International Journal of Pharmaceutics 434 (2012) 235–242

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Development and evaluation of taste-masked drug for paediatric medicines – Application to acetaminophen

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ARTICLE INFO

Article history:
Received 4 April 2012
Received in revised form 18 May 2012
Accepted 21 May 2012
Available online 29 May 2012

Keywords:
Taste-masked drug
Spray-drying
Electronic tongue
X-ray photoelectron spectroscopy (XPS)
Drug release studies

ABSTRACT

The aim of this work was to produce and characterize taste-masked powders of a model drug (acetaminophen) prepared using potentially tolerable and safe excipients for paediatric use, i.e. sodium caseinate and lecithin. The powders were produced by spray-drying aqueous dispersions. The characteristics of taste-masked drug particles were determined by scanning electron microscopy, differential scanning calorimetry and X-ray photoelectron spectroscopy to analyse the surface composition of particles. Taste assessment was approached by an indirect method through drug release studies. We developed a method with a syringe pump using small volumes of aqueous medium and low flow rates, to mimic the behaviour in the mouth. This method was compared to the electronic tongue analysis. SEM, DSC and XPS analysis indicated differences in surface composition of spray-dried particles according to the caseinate/lecithin ratio and to relate it with taste-masking. The "coating" consisting of caseinate and lecithin had a significant role in decreasing the release of drug during the first 2 min and so in taste-masking. Higher content in lecithin results in higher taste-masking efficiency. The association of sodium caseinate and lecithin seems to be promising to mask the bitterness of acetaminophen. A good agreement between release study and electronic tongue analysis was established.

1. Introduction

Medicines for children have long been a neglected area. The lack of appropriate dosage forms results in children frequently prescribed medicines that are off-label, unlicensed without any data regarding their bioavailability, efficacy and toxicity. Consequently, vulnerable patients within this age group are exposed to a rate of medication errors higher than that for adult patients. Following the implantation of European regulation with respect to medicinal products for paediatric use, scientist community has to speed up for making medicine available for children by encountering multiple problems of paediatric formulation (Ernest et al., 2007). Indeed, the taste of oral medicine is one of the most crucial factors influencing adherence to therapeutic regimens and therapeutic outcomes (Matsui, 2007). As a lot of active pharmaceutical ingredients exhibit an unpleasant taste, taste-masking becomes particularly important. Basically, taste is transmitted by the interaction of dissolved molecules with different targets located in taste buds on the tongue. The mechanisms of signal transduction after binding of the taste substance can be different depending on the taste quality (Lindemann, 2001). Hence, taste-masking strategy implies variety of technologies in order, (i) to provide a physical barrier between the active substance and the taste buds during drug uptake by coating, granulation, encapsulation; (ii) to modify the drug solubility by chemical derivatisation, complexation, use of ion-exchange resins, solid dispersions; or (iii) to alter the human taste perception by using sweetener and flavour, bitter blocker substances, etc. (Douroumis, 2007; Ayenew et al., 2009). The question raised is if these approaches can respond to requirements that effectively mask the bitterness of drug without alter the bioavailability upon administration (Cram et al., 2009). In particular, as the safety data of existing excipients and new excipients in children stay restrictive and insufficient, the selection of excipients types and levels must be more carefully taken (Ernest et al., 2007; Fabiano et al., 2011).

Spray-drying is a well-established, inexpensive and straightforward technology which permits to mask the unpleasant taste of certain ingredients through encapsulation (Gouin, 2004; Gharsallaoui et al., 2007). During this process, appropriate encapsulating materials enable the film formation at the droplet surface as water evaporates. The functional properties of encapsulating agent have an important role on resultant product characteristics e.g. solubility, and therefore the taste-masking efficiency.

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http://dx.doi.org/10.1016/j.ijpharm.2012.05.047

Casein is a phosphoprotein making up 20–40% of the protein in human milk and about 80% in bovine milk which also constitutes required nutrient composition for infant formulas (Keenan and Patton, 1995; Raiten et al., 1998; Abayomi, 2005). Derived product of casein – sodium caseinate – is stated to be unhazardous and may be regarded as food with not limited acceptable daily intake (SCOGS, 2012; WHO, 2012). Thanks to surface activity and desirable neutral flavour, this latter has been extensively investigated and utilized as an encapsulating agent in a number of applications for food through spray-drying (Imagi et al., 1992; Hogan et al., 2001; Bao et al., 2011). Also, lecithin is a mixture of surface-active agents called phospholipids. Considered as a GRAS (Generally Recognized As Safe) substance, there is evidence that phosphatidylcholine, a major component of lecithin, is important as a nutritional supplement to foetal and infant development. Furthermore, choline is a required component of FDA-approved infant formulas (Raiten et al., 1998). In a preliminary study, lecithin is shown to have complementary effect on slowing down the wettability of spray-dried powder and thus the dissolution of taste-masked powder.

The aim of this study is to produce and characterize taste-masked powders of acetaminophen (used as model drug) prepared by spray-drying using potentially tolerable and safe excipients for paediatric use, i.e. sodium caseinate and lecithin. Taste assessment is approached in vitro by an indirect method through drug release studies. We developed a method with a syringe pump using small volumes of aqueous medium and low flow rates, to mimic the behaviour in the mouth. This method is compared to the electronic tongue analysis. To explain the taste-masking, we analysed the composition at the particle surface with the X-ray photoelectron spectroscopy.

2. Materials and methods

2.1. Materials

Pulverised acetaminophen from Cooper (Melun, France); casein sodium salt from bovine milk (sodium caseinate) from Sigma–Aldrich (Missouri, USA); refined soybean lecithin from Alfa Aesar (Massachusetts, USA); acetonitrile HPLC grade (99.9%) and triethylamine HPLC grade (99.9%) from Fisher Chemical (Leicestershire, England); phosphoric acid powder analytical grade (99.9%) from Merck (Darmstadt, Germany). The materials were used as received.

2.2. Methods

2.2.1. Spray-drying experiment

The feed dispersions, whose compositions are given in Table 1, were made by combining acetaminophen, sodium caseinate and lecithin in distilled water and stirring overnight before being spray-dried in a Mini Spray Dryer B-190 (Büchi Labortechnik, Flawil, Switzerland). The spray-dryer equipped with a spray nozzle of 0.5 mm orifice diameter was a co-current model, using compressed air as atomising and drying air. The process parameters were described as follow: the temperature of drying air (inlet temperature) was 130 °C, resulting in outlet temperature of about 75 °C; the spray flow was 300 L/h; the pump feed was 4 mL/min with maximum aspiration. The spray-dried powders were stored at 20 °C and 12%RH before analysis.

