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Research Article

Enteric Micro-Particles for Targeted Oral Drug Delivery

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Abstract. This work is focused on production of enteric-coated micro-particles for oral administration, using a water-in-oil-in-water solvent evaporation technique. The active agent theophylline was first encapsulated in cellulose acetate phthalate (CAP), a pH-sensitive well-known polymer, which is insoluble in acid media but dissolves at neutral pH (above pH 6). In this first step, CAP was chosen with the aim optimizing the preparation and characterization methods. The desired release pattern has been obtained (low release at low pH, higher release at neutral pH) but in presence of a low encapsulation efficiency. Then, the CAP was replaced by a novel-synthesized pH-sensitive poly(methyl methacrylate–acrylic acid) copolymer, poly(MMA–AA). In this second step, the role of two process parameters was investigated, i.e., the percentage of emulsion stabilizer (polyvinyl alcohol, PVA) and the stirring power for the double emulsion on the encapsulation efficiency. The encapsulation efficiency was found to increase with PVA percentage and to decrease with the stirring power. By increasing the PVA content and by decreasing the stirring power, a high stable double emulsion was obtained, and this explains the increase in encapsulation efficiency found.

KEY WORDS: coating; drug targeting; emulsion; microencapsulation; polymeric drug delivery systems.

INTRODUCTION

The therapeutic potential of advanced molecules (peptides and DNA recombinant drugs) produced by the recent applied biotechnologies is often limited by low absorption and instability of these new active substances. In particular, in oral drug route, the degradation after administration of the active ingredients can be due to their pH instability, hydrolysis by enzymes, and short half-life. Microencapsulation is one of the techniques able to overcome the drug stability problem, and moreover, the possibility of formulating encapsulated drug delivery systems with controlled release rates is highly desiderated (1).

On these bases, oral-controlled release multiple-unit dosage forms (e.g. pellets, granules or micro-particles) produced by microencapsulation techniques represent effective new therapeutic platforms. The active molecules are protected as long as they reach their specific action site. Moreover, multiple-unit dosage forms offer several advantages over single-unit dosage forms (e.g., capsules or tablets), such as avoiding local drug concentration and lowering risk of toxicity by an uniform spread throughout the gastrointestinal tract.

Most of the applied techniques of micro-encapsulation are based on modifications of the three basic methods: spray-drying, phase separation (coacervation), and solvent extraction/evaporation.

By spray drying, particles are produced from liquid streams atomized in fine drops. The fundamental principle of disintegrating a liquid (solutions, emulsions, dispersions, slurries, and gels) consists in increasing its surface area until it becomes unstable and then disintegrates. The performance of a spray-drying process critically depends on the drop size produced by the atomizer and on the way the gaseous medium (used to dry the spray) mixes with the drops. The method is suitable to high throughput but not in treatments of temperature-sensitive streams (2).

Coacervation consists of a separation process of an aqueous polymeric solution into two miscible liquid phases: a dense coacervate phase and a dilute equilibrium phase. The dense coacervate wraps as a uniform layer around suspended core materials. Coacervation effect spontaneously results upon mixing of oppositely charged polyelectrolytes in aqueous media. Coacervation parameters are: pH, ionic strength, temperature, molecular weight, and solution concentration. Coacervation technique has shown potential applicability in many fields (pharmacology, fine foods, microbiology); its diffusion is limited due to residual solvents in the final micro-partlcles and relatively high costs (3).

Solvent extraction/evaporation neither requires elevated temperatures nor phase separation-inducing agents (4). The water-in-oil-in-water (W/O/W) emulsion solvent evaporation is the most used method to encapsulate water soluble drugs, and the encapsulation efficiency can be quite high (5). However, the reproducible manufacturing of micro-particles with the desired properties (good encapsulation efficiency, suitable release profiles and particle distribution, acceptable

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solvent residuals) can be difficult, due to the large number of factors influencing the final products, such as solvent composition, total volume, and phase–volume ratio of the phases, polymer concentration, type of stabilizer, stirring time, stirring speed, etc. For example, the increase of the stirring time of double emulsion reduces the encapsulation efficiency (6) and the drug content (7), owing to drug partitioning into the external aqueous medium. Reduced encapsulation efficiencies occurs using hydrophilic coating polymers (6): a slower solidification of the primary emulsion droplets in the W_2 phase causes the diffusion of a larger amount of drug out of the micro-particles (8). Moreover, a greater concentration of polymer increases the viscosity of the middle organic phase (O), stabilizing the film around the internal water droplets and thus reducing possible coalescence of the internal aqueous phase with the external one (7). The organic polymer phase acts as a diffusion barrier for drug; the thickness of this barrier increases with a decrease of the volume of the internal aqueous phase (5). However, the effect of the preparation parameters on the micro-particles obtained by double-emulsion solvent evaporation method has to be empirically determined as predictions and scale-up remain difficult steps (1).

