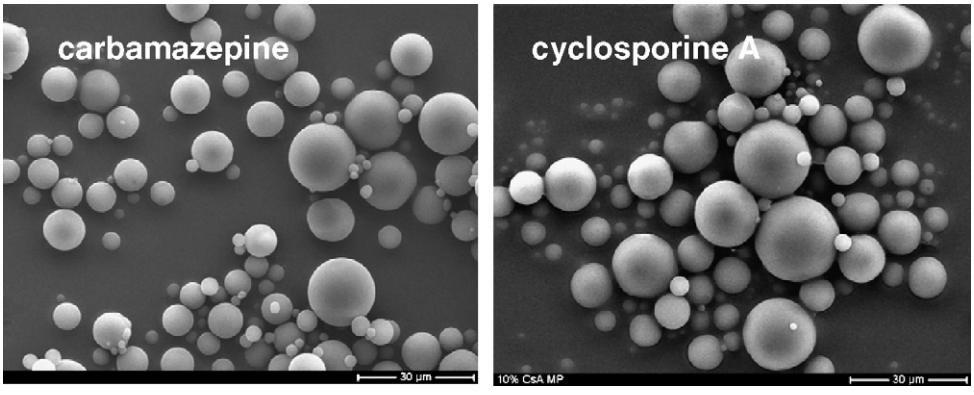


Fig. 7. Scanning electron micrographs of carbamazepine- and cyclosporine A-loaded (10%, w/w) Eudragit® L100-55 microparticles.

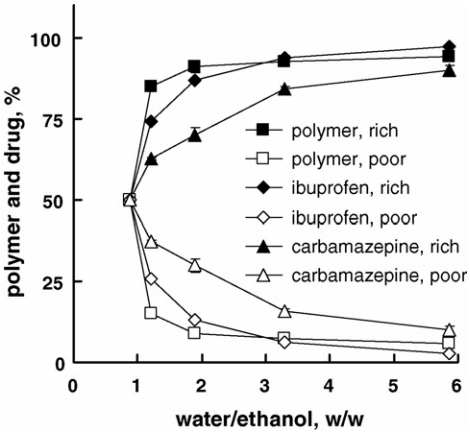


Fig. 8. Amount of Eudragit® L100-55, ibuprofen and carbamazepine in polymer-rich and -poor regions.

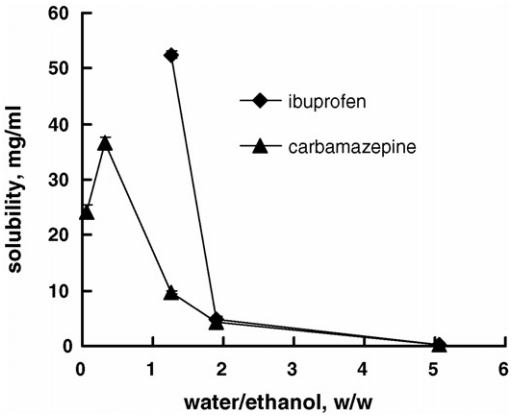


Fig. 9. Solubility of ibuprofen and carbamazepine in water/ethanol mixtures at room temperature.

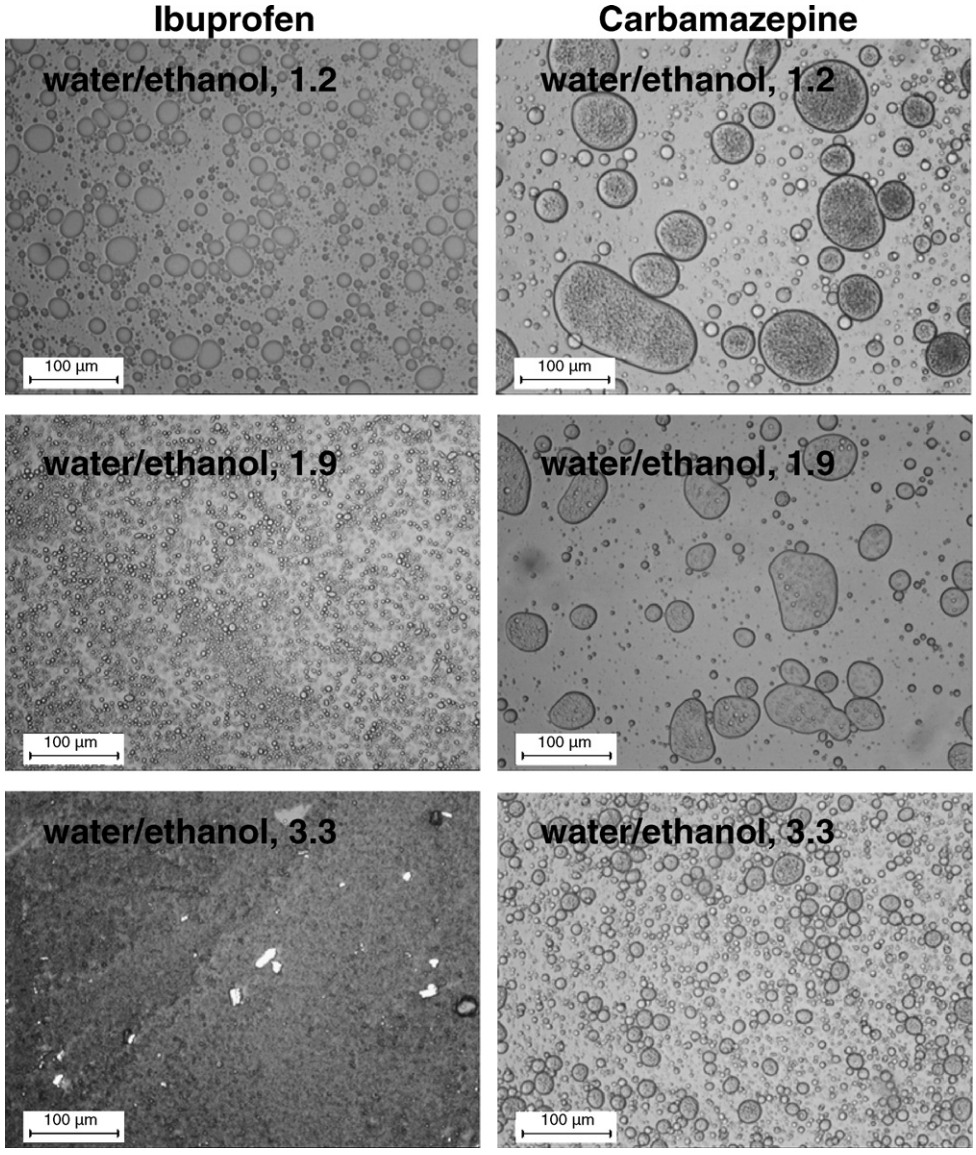


Fig. 10. Photographs of coacervate droplets and hardened enteric microparticles containing ibuprofen and carbamazepine (20%, w/w) as a function of water/ethanol ratio.

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