Table 1
Feed dispersion composition in distilled water for spray-drying experiments.

Formulation	% (w/w)		
	Acetaminophen	Sodium caseinate	Lecithin
1:0.5[a]	1.0	1.0	0.5
5:1.5[a]	1.0	5.0	1.5

[a] Ratio of sodium caseinate to lecithin.

2.2.2. Determination of the drug content

A quantity of powder equivalent to 10 mg of drug was completely dissolved in distilled water and analysed by HPLC in order to determine the drug content of 1:0.5 and 5:1.5 formulations after spray-drying. The analysis was performed on six replicates. The average content and the recovery rate related to the nominal dose were calculated.

The HPLC system was equipped with a ProStar 230 pump, a ProStar 410 auto-sampler, a ProStar 325 UV-Vis detector (Varian Inc., Les Ulis, France). The separation was performed on a Synergi Hydro-RP column (4 μm, 250 × 4.6 mm i.d.) (Phenomenex Inc., Le Pecq, France). The column temperature was maintained at 30 °C. The mobile phase was a mixture (16:84, v/v) of acetonitrile and an aqueous phosphate buffer containing monobasic potassium phosphate (20 mM), triethylamine (0.2 mL/L) and adjusted to pH 3.3 with phosphoric acid solution (3 N). The flow rate was 1.0 mL/min and the injection volume was 15 μL. The effluent peak was monitored at 243 nm. Chromatographic data were acquired by Galaxie Software.

2.2.3. Particle size distribution by laser diffraction

The particle size distribution of spray-dried powder was measured by a Mastersizer S (Malvern Instruments, Orsay, France) using a 300 mm lens. The sample was dispersed in the dry state with compressed air at 4 bar by a powder feeder.

2.2.4. Scanning electronic microscopy (SEM)

The morphology of spray-dried particle was visualized by a Hitachi S4700 apparatus (Tokyo, Japan) operated at an accelerating voltage of 3 kV. The micrographs were taken from the powder surface previously coated with carbon.

2.2.5. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD)

The experiment was performed on a DSC 1 (Mettler Toledo, Greifensee, Switzerland). Samples were placed into non-hermetic aluminium pans and heated from 25 to 250 °C at 10 °C/min under a nitrogen purge. The reference was an empty aluminium pan. Temperature and enthalpy readings were calibrated using pure indium and zinc.

The crystallinity of the powders was assessed by X-ray diffraction (XRD) with a PANalytical X'Pert Pro MPD diffractometer, equipped with a Cu X-ray tube (λCuKα: 1540 Å). Samples were placed into Lindemann glass capillaries (diameter 0.7 mm). The measurements were performed in transmission mode with incident beam parabolic mirror and X'celerator detector.

2.2.6. X-ray photoelectron spectroscopy (XPS)

The XPS measurements were carried out by an AxisUltra DLD spectrometer (Kratos Analytical, Manchester, UK) using a monochromatized aluminium source (Al Kα = 1486.6 eV). The spectrometer binding energy scale was initially calibrated against the Ag 3d5/2 (368.2 eV) level. The powder sample was attached on the sample holder using a double side conductive tape. The experiment was conducted under vacuum of less than 10^{-10} Torr. The photoelectron take-off angle was perpendicular to the sample. Survey scan was acquired with 160 eV analyzer pass energy at 1.0 eV step for 100 ms dwell time and the high-resolution spectra with 20 eV pass energy at 0.05 eV step for 300 ms dwell time. The analysed area of the powder was approximately 700 × 400 μm. The C 1s hydrocarbon (285.0 eV) binding energy was used as internal reference. Charge compensation was applied to compensate for the charging

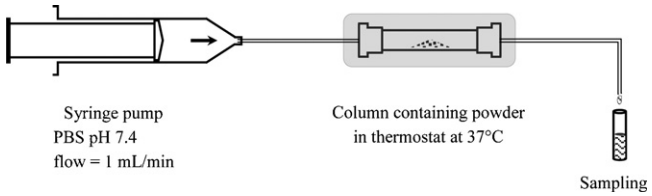

Fig. 1. Schematic illustration of continuous flow system for in vitro drug release study.

effects that occurred during the analysis. Spectra were analysed using CasaXPS software.

2.2.7. In vitro drug release study

The experiment was performed on a continuous flow system (Fig. 1). A quantity of powder equivalent to 10 mg of drug were placed in an unpacked Omega column tube (4.6 mm × 5 cm) fitted with 0.5 μm frits and connected with 1.6 mm o.d. tubing at each end. The column assembly, frits and tubing consisted of PEEK polymer were purchased from Upchurch Scientific (Washington, USA). The phosphate buffer saline pH 7.4 (European Pharmacopeia 7.5) was supplied to the column inlet at 1 mL/min by a PhD 2000 syringe pump (Havard Apparatus, Massachusetts, USA) that simulates the stimulation rate of saliva in human (Preetha and Banerjee, 2005). Heating (37 °C) of the column was achieved using a column heater. Sampling was carried out by collecting the solution at the outlet of tubing at different time points: 2, 4, 6, 8, 10, 15, 20, 25 and 30 min. The released quantity of drug was then determined by HPLC. The release study was also performed with the pure drug for comparison.

2.2.8. Electronic tongue (e-tongue) analysis

The Astree electronic tongue (Alpha MOS, Toulouse, France) was equipped with an Alpha MOS sensor set # 2, a 48-position auto-sampler and a stirrer. The sensor set consisted of seven cross-selective liquid sensors (ZZ, AB, BA, CA, DA and JE) for pharmaceutical applications, based on chemically modified field effect transistors (ChemFET), i.e. each sensor was enabled to react to several different chemical substances with different sensitivity. The potentiometry was performed using an Ag/AgCl reference electrode. Data were acquired and analysed by AlphaSoft software. The active samples containing 0.4% of drug (w/v) were prepared by adding the powder of pure drug (reference), the 1:0.5 and 5:1.5 taste-masked formulations in deionized water. The corresponding placebo therefore contains water (versus the active sample of pure drug) or aqueous solution of sodium caseinate and lecithin (versus the active samples of taste-masked formulations) at the same excipient content, which manifest no unpleasant taste at the used ratio. For measurement, the electric potential was recorded for 2 min but only the signals of the last 20 s were taken into account. Samples were replicated at least four times and only the last three replicates were considered in data analysis. The sensors were rinsed with deionized water following each analysis.