Micro-particles can be engineered to gradually release active ingredients. A coating may also be designed to open in specific areas of the body (9). It would be highly beneficial if the active agents were delivered by a system that sensed the signal caused by disease, judged the magnitude of a signal, and then acted to release the right amount of drug in response. Such a system would require coupling of the drug delivery rate with the physiological need by means of some feedback mechanism (10). The environment-sensitive polymers, called "smart" polymers, are ideal candidates for developing self-regulated drug delivery systems. Maybe the most important stimulus which can occur in physiology is the change in environment pH. The pH-sensitive polymers have been most frequently used to develop enteric formulations for oral administration. The pH in the stomach (<3) is quite different from the neutral pH in the intestine, and such a difference is large enough to elicit pH-dependent behavior of polyelectrolyte polymer. Enteric-coated products are designed to remain intact in the acidic juices of the stomach and then to release the drug at the higher pH of the small intestine (above pH 5.5) or at the even higher pH in the colon (above pH 6.5): the drug effectiveness would be reduced by stomach acids and enzymes if left unprotected (11). Release profiles of spray-dried cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT) micro-particles containing flavonoids, such as the water soluble Rutin, exhibited a loss of drug in acidic medium of about 20%, then a complete release after approximately 10 min of being kept at pH 6.8 (12). Eudragit S100 μ-particles containing theophylline, obtained by an oil in oil (O/O) emulsion solvent evaporation method, showed about 25% rapid initial drug release just a few minutes after suspending the microspheres in the acid dissolution medium. After the initial stage, a slight increase in the amount of theophylline released in acid medium was observed. Higher release rates were noticed, during the dissolution in the slightly neutral buffered medium (pH 6.5, 37°C), due to the creation of pores and channels and probably to the polymer swelling (13).

Eudragit, CAP, and CAT are some of polymers with different chemical structure adopted for the dissolution at different pH values. Recently, copolymers of methyl methacrylate (MMA) and AA, which can dissolve at tailored pH values (in the interval 3–7) only changing the volumetric percentage of MMA, were synthesized. Their use for the matrix allows the drug release in correspondence of any desired pH target (14,15). The availability of such a class of copolymers, able to give the desired release at any physiological pH level, represents an advantage—with respect to the enteric polymers already available on the market—since they have the same chemical structure, and they require the same technological steps to be processed. Therefore, changing the target from an upper GI medication to a colonic delivery system would not ask for a complete change of the enteric polymer (and consequently for a complete change of processing conditions). Using the novel class of materials, it will be enough to change simply the MMA/AA ratio in the polymer synthesis mixture.

The ideal drug release should be negligible at low pH, then controlled in neutral media. Enteric microparticles, i.e. particles made of polymers which dissolve only at high pH levels observed in the GI tract, are drug delivery systems with this desired ability. Several techniques and different materials are available to the purpose, but the relation between process parameters and features of obtained products for different methods are not well investigated. Furthermore, a unique class of materials, able to dissolve at each desired pH level observed in different position along the GI tract and in function of the body conditions, is not available on the market. Therefore, systems for the delivery in the upper GI tract and for the colonic delivery have to be based on different kind of enteric polymers. Aims of this work are to optimize the use of a novel class of polymeric materials, synthesized by ourselves, which can dissolve at the desired pH and to carry out a systematic analysis of the effect of two processing parameters on the encapsulation efficiency in the double emulsion method.

EXPERIMENTAL

Materials

Copolymer Synthesis

MMA and AA were purchased from Sigma–Aldrich (Milan, Italy); initiator 2,2′-azobis 2,4-dimethylvaleronitrile (AMVN) was a Cayman Chemical Company product.

Micro-Particles Preparation

Two different enteric polymers were used to prepare micro-particles: CAP and poly(MMA–AA) with 70% (*v*/*v*) of MMA. Theophylline (TP) was the model drug. The solvents were: methyl ethyl ketone (MEK), dichloromethane (DCM), ethanol (ET), and isopropanol (IS). Tween 80 and Span 80 were used as surfactants. Polyvinyl alcohol (PVA) was the emulsion stabilizer. They were all Sigma–Aldrich (Milan, Italy) products. Hydroxypropyl-methylcellulose (HPMC, Methocel K15M Premium Grade, kindly supplied by Color-

con) was also used as stabilizer of the internal aqueous phase. Deionized water was used for all the experiments.

