Scientific paper

The Role of co-Spray-Drying Procedure in the Preformulation of Intranasal Propranolol Hydrochloride

Rita Ambrus,[1,*] Matild Gergely,[2] Alenka Zvonar,[3] Piroska Szabó-Révész[1] and Emese Sipos[2]

[1] *Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary*

[2] *University of Medicine and Pharmacy Targu-Mures, Gh. Marinescu street 38, 540139 Targu-Mures, Romania*

[3] *Faculty of Pharmacy, University of Ljubljana, 1000 Ljubljana, Askerceva 7, Slovenia*

* *Corresponding author: E-mail:* arita@pharm.u-szeged.hu
Tel: +3662545571

Received: 15-01-2014

Abstract

The use of dry powder formulations presents an alternative through which to achieve better deposition and residence time in the nasal cavity, increased stability and possible absorption enhancement. The most important factors involved in the preformulation are particle size and physical stability. Propranolol hydrochloride a model drug was subjected to spray-drying technology to form an intranasal dry powder. Particle size reduction of the drug was carried out by integration (spray-drying) methods, using different excipients. The micrometric properties were characterized by size and morphology. The structure was determined through the use of differential scanning calorimetry, X-ray powder diffraction and Fourier transform infrared spectroscopy investigations. It was concluded that the intranasal dry powder formulation of propranolol hydrochloride can be achieved with a suitable particle size without polymorph modification or chemical decomposition.

Keywords: Intranasal powder formulation; micronization; propranolol hydrochloride; spray-drying; structural analysis

1. Introduction

An important objective of original and generic drug research is to find new alternative pathways for the introduction of drugs into the human body in order to achieve a systemic effect.

Research has recently interest focused on delivery via the nasal route as this has a number of advantages, such as a rich blood supply, a large surface area for drug absorption and a comparatively good possibility of blood-brain barrier penetration.[1–3] Regulatory guidelines (the Food and Drug Administration and the European Medicines Evaluation Agency) recommend particles or droplets of around 10 μm and above, or fine particle formulations (5–10 μm), tested by laser diffraction-based particle size analysis.[4–6] Several investigations have demonstrated positive results for the nasal delivery of mucoadhesive microparticulate systems, i.e. micron-sized particles of drug and excipients or microcomposites/microspheres, in comparison with liquid formulations or the pure drug.[7–9]

Mucoadhesive polymer-based microparticles have a number of advantages: they increase the bioavailability of poorly soluble drugs, increase the stability of active substances which have low stability in an aqueous phase, and behave considered as carriers for the nasal membrane transport process.[10–13]

Various potential additives, both absorption promoters and mucoadhesive agents, have been evaluated from the aspect of overcoming the problems of nasal formulations. Sodium hyaluronate (a mucopolysaccharide consisting of repeating units of D-glucuronic acid and N-acetyl-D-glucosamine, found in the extracellular tissue matrix) has an excellent mucoadhesive capacity, and is an ideal biomaterial for pharmaceutical applications due to

its advantages as concerns biocompatibility, non-immunogenicity, biodegradability and viscoelasticity, and it may be used with polyethyleneglycol (PEG) (a solubilizer and stabilizer) in the formulation of a bioadhesive drug delivery system (as microspheres). To achieve a uniform particle size and to prevent the aggregation of reduced particles, the application of a carrier-based spray-drying technique involving the use of additives may be necessary. Mannitol, as a hydrophilic carrier which ensures the homogeneous distribution of the drug in products and provides stabilization during the spray-drying process, is frequently used in co-spray-dried systems (as microcomposites).[14–17]

Propranolol hydrochloride (PHCl), a β-andrenergic-blocking agent, is widely used in the treatment of hypertension, angina pectoris, arrhythmias and other cardiac conditions. It is highly hydrophilic and is almost completely absorbed after oral administration. However, much of the drug is metabolized by the liver during its first passage through the portal circulation; on average, only about 25% reaches the systemic circulation. Its solubility is pH dependent: at pH 1.2 it is 225 mg ml^{-1} and at pH 6.8 it is 130 mg ml^{-1}. At present, only PHCl injection, oral solution and tablets are available as dosage forms for patients. The nasal administration of the drug in aqueous solution has been shown to result in a similar bioavailability as that following intravenous administration.[18–22] The solubility of PHCl in water is 1:30, and the pH of this solution is between 5 and 6. The ideal solution pH for application to the nasal mucosa is between 6 and 7.5 but at these higher pH levels PHCl trends to decompose.[23–25]

The objective of the present work was a preformulation study of solid nasal products containing PHCl with a suitable particle size achieved through the use of an integration method with different excipients (mucoadhesive polymers and carrier). The advantage of this procedure is the one-step process to decrease the size and reach the final solid form of the drug for nasal administration meet with the regulatory guidelines.