3. Results and discussion

3.1. Characteristics of taste-masked drug particles

The drug content of spray-dried powders is determined in the range of 39% and 13.4%, which corresponds to a recovery rate of about 97% and 100% for the 1:0.5 and 5:1.5 formulations, respectively.

The Fig. 2 represents the particle size distribution of spray-dried powders. Given that the 1:0.5 formulation has a lower solid content in the initial feed dispersion (2.5%, w/w against 7.5%, w/w

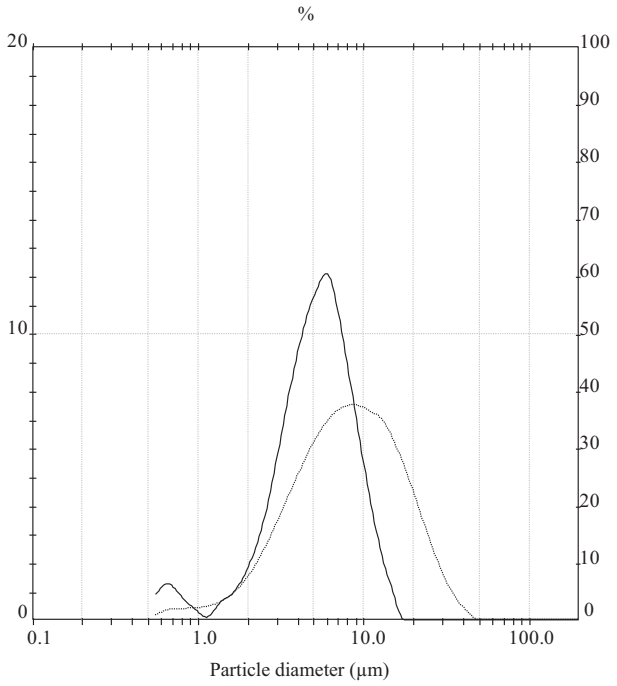

Fig. 2. Particle size distribution of spray-dried powders obtained from 1:0.5 taste-masked formulation (full line) and 5:1.5 taste-masked formulation (dashed line).

for 1:0.5 and 5:1.5 formulations, respectively), this one results in smaller particles with a mean diameter of 5.6 μm and span of 1.4 in comparison to 10.1 μm and span of 2.2 for the 5:1.5 formulation.

The scanning electron micrographs shown in Fig. 3 demonstrate a great difference in the spray-dried particle morphology according to the different ratio of sodium caseinate to lecithin. In the case of the 1:0.5 formulation, the particle is shown to be spherical and to have some attached crystals which are probably due to the crystallisation of drug onto the surface. In contrast, the 5:1.5 formulation gives a "smooth" surface without appearance of crystalline form and the particle exhibits an irregular form. Such morphology has been typically reported for spray-dried proteins in the literature (Maa et al., 1997, 1998; Chew and Chan, 2001; Elversson and Millqvist-Fureby, 2006; Vehring, 2008). It has pointed out that surface-active molecules such as protein absorb preferentially at the air–liquid interface of multi-component droplets and are thus detected with an increased concentration at the surface of the dried particle. In addition, the enrichment of protein on the surface up to a certain extent can modify the particle morphology, which might be the case of 5:1.5 formulation (Hogan et al., 2001; Vehring, 2008; Fäldt and Bergenståhl, 1994, 1996).

As shown in Fig. 4, the DSC curve of pure drug shows a melting point onset at 169.2 °C and a fusion enthalpy of 27.1 kJ/mol (expressed as absolute value). This confirms that the initial acetaminophen used in this study is of monoclinic polymorph (form I). The DSC patterns of corresponding physical mixtures of the 1:0.5 and 5:1.5 formulations reveal also a large endothermic peak of fusion onset at 169.2 °C and 169.8 °C with a lower fusion enthalpy in the range of 18.1 kJ/mol and 16.1 kJ/mol, respectively. This phenomenon might be explained by the fact that the increasing isolation of the crystalline component prevents an effective heat transmission within the mass of the physical mixture (Giordano et al., 2002). In particular, this effect is more pronounced in the case of the 5:1.5 mixture with higher content of excipients. Observed derivation of the fusion peak characterizes thus a pre-fusion followed by the fusion of acetaminophen form I. The DSC pattern displays also an only endotherm event at the onset temperature

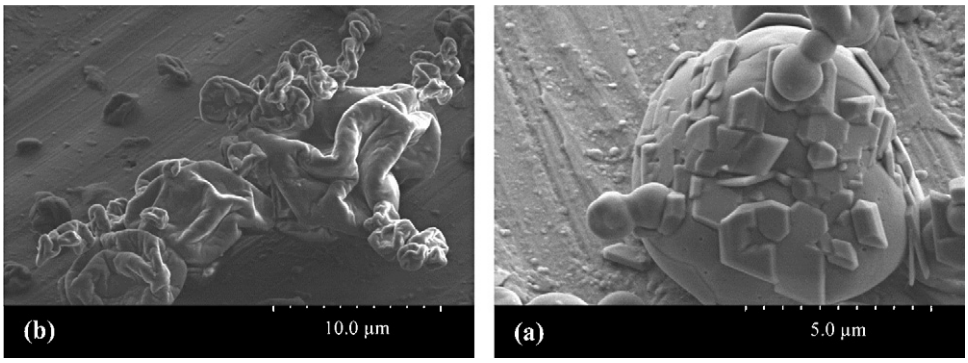

Fig. 3. SEM micrographs of spray-dried particles obtained from (a) 1:0.5 taste-masked formulation and (b) 5:1.5 taste-masked formulation.

of 158.5 °C and an enthalpy of 16.1 kJ/mol for the 1:0.5 spray-dried powder. This implies that, in the case of the 1:0.5 formulation, the crystalline drug present at the surface (as observed on SEM micrographs) and/or drug substance constituted in the core might exist in orthorhombic polymorph of acetaminophen (form II) and melt at a lower temperature with a relatively lower fusion enthalpy (Di Martino et al., 1997; Nichols and Frampton, 1998; Sacchetti, 2000; Espeau et al., 2005). It is likely that the crystallisation of form II occurs at the air–liquid boundary of the droplet, where drug substance becomes concentrated so far as the droplet is dried. The form II has remained stable for several months under controlled storage conditions (20 °C and 12%RH) since the moisture was effectively removed through spray-drying. In contrast, no particular peak is recorded for the 5:1.5 spray-dried powder, which indicates that drug might exist under molecular state. It can be explained by the fact that drug molecules in the solution of droplet remain dispersed in the dried particle by the higher amount of available excipients, i.e. sodium caseinate and lecithin.