METHODS AND APPARATUSES

Copolymer Synthesis

The poly(MMA–AA) copolymers were obtained by a free radical polymerization method proposed by Abusafieh et al. (14) for potential applications of cross-linked poly(MMA–AA) copolymer in bone implants and applied in our recent studies on oral drug delivery (15). In particular, the polymerization was carried out in bulk, using AMVN as initiator whose amount was fixed to 0.4 g/100 mL of total mixture. The initiator was added to various volumetric ratios of MMA/AA monomers and thoroughly mixed by sonication (Vibra-CellTM Ultrasonic Processor, Sonics, Newtown, CT) for 3 min. The reaction mixture was poured into glass tubes, sealed, and placed vertically in a water bath which provided a uniform and accurate temperature control. The tubes were then taken out from the bath and broken under slight clamp pressure. The samples were removed from the broken glass tubes and placed in an oven in which the temperature was slowly raised up to 70°C, followed by overnight cooling. The samples were crushed and stored at room temperature. The important feature of the novel synthesized poly(MMA–AA) was the linear relationship holding between dissolution pH and volumetric percentage content of MMA (15).

Micro-Particles Preparation

Micro-particles were prepared by a double emulsion ($W_1/O/W_2$) solvent evaporation method. For both CAP and poly(MMA–AA) micro-particles, the internal aqueous phase (W_1) was obtained by mixing at room temperature 200 mg of TP in 40 mL of deionized water and then adding 400 mg of HPMC: the mixing was continued until the solution became clear. Purpose of eventually adding HPMC was to increase W_1 viscosity in order to limit the loss of TP during micro-particles formation (16).

The organic phase (O) in CAP micro-particles preparation consisted of 400 mg of CAP in 40 mL of MEK. MEK is a good solvent for the aim of this work: the dissolution of CAP in MEK is fast and complete and the partial solubility of MEK itself in water (290 g/L in water at 20°C) allows its quick diffusion into the external aqueous phase.

In the poly(MMA–AA) micro-particles preparation, the double-emulsion solvent evaporation method proposed by Jain *et al.* (17) was adopted. The organic phase was composed of 200 mg of poly(MMA–AA) solubilized by a mixture of DCM/IS/ET (20/4/3 mL). This mixture (DCM/IS/ET) is a good solvent for both pH-sensitive Eudragit and poly(MMA–AA), since both have similar functional groups.

A drop of Span 80 was mixed with the oil phase in both the preparations. The external water phase (W_2) was 100 mL of water with: (1) a drop of Tween 80 and some drops of HCl for CAP micro-particles; (2) a variable amount of PVA for poly(MMA–AA) micro-particles.

The primary W/O emulsion was prepared under high mixing conditions (ultrasonication), while the secondary emulsification step was carried out without any severe mixing (any excess of mixing could cause the rupture of the drops resulting in a simple oil-in-water emulsion) (18). Therefore, the oil phase (O) was emulsified at room temperature with the internal aqueous phase (W_1) using an ultrasonic mixing in order to obtain the emulsion W_1/O. The primary emulsion was poured in W_2, and the resulting $W_1/O/W_2$ emulsion was mixed with a magnetic stirrer. Fundamental operative parameters are summarized in Table I.

$W_1/O/W_2$ was placed in a rotavapor (Laborota 4002 control, Heidolph), under vacuum, with a temperature increase from 20°C to 50°C at a speed of 18 rpm, to allow the solvent to evaporate. The suspended micro-particles were washed thrice with distilled water by centrifugation at 6,000 rpm for 5 min; then, they were analyzed by optical microscope (Leica DM LP). The final product was obtained by evaporation of residual water in an oven at 60°C (Fig. 1). The micro-particles were collected, weighted, and stored at room temperature.

Dissolution Tests

To test the enteric nature of micro-particles and drug release, a given amount of micro-particles, about 10 mg, was put in 75 mL of 0.1 N hydrochloric acid (pH 1). After a time span of 70–100 min, 25 mL of 0.2 M tribasic sodium phosphate were added in order to reach pH 6.8. The dissolution was carried out in 200-mL beaker stirred by magnetic anchors at 400 rpm. Samples of 3 mL were taken at given times and assayed for TP release by UV-visible spectrometer (Lambda 25 by Perkin Elmer) at a wavelength of 270 nm. The samples were then put back in the dissolution medium: in fact, especially in medium at pH 1, where the micro-particles are undissolved (the dissolution bulk presents heterogeneous properties), 3 mL of sample could still contain significant quantity of micro-particles.

Difficulties in evaluation of drug concentration could arise because of polymer presence as CAP that is progressively eroded during the dissolution test consequently falsing the spectrometric determination of the TP. To overcome this, the method for simultaneous measurements of TP and CAP concentrations pointed out in a previous work (19) was applied here. The method consisted in fitting spectra collected at wavelength between 200 and 400 nm, with a step of 1 nm, by UV-visible spectrometer. In mentioned work (19), the absorption spectra of pure TP and CAP were taken at several concentrations, and they were described by summing a number of Gaussian peaks (three Gaussians for CAP and four Gaussians for TP). The height of a reference peak for each compound was taken as proportional to the specie

Table I. Operative Parameters for CAP and Poly(MMA–AA) Micro-Particles Preparation