2. Materials and Methods

2. 1. Materials

Propranolol hydrochloride (PHCl) (Microsin, Romania), β-D-mannitol (M) (Hungaropharma, Budapest), sodium hyaluronate (Na-HA) (PannonPharma, Hungary), and PEG 6000 (PEG) (Fluka, Germany).

2. 2. Methods

Sample preparation by the integration method

Aqueous solutions of PHCl (4 m/m %) and of PHCl (4 m/m %) + M (4 m/m %) were spray-dried (denoted, as PHCl-spd and PHCl+M-spd in the text) by using a Büchi Mini Dryer B-191 (Switzerland) with a 120 °C inlet and a 70 °C outlet temperature; the aspirator capacity was 60%, the aspirator pressure was –25 mbar (i.e. lower by 25 mbar than atmospheric pressure), the feed rate was 0.065 l h^{-1} and the flow rate was 750 l h^{-1}. We have also applied the same procedure to form microcomposites (PHCl mcomp) containing PHCl (500 mg), PEG (500 mg) and M (500 mg), with Na-HA (300 mg) as carrier (Table 1).

Table 1. Composition of aqueous solution (ad 50 g) for spray-drying

Sample name	PHCl [mg]	M [mg]	Na-HA [mg]	PEG [mg]
PHCl-spd	2000	–	–	–
PHCl+M-spd	2000	2000	–	–
PHCl-mcomp	500	500	300	500

Particle size analysis

The particle size distributions of the dried samples prepared with a dry dispersion unit were estimated by laser diffraction (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd., UK). In the dry analysis method, air was used as the dispersion agent for the sample particles from the inlet to the sample cell. Approximately 2 g samples of the products were loaded into a feeding tray. The dispersion air pressure was adjusted to 2.0 bar in order to determine whether particle attrition had occurred. Between 10.0% and 13.0% obscrurtion was achieved throughout the entire measurement. At least three repeat measurements were made on each sample, and the mean value was calculated. The residual value was always <1.0%. The products analysed in the vacuum cleaner were collected for further studies once the dry analysis had been completed.

Morphology

The morphology of the particles was examined by scanning electron microscopy (SEM) (Hitachi S4700, Hitachi Scientific Ltd., Japan). A sputter coating apparatus (Bio-Rad SC 502, VG Microtech, England) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3–13.0 mPa.

Differential scanning calorimetry (DSC)

The DSC measurements were made with a Mettler Toledo DSC 821^e thermal analysis system with the $STAR^e$ thermal analysis program V9.1 (Mettler Inc., Schwerzenbach, Switzerland). Approximately 2–5 mg of product was examined in the temperature range between 25 °C and 300 °C. The heating rate was 5 °C min^{-1}. Argon was used as the carrier gas at a flow rate of 10 l h^{-1} during the DSC investigation. DSC was employed to investigate the crystallization behaviour and the melting behaviour of conventional PHCl and the products. The measured crystallinity depends on the size and the preparation procedure.

X-ray powder diffraction (XRPD)

XRPD was carried out in order to determine the crystalline form of the produced materials. Samples were measured with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). Data collection was carried out at room temperature, using monochromatic Cu K α1 radiation (α = 0.154060 nm) in the 2θ region between 3° and 50° in 0.02 steps. Data were evaluated with the Bruker program EVA.

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra were measured on an Avatar 330 FT-IR apparatus (Thermo Nicolet, USA), in the interval 400–4000 cm^{-1}, at an optical resolution of 4 cm^{-1}. Standard KBr pellets were prepared from 150 mg of KBr and 0.5 mg of the drug compressed at 10 tons.

3. Results and Discussion

3. 1. Micrometric Properties

Microparticles with different sizes and forms were made by the integration (spray-drying) method, and the particle size distributions were examined by laser diffraction and the results are shown in Table 2. The particle size analysis revealed that the size of the raw PHCl particles was around 40 μm. The particle size of PHCl+M-spd was higher than those of PHCl and PHCl spd, probably because of the recrystallization of the excipient M after the drying procedure. A relevant particle size decrease was observed in the case of PHCl-mcomp, where only 10% of the particles were larger than 