The X-ray diffraction (Fig. 5) confirms the DSC results. In a preliminary study, X-ray diffraction was carried out for spray-dried powders containing the same ratio of drug to sodium caseinate as the two investigated formulations in this paper, except that no lecithin was incorporated. As it can be seen on Fig. 5, only the 1:1 mixture (equivalent to the 1:0.5 formulation) presents some peaks that match with the pure drug and that are not present in the 1:5 mixture (equivalent to the 5:1.5 formulation). The XRD confirms the crystalline form of drug in the 1:0.5 formulation, but it is not the case for the 5:1.5 formulation.

The XPS is a well-established technique that allows getting greater insight about the 10 nm-outermost layer composition of particles which may determine the product properties such as flowability, stability, wettability and even solubility. As shown in Fig. 6, the deconvoluted C 1s spectra of acetaminophen, 1:0.5 and 5:1.5 formulations reveal multiple chemical environments. Only acetaminophen exhibits peaks at 291 and 292.5 eV assigned to the π electrons and π–π transitions within the phenyl ring, respectively. So, it seems that there is no drug molecule absorbed on the surface of spray-dried particles. This trend seems to be contradictory to the results of SEM and DSC for the 1:0.5 formulation. It suggests that, according to the crystallisation conditions, the growth habit results in different manner of molecular stacking for each facet of crystal (Espeau et al., 2005; Beyer et al., 2001). As described by (Heng and Williams, 2006; Heng et al., 2006), there are strong variations in the surface chemistry of each facet. Also, the noted contributions of acetaminophen might be induced in the arrangement of crystal lattice and is therefore not detectable. In the other hand, the depletion of acetaminophen observed for the 5:1.5 formulation is in agreement with SEM study and will be further discussed. The composition of sodium caseinate involves a small atomic concentration of Na 1s and S 1s attributed to the alkali trace due to the manufacture and the cysteine of polypeptide chains, respectively. These elements imply the presence of sodium caseinate at the surface of both spray-dried powders (Table 2). In particular, more intense intensity around 531 eV assigned to C=O function corresponding to the peptide bonding of casein (Fig. 7) is observed for 5:1.5 formulation in the O 1s spectra. Moreover, the deconvoluted spectrum of the latter is very similar to sodium caseinate in the relative ratio of C=O/C–O (Table 3). It indicates an over-representation of sodium caseinate on the surface of the 5:1.5 spray-dried powder. The elemental composition determined by XPS shows the most abundance of P 1s for lecithin such that the

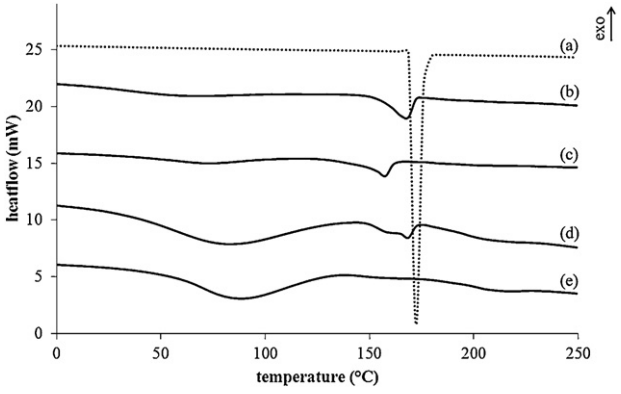

Fig. 4. DSC thermographs of (a) pure drug, (b) 1:0.5 physical mixture, (c) spray-dried sample, (d) 5:1.5 physical mixture and (e) spray-dried sample.

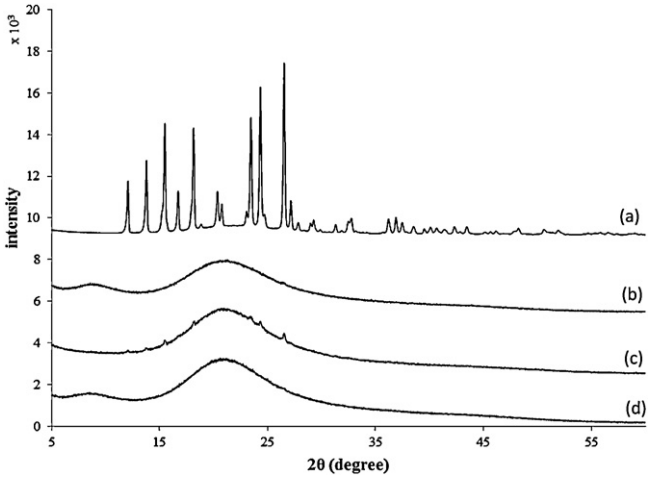

Fig. 5. XRD patterns of (a) pure drug, (b) sodium caseinate, (c) 1:1 mixture and (d) 1:5 mixture.