	CAP	Poly(MMA–AA)
W_1/O	10 mL/40 mL	1 mL/5 mL
W_1/O in W_2	5 mL in 45 mL	6 mL in 100 mL
Sonication time W_1/O	60 s	30 s
stirring time $W_1/O/W_2$	1 h	1 h

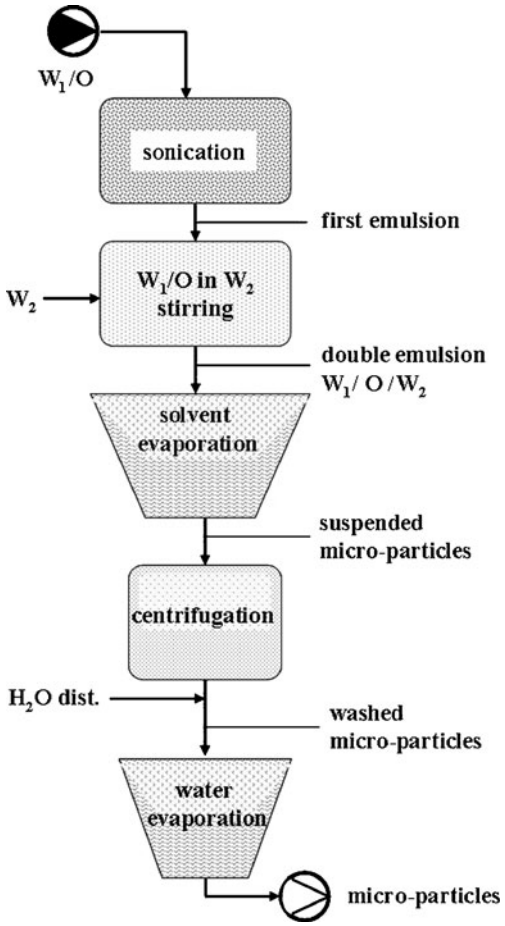

Fig. 1. W/O/W solvent evaporation method

concentration. Therefore, a code to fit the spectrum obtained analyzing some solutions of TP and CAP was developed (the data were fitted by the seven Gaussian peaks, three for CAP, and four for TP), and the code itself was found able to measure the concentration of the two species with a good accuracy.

For poly(MMA–AA) micro-particles, there was no need for the spectra fitting procedure because of the very low interference of polymer and HPMC absorbances on TP absorbance at the characteristic wavelength of 270 nm. Therefore, only peak value of spectra was considered.

Definitions of theoretical, loaded, and encapsulated TP are reported in Eqs. 1–3, respectively; the yield of encapsulation and the performed loading are expressed as described in Eqs. 4 and 5, respectively:

$$\text{Theoretical TP \%} = \frac{\text{initial amount of TP}}{\text{total weight of microparticles}} \cdot 100 \quad (1)$$

$$\text{Loaded TP \%} = \frac{\text{TP released at pH 6.8}}{\text{amount of analyzed powder}} \cdot 100 \quad (2)$$

$$\text{Encapsulated TP \%} = \text{TP\% at pH 6.8} - \text{TP \% at pH 1} \quad (3)$$

$$\text{Yield of encapsulation \%} = \frac{\text{encapsulated TP}}{\text{loaded TP}} \times 100 \quad (4)$$

$$\text{Loading \%} = \frac{\text{loaded TP}}{\text{theoretical TP}} \times 100 \quad (5)$$

The loaded TP percentage, as the ratio between TP fully released at neutral pH and the amount of analyzed powder (Eq. 2), has to be compared to the theoretical TP percentage (Eq. 1, also named expected TP), defined as the ratio between the amount of TP added to the W_1 phase and the total weight of micro-particles themselves (sum of TP, polymer, and other solid ingredient quantities). Furthermore, the encapsulated TP percentage, as difference between the percentage of TP released at pH 6.8 and the one released at pH 1 (Eq. 3), and yield of encapsulation, as ratio between encapsulated TP and loaded TP (Eq. 4), will be evaluated for each test. The last evaluated parameter is the loading