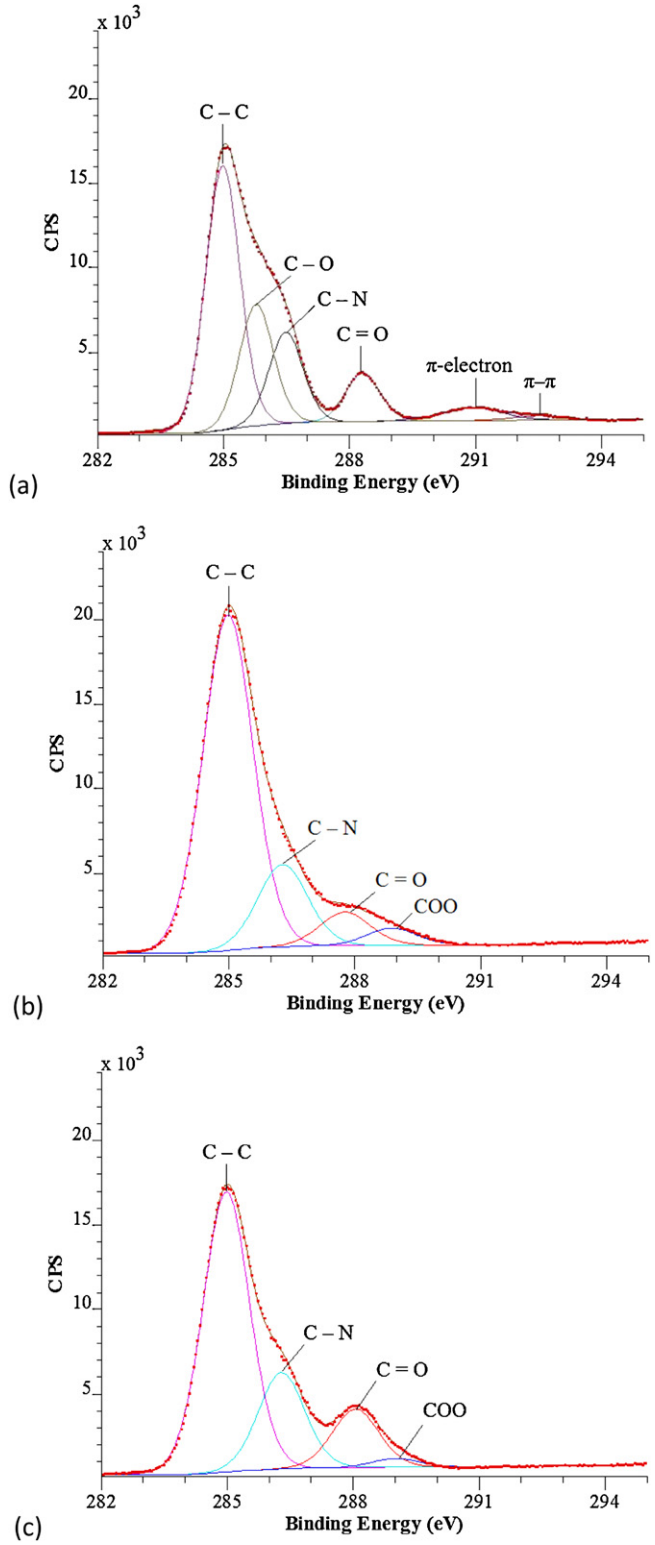

Fig. 6. Deconvoluted C 1s XPS spectra for (a) acetaminophen, (b) 1:0.5 taste-masked formulation and (c) 5:1.5 taste-masked formulation.

presence of lecithin contributes to a higher atomic concentration of the 1:0.5 formulation in comparison to the 5:1.5 formulation (Table 2). Briefly, the 1:0.5 formulation generates particles with all components in the bulk composition found on the surface, whereas the 5:1.5 particle surface is mostly covered by sodium caseinate.

Table 2
Elemental composition for acetaminophen, sodium caseinate, lecithin, the 1:0.5 and 5:1.5 formulations.

	% in atomic concentration					
	C 1s	O 1s	N 1s	P 1s	Na 1s	S 1s
Acetaminophen	76.0	15.9	8.1	–	–	–
Sodium caseinate	70.7	15.2	13.3	0.2	0.3	0.2
Lecithin	81.1	16.2	1.0	1.3	–	–
1:0.5 formulation	79.2	14.3	5.5	0.8	0.1	0.1
5:1.5 formulation	75.1	14.5	9.7	0.4	0.2	0.2

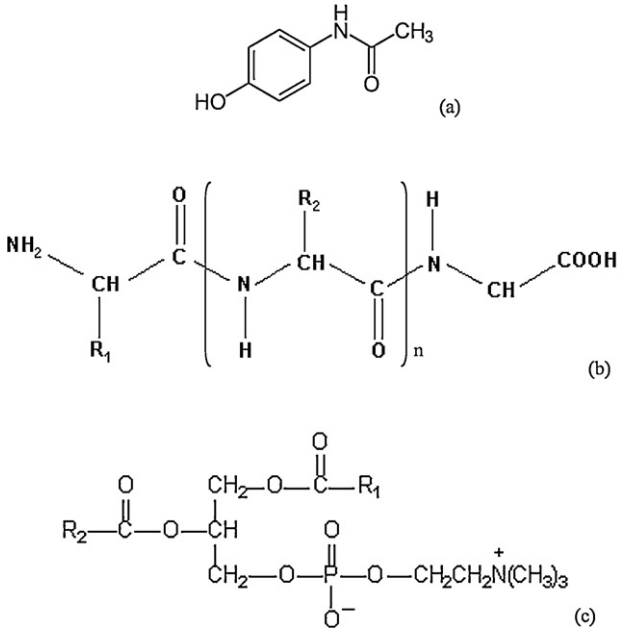

Fig. 7. Chemical structure of (a) acetaminophen, (b) sodium caseinate, and (c) lecithin.

3.2. Taste-masking evaluation by drug release study and e-tongue analysis

Although the human taste panel is a preferential method for taste assessment, this is challenging for paediatric population as the taste panel established in children is quite difficult to perform because of safety, children's cognitive ability, sociocultural difference, cost and ethical issues, etc. In addition, if adults are implied as assessor, it is not consistent to extrapolate the result onto the paediatric population (Anand et al., 2007; Davies and Tuleu, 2008). In this study, two in vitro methods are utilized for taste-masking evaluation, including drug release study and Astree e-tongue analysis. A good agreement between these two methods is established

Table 3
Deconvolution of O 1s spectra for acetaminophen, sodium caseinate, lecithin, 1:0.5 and 5:1.5 formulations.

	Function	Binding energy (eV)	% in atomic concentration
Acetaminophen	C=O	531.9	35.6
	C—O	533.3	63.0
Sodium caseinate	C=O	531.6	72.0
	C—O	533.1	24.6
Lecithin	C=O	531.4	25.0
	C—O	533.6	25.0
1:0.5 formulation	C=O	531.4	35.1
	C—O	533.6	14.1
5:1.5 formulation	C=O	531.6	72.1
	C—O	533.1	27.9

and thus may offer alternative solutions for taste assessment in the early stage of drug development.