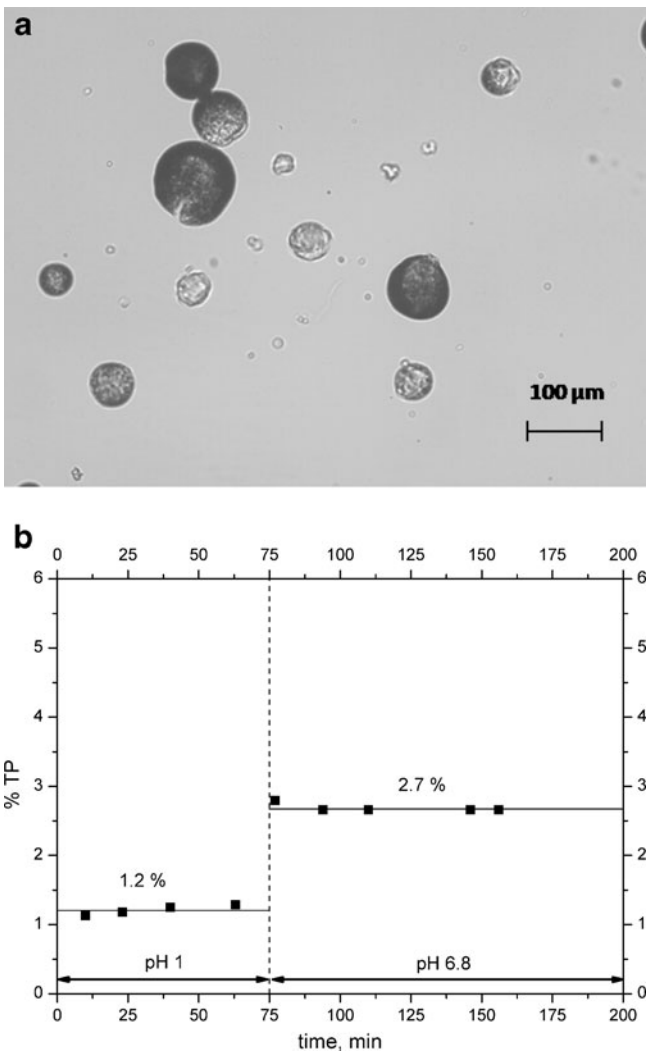

Fig. 2. a, **b** Optical microscope picture and dissolution profiles of CAP micro-particles (the percentage of TP released was referred to the ratio between mass of TP released and total mass of micro-particles put in dissolution medium)

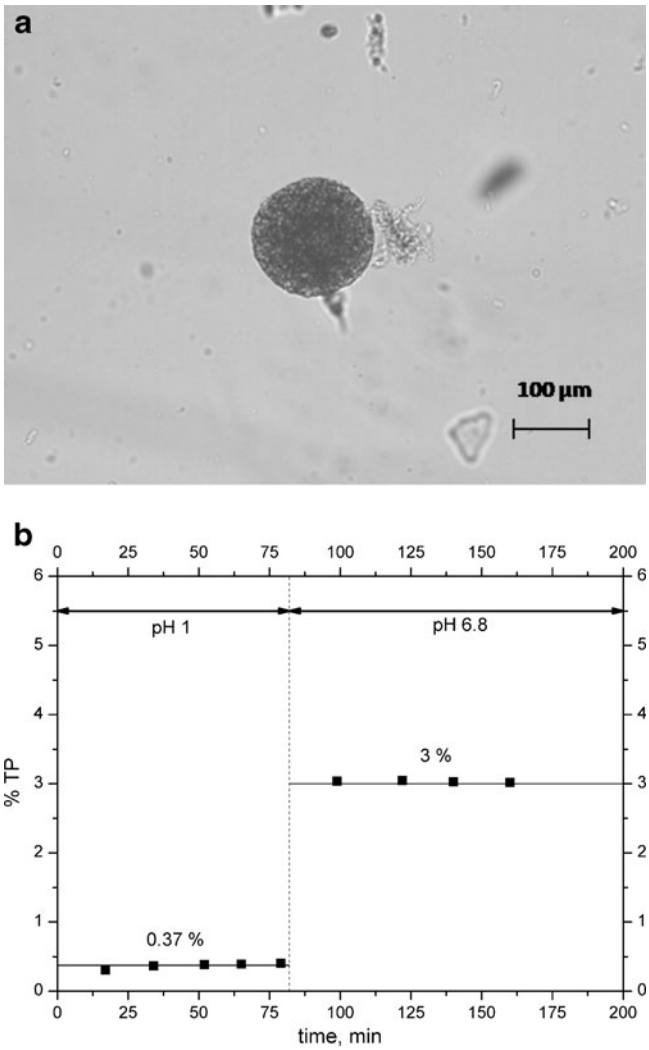

Fig. 3. **a**, **b** Optical microscope picture and dissolution profiles of poly (MMA–AA) micro-particles with P_1=1% and P_2=1.25·10^8 (the percentage of TP released was referred to the ratio between mass of TP released and total mass of micro-particles put in dissolution medium)

percentage (defined as the ratio between loaded TP and theoretical TP, Eq. 5).

RESULTS AND DISCUSSIONS

Release from CAP-Based Particles

Release tests of CAP/TP micro-particles have shown the expected trends: the theoretical load ratio (expected TP, calculated by Eq. 1) was 9.1% (50 mg of TP over 550 mg of total powder, TP+HPMC+CAP), Fig. 2 shows a relatively low percentage of TP released in the acidic medium (1.2%), then a complete and instantaneous TP release (2.7%) after reaching pH 6.8 owing to the sudden dissolution of CAP. Thus, the loaded TP was 2.7% (i.e. the TP which was released at neutral pH, taken from Fig. 2, calculated by Eq. 2). Therefore, the loading percentage, calculated by Eq. 5, is about 30%. The loading value is not too high, but this is a common result when working with this method of microencapsulation. As above reported, the percentage of encapsulated TP is given by the difference between the total load and the TP released at pH 1, and in this case is 1.2% (see Fig. 2). Therefore, the encapsulated TP is 1.5% (calculated by Eq. 3), giving a yield of encapsulation (calculated by Eq. 4) larger than 50%. This means that a little less than one half of the encapsulated TP is dispersed on the surface of the particles, and then it is available in the acid environment (gastric tract). The remaining will be released only in the neutral environment (intestinal tract). The overall results of this first step of the experimentation are: the emulsion solvent evaporation method allows to obtain drug loading ratio acceptable for industrial purposes (about 30%) and yield of encapsulation could be useful for the practical uses (more than 50%).

Release from Poly(MMA–AA)-Based Particles

Since emulsion solvent evaporation method was successfully applied in the production of enteric coated micro-particles, CAP was replaced with one of the poly(MMA–

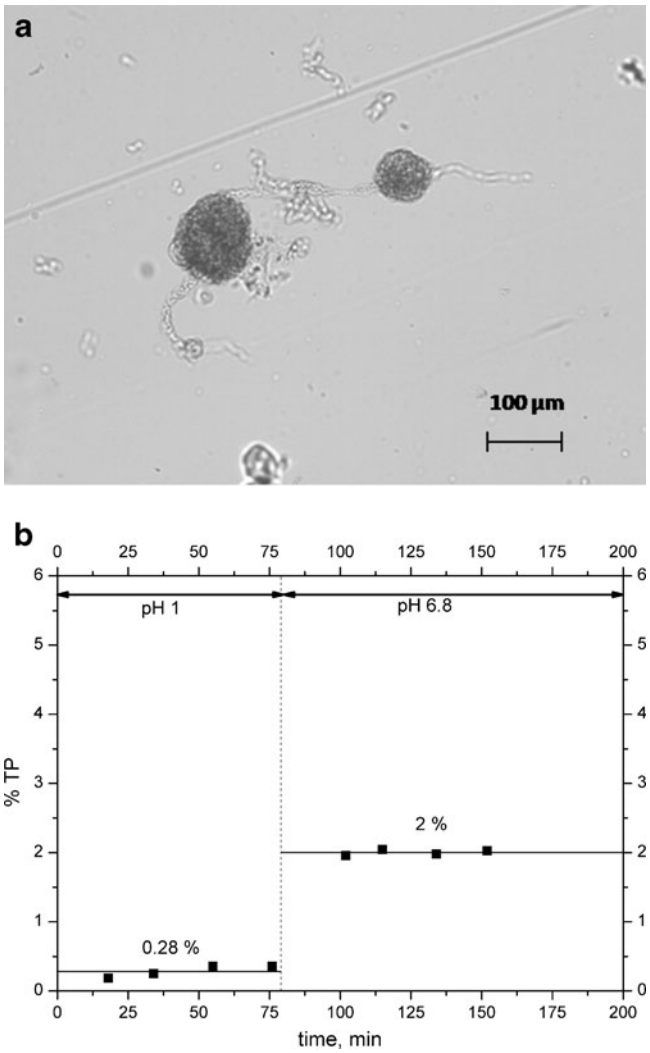

Fig. 4. **a**, **b** Optical microscope picture and dissolution profiles of poly (MMA–AA) micro-particles with P_1=1% and P_2=2.05·10^8 (the percentage of TP released was referred to the ratio between mass of TP released and total mass of micro-particles put in dissolution medium)