Taste-masking is achieved if, within the frame of 1–2 min, drug substance is either not released or the released amount is below the human threshold for identifying its bad taste. In this study, the release of drug is monitored using a novel continuous flow system that allows not only mimicking the realistic conditions in the mouth, but also effectively predicting the taste-masking effect. The Fig. 8 shows the release profiles as a function of time for unmasked acetaminophen (pure drug), the 1:0.5 and 5:1.5 formulations. Considering the concentration of released drug within the first 2 min, we obtained 0.91 mg/mL and 0.76 mg/mL for the 1:0.5 and 5:1.5 formulations respectively. The bitterness threshold reported in the literature is highly varying. For example, Albertini et al. (2004) found a value of 1.08 mg/mL whereas Shiino et al. (2010) found 35 μg/mL. We are under the value found by Albertini et al. but not under the one of Shiino et al. So, further works are carried out in order to decrease the release within the first 2 min.

It is clear that the "coating" consisted of sodium caseinate and lecithin has a significant role in decreasing the release of drug. Indeed, during first 2 min, the 1:0.5 and 5:1.5 formulations demonstrate lower released amounts at 1.7 and 2.5 folds less than the unmasked drug, respectively. As discussed above, in the case of the 1:0.5 formulation, a partial drug content present on the surface enables a relatively higher release compared to the 5:1.5 formulation (18% against 12%, respectively) in the early minutes. Once the

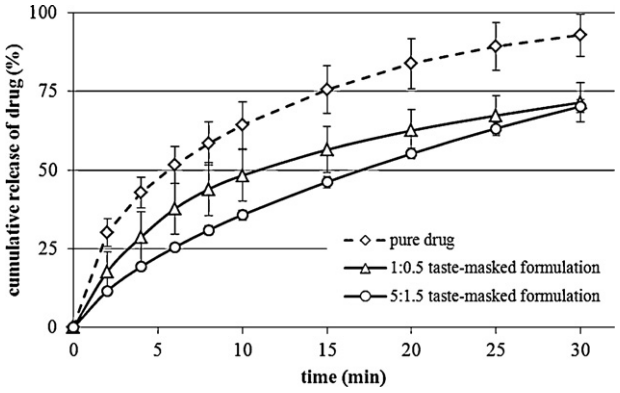

Fig. 8. Drug release profiles as a function of time of the 1:0.5 and 5:1.5 taste-masked formulations in comparison to the pure drug studied by the continuous flow system.

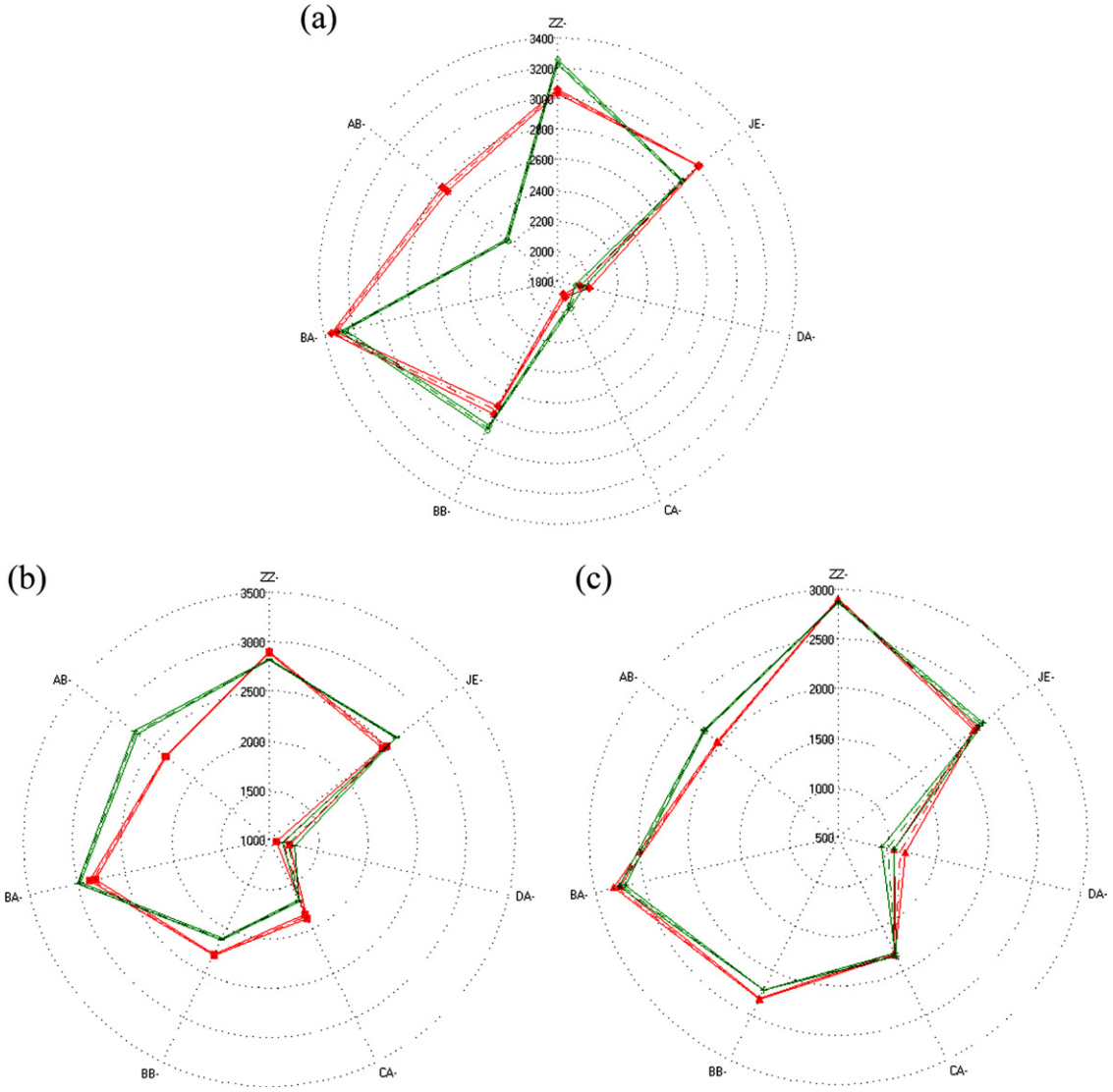

Fig. 9. Radar plots of all sensor responses to active samples (in red) and corresponding placebo (in green) through the last three replicates obtained from (a) pure drug, (b) 1:0.5 taste-masked formulation and (c) 5:1.5 taste-masked formulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