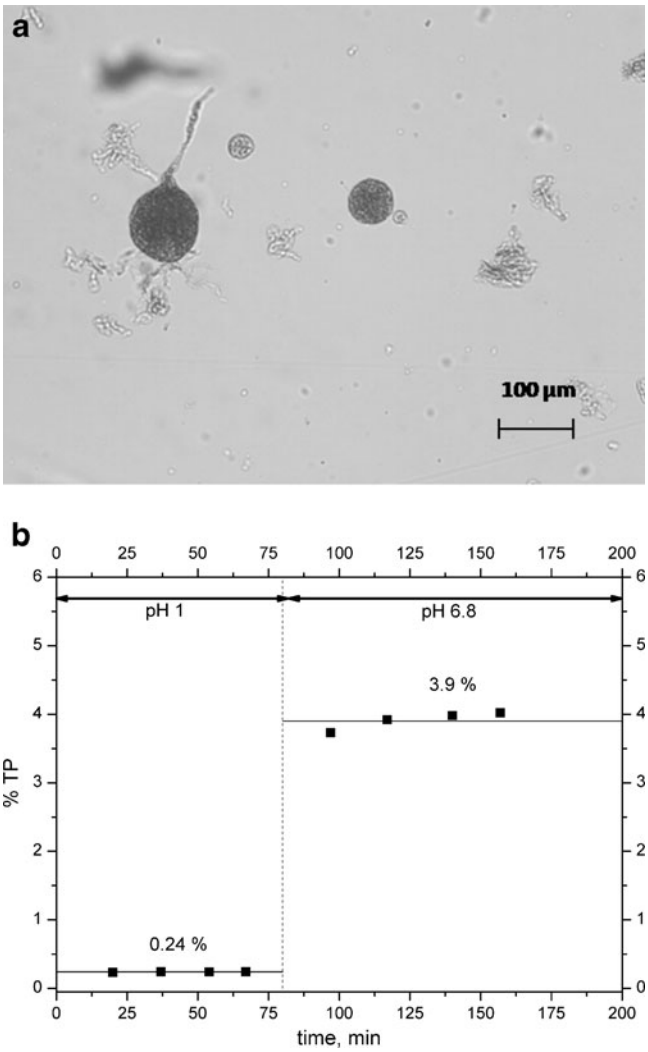

Fig. 5. **a**, **b** Optical microscope picture and dissolution profiles of poly (MMA–AA) micro-particles with P_1=1.75% and P_2=2.19·10^8 (the percentage of TP released was referred to the ratio between mass of TP released and total mass of micro-particles put in dissolution medium)

AA) copolymer synthesized. In particular, the copolymer with 70% of MMA monomer was used, which dissolves at pH>6.6 (15).

The influence of two parameters on preparation of poly (MMA–AA) micro-particles was tested. The two parameters are: the weight in volume percentage (*w*/*v* %) of the emulsion stabilizer PVA and a parameter proportional to the power of stirring of double emulsion.

The values 0.5%, 1%, 1.5%, 1.75%, and 2% were adopted for the weight in volume percentage of the emulsion stabilizer PVA, denoted as P_1 in the following. The addition of protective colloids with the scope of stabilizing the emulsion could lead to uniform and dispersed droplets and, thereby, of minimizing the formation of irregular and undesired micro-particles (5). Therefore, the effect of the parameter P_1 deserves to be investigated.

A parameter proportional to the power of stirring of double emulsion, P_S, was denoted as P_2 in the following. P_S can be assumed to be proportional to the product between the drag force, F_D, and to the stirring rate, u.

$$P_2 \propto P_S = F_D \cdot u = \left(fA\frac{\rho u^2}{2}\right)\cdot u \propto \mu A\frac{\rho u^2}{2}\cdot u$$
$$= (\mu_a + kP_1)A\frac{\rho u^2}{2}\cdot u \cong kP_1A\frac{\rho u^2}{2}\cdot u \propto P_1\cdot\omega^3 \quad (6)$$

The drag force, in turn, could be obtained by multiplying the friction factor, f, by a suitable area, A, and the fluid kinetic energy, $\rho u^2/2$. The friction factor could be taken as proportional to the PVA solution viscosity, $\mu=\mu_a+kP_1$; then, leaving out the pure water viscosity, μ_a, which is much lower than μ, a linear relationship between μ and the percentage of PVA (P_1) can be considered. Thus, as remarked in Eq. 6, the parameter P_2—proportional to the stirring power—is given by the product between P_1 (from friction factor) and the cube of the angular velocity of the impeller ω (ω=410, 500, 590, 680, 770 rpm). The third power of the angular velocity is due to a quadratic power in the kinetic energy (used in the calculation of the drag force), plus a single power to obtain the power starting from the force. On the bases of this consideration, the values of the parameter P_2 can be calculated by Eq. 7:

$$P_2 = P_1\cdot\omega^3 \quad (7)$$

Dissolution profiles of TP/poly(MMA–AA) micro-particles, with P_1=1% and P_2=1.25·10^8 (stirring speed of 500 rpm; Fig. 3) show that TP release at pH 1 was of about 0.4%, then the encapsulated TP (3.0%) was fully released in neutral medium.

Figure 4 remarks dissolution profiles of micro-particles whose preparation differentiated from the previous case (Fig. 3) only for the stirring power P_2, which was set at 2.05·10^8 rather than 1.25·10^8 (stirring speed—590 rpm rather than 500 rpm). The encapsulated TP (2.0%) was lower than for the previous case, confirming that higher stirring power can cause a predominant broken capsule structure with a consequent decrease in encapsulated TP.