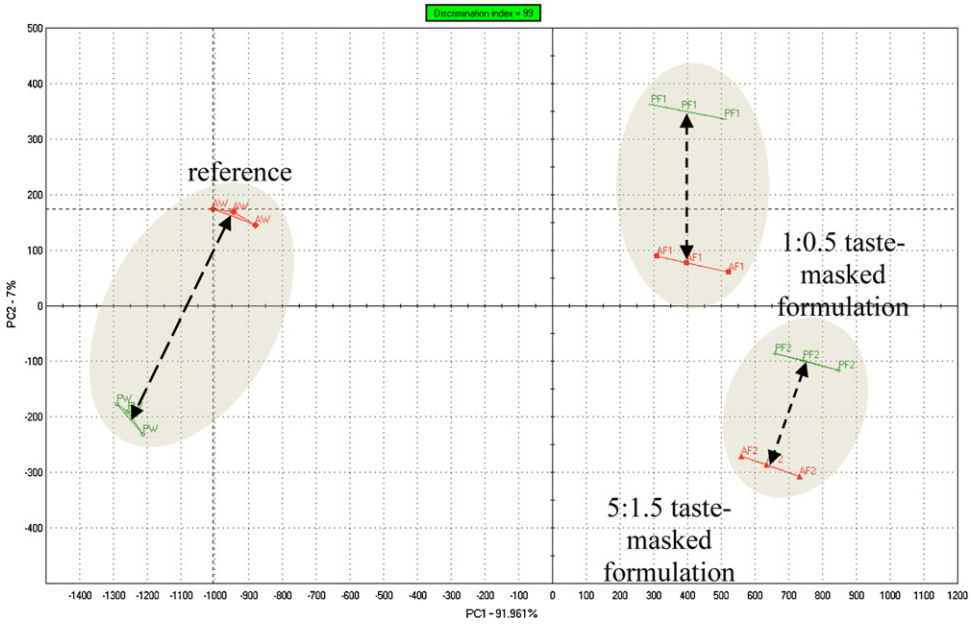

Fig. 10. Electronic tongue "taste map": global signal comparison (PCA analysis of the electrode responses) between pure drug (reference) and taste-masked formulations.

outer layer is washed out, drug released amounts attain the same extent of about 71% after 30 min for both taste-masked formulations.

More insight about the general taste of taste-masked formulations is also evaluated by means of Astree e-tongue. Fig. 9 plots the responses of seven sensors to sample through the last three replicates. All sensors show stable signals with satisfactory repeatability (RSD < 5%). The responses from all seven sensors are thus taken into account for data analysis. Based on the 7-dimensional data set obtained from these sensors, a principal component analysis (PCA) is applied in order to reduce the dimensional space without losing information. The variance of original data can be almost conveyed within two new axes, i.e. PC1 and PC2. The methodology of the Astree e-tongue in taste assessment bases on the comparison of distances "active versus placebo" calculated from the PCA map between formulations. A shorter distance reveals higher similarity of the active sample to the corresponding placebo in term of taste, i.e. neutral or close to neutral taste of placebo. As shown in the Fig. 10, the PC1 and PC2 explain 91.96% and 7% of data variance, respectively. It appears that both 1:0.5 and 5:1.5 formulations are closer to the corresponding placebo, in comparison to the reference of pure drug, therefore reflect a better taste improvement for taste-masked formulations. The masking efficiency is particularly remarkable for the 5:1.5 formulation which represents the lowest distance. Interestingly, this is in good accordance with results obtained from the drug release study.

4. Conclusion

The association of sodium caseinate and lecithin seems to be promising to mask the bitterness of acetaminophen. Through spray-drying process, acetaminophen seems to be well encapsulated within the skin former composed of sodium caseinate and lecithin. The spray-dried particle morphology differed according to the ratio of sodium caseinate to lecithin. The SEM, DSC and XPS analysis made it possible to observe differences in the surface composition of spray-dried particles and to relate it with taste-masking. With a ratio caseinate:lecithin of 1:0.5, crystals of drug were observed at the surface whereas with the 5:1.5 ratio, particle surface was mostly covered by caseinate. The "coating" consisting of sodium caseinate and lecithin had a significant role in decreasing the release of drug during the first 2 min and therefore is able to mask the drug bitterness upon administration into the mouth. Higher content in lecithin seems to result in higher taste-masking efficiency. A good agreement between the in vitro release study developed and the electronic tongue analysis was established and thus may offer alternative solutions for taste assessment in the early stage of drug development.

Acknowledgments

The authors would like to thank Dr. Anne-Sophie Mamede and Dr. Arnaud Beaurain (Unité de Catalyse et de Chimie du Solide, UMR CNRS 8181, Ecole Nationale Supérieure de Chimie de Lille) for XPS measurements and for interpreting the XPS results.

The authors also thank Pr. Marc Descamps and Dr. Florence Danède (Laboratoire de dynamique et structure des matériaux moléculaires, UMR CNRS 8024, Université de Lille 1) for the XRD measurements.

References

Abayomi, J., 2005. Infant formula – evaluating the safety of new ingredients. J. Hum. Nutr. Diet. 18, 226.

Albertini, B., Cavallari, C., Passerini, N., Voinovich, D., González-Rodrıĭguez, M., Magarotto, L., Rodriguez, L., 2004. Characterization and taste-masking evaluation of acetaminophen granules: comparison between different preparation methods in a high-shear mixer. Eur. J. Pharm. Sci. 21, 295–303.

Anand, V., Kataria, M., Kukkar, V., Saharan, V., Choudhury, P.K., 2007. The latest trends in the taste assessment of pharmaceuticals. Drug Discov. Today 12, 257–265.

Ayenew, Z., Puri, V., Kumar, L., Bansal, A.K., 2009. Trends in pharamaceutical taste masking technologies: a patent review. Recent Pat. Drug Deliv. Formul. 3, 26–39.