Table II. Final Properties Calculated for Poly(MMA–AA) Micro-Particles

	Expected TP %	Loaded TP %	Encapsulated TP %	Yield of encapsulation %	Loading %
P_1=1% P_2=1.25·10^8	9.6	3.0	2.7	88	32
P_1=1% P_2=2.05·10^8	9.6	2.0	1.7	86	21
P_1=1.75% P_2=2.19·10^8	9.6	3.9	3.7	94	41

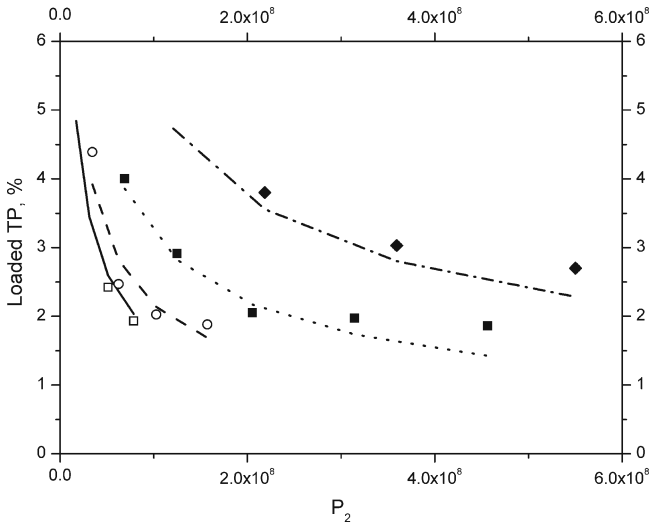

Fig. 6. Actual TP percentage *vs* P_2, a parameter proportional to the stirring power of W/O/W, for different values of the percentage of PVA in W_2 (P_1 0.25%, 0.5%, 1%, 1.75%): experimental data and fitting curves (*unfilled squares* exp(P_1=0.25%) *solid line* fit (P_1=0.25%); *unfilled circles* exp(P_1=0.5%), *dashed line* fit (P_1=0.5%); *filled squares* exp(P_1=1%), *dotted line* fit (P_1=1%); *filled diamonds* exp(P_1=1.75%), *dashed–dotted line* fit (P_1=1.75%))

In Fig. 5, the TP release in acid and neutral media are, respectively, 0.2% and 3.9%. The difference from the previous case (P_1=1%; P_2=2.05·10^8) was the higher percentage of PVA, P_1=1.75%; instead, the power stirring was almost the same (P_2=2.19·10^8, less than 10% higher than the previous case). In this case, the yield of encapsulation (94%) and the actual loading (41%) were very high confirming the better stabilization of double emulsion by a bigger percentage of PVA (even if in presence of a little higher stirring power).

The results obtained in the previous three cases were summarized in Table II. Comparison between the three runs confirms that the presence of PVA improves the process, and the stirring power has to be kept at the lower level which allows obtaining the emulsion.

Carrying out other runs, whose results are not reported here in details, the effect of both parameters has been better defined. Figure 6 shows the trend of the percentage of loaded TP (Eq. 2) as a function of the stirring power, P_2, for some values of the percentage of PVA, P_1. Figure 6 confirms that loaded TP decreases by increasing the stirring power of the double emulsion, P_2, which can cause the breaking of the micro particles. Furthermore, the effect of the PVA percentage, P_1, is to produce micro-particles with high TP loads, likely because of a better stabilization of the double emulsion.

The loaded TP was also fitted by a simple power law equation, with respect to P_2, where the coefficients are linearly dependent upon P_1:

$$TP_L = (c_1 + c_2 \cdot P_1) \cdot P_2^{-(c_3 + c_4 \cdot P_1)} \quad (8)$$

In Eq. 8, TP_L is the percentage of loaded TP, and the parameters are c_1=71,164, c_2=−20,000, c_3=−0.58666, c_4=−0.06067. Equation 8 is not a physically based model; it is only a fitting relationship which allows to predict the level of loaded TP obtainable working with different values of parameters P_1 and P_2 (different operative conditions). Of course, a fitting model is not reliable in extrapolation, but the model, as well as the location of the experimental data points, confirms that an increase of PVA increases the loaded TP. Furthermore, the behavior of loaded TP with P_2 seems to be asymptotical: the increase of stirring power above a certain limit causes the loaded TP to reach a lower limit; the decrease of stirring power below a certain limit simply does not allow producing the second emulsion; thus, a minimum value of P_2 has to be used in the production process.

CONCLUSIONS

In this work, a method to produce microencapsulated drug, based on the solvent evaporation from double emulsion (W_1/O/W_2), was pointed out by using a model drug, the TP, and two enteric polymers, the well-known CAP and a home-synthesized poly(MMA–AA). The CAP was used to test the preparation method; then, one of the copolymers (the one obtained using 70% of MMA monomer, which dissolves at pH>6.6 (15)) was used to microencapsulate the TP.

Good loading percentages were realized (up to 40% of the theoretical loading), and excellent encapsulation percentages were obtained (more than 90% of loaded TP was released in neutral media).

At last, a parametric analysis of the process was carried out, confirming that the loading and the encapsulation efficiencies increase with the stabilizer content in the external water phase (P_1 = percentage of PVA in W_2) whereas decrease with the stirring power (P_2) used to produce the second emulsion. Therefore, it is possible to conclude that to maximize the process yields, the production of the second emulsion is the key step, and a second emulsion as stable as possible has to be obtained.

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