Bao, S.S., Hu, X.C., Zhang, K., Xu, X.K., Zhang, H.M., Huang, H., 2011. Characterization of spray-dried microalgal oil encapsulated in cross-linked sodium caseinate matrix induced by microbial transglutaminase. J. Food Sci. 76, E112–E118.

Beyer, T., Day, G.M., Price, S.L., 2001. The prediction, morphology, and mechanical properties of the polymorphs of paracetamol. J. Am. Chem. Soc. 123, 5086–5094.

Chew, N.Y.K., Chan, H.K., 2001. Use of solid corrugated particles to enhance powder aerosol performance. Pharm. Res. 18, 1570–1577.

Cram, A., Breitkreutz, J., Desset-Brèthes, S., Nunn, T., Tuleu, C., 2009. Challenges of developing palatable oral paediatric formulations. Int. J. Pharm. 365, 1–3.

Davies, E.H., Tuleu, C., 2008. Medicines for children: a matter of taste. J. Pediatr. 153, 599–604.

Di Martino, P., Conflant, P., Drache, M., Huvenne, J.P., Guyot-Hermann, A.M., 1997. Preparation and physical characterization of forms II and III of paracetamol. J. Therm. Anal. Calorim. 48, 447–458.

Douroumis, D., 2007. Practical approaches of taste masking technologies in oral solid forms. Expert Opin. Drug Deliv. 4, 417–426.
Elversson, J., Millqvist-Fureby, A., 2006. In situ coating – an approach for particle modification and encapsulation of proteins during spray-drying. Int. J. Pharm. 323, 52–63.
Ernest, T.B., Elder, D.P., Martini, L.G., Roberts, M., Ford, J.L., 2007. Developing paediatric medicines: identifying the needs and recognizing the challenges. J. Pharm. Pharmacol. 59, 1043–1055.
Espeau, P., Céolin, R., Tamarit, J.L., Perrin, M.A., Gauchi, J.P., Leveiller, F., 2005. Polymorphism of paracetamol: relative stabilities of the monoclinic and orthorhombic phases inferred from topological pressure–temperature and temperature–volume phase diagrams. J. Pharm. Sci. 94, 524–539.
Fabiano, V., Mameli, C., Zuccotti, G.V., 2011. Paediatric pharmacology: remember the excipients. Pharmacol. Res. 63, 362–365.
Fäldt, P., Bergenståhl, B., 1994. The surface composition of spray-dried protein – lactose powders. Colloids Surf. A: Physicochem. Eng. Asp. 90, 183–190.
Fäldt, P., Bergenståhl, B., 1996. Changes in surface composition of spray-dried food powders due to lactose crystallization. Lebensm. Wiss. Technol. 29, 438–446.
Gharsallaoui, A., Roudaut, G., Chambin, O., Voilley, A., Saurel, R., 2007. Applications of spray-drying in microencapsulation of food ingredients: an overview. Food Res. Int. 40, 1107–1121.
Giordano, F., Rossi, A., Bettini, R., Savioli, A., Gazzaniga, A., Novák, C., 2002. Thermal behavior of paracetamol–polymeric excipients mixtures. J. Therm. Anal. Calorim. 68, 575–590.
Gouin, S., 2004. Microencapsulation: industrial appraisal of existing technologies and trends. Trends Food Sci. Technol. 15, 330–347.
Heng, J.Y.Y., Williams, D.R., 2006. Wettability of paracetamol polymorphic forms I and II. Langmuir 22, 6905–6909.
Heng, J.Y.Y., Bismarck, A., Lee, A.F., Wilson, K., Williams, A.R., 2006. Anisotropic surface energetics and wettability of macroscopic form I paracetamol crystals. Langmuir 22, 2760–2769.
Hogan, S.A., McNamee, B.F., O'Riordan, E.D., O'Sullivan, M., 2001. Microencapsulating properties of sodium caseinate. J. Agric. Food Chem. 49, 1934–1938.
Imagi, J., Yamanouchi, T., Okada, K., Tanimoto, M., Matsuno, R., 1992. Properties of agents that effectively entrap liquid lipids. Biosci. Biotechnol. Biochem. 56, 477–480.
Keenan, T.W., Patton, S., 1995. The structure of milk: implications for sampling and storage. In: Handbook of Milk Composition. Academic Press, pp. 5–85.
Lindemann, B., 2001. Receptors and transduction in taste. Nature 413, 219–225.
Maa, Y.F., Costantino, H.R., Nguyen, P.A., Hsu, C.C., 1997. The effect of operating and formulation variables on the morphology of spray-dried protein particles. Pharm. Dev. Technol. 2, 213–223.
Maa, Y.F., Nguyen, P.A., Hsu, S.W., 1998. Spray-drying of air–liquid interface sensitive recombinant human growth hormone. J. Pharm. Sci. 87, 152–159.
Matsui, D., 2007. Current issues in pediatric medication adherence. Paediatr. Drugs 9, 283–288.
Nichols, G., Frampton, C.S., 1998. Physicochemical characterization of the orthorhombic polymorph of paracetamol crystallized from solution. J. Pharm. Sci. 87, 684–693.
Preetha, A., Banerjee, R., 2005. Comparison of artificial saliva substitutes. Trends Biomater. Artif. Organs 18, 178–186.
Raiten, D.J., Talbot, J.M., Waters, J.H., 1998. Assessment of nutrient requirements for infant formulas. J. Nutr. 128, 2059S–2293S.
Sacchetti, M., 2000. Thermodynamic analysis of DSC data for acetaminophen polymorphs. J. Therm. Anal. Calorim. 63, 345–350.
Database of Select Committee on GRAS Substances (SCOGS) Reviews [WWW Document], 2012. Available from: http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=290.
Shiino, K., Iwao, Y., Miyagishima, A., Itai, S., 2010. Optimization of a novel wax matrix system using aminoalkyl methacrylate copolymer E and ethylcellulose to suppress the bitter taste of acetaminophen. Int. J. Pharm. 395, 71–77.
Vehring, R., 2008. Pharmaceutical particle engineering via spray-drying. Pharm. Res. 25, 999–1022.
WHO. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2012. WHO. URL. Available from: http://apps.who.int/ipsc/database/evaluations/chemical.aspx?chemID=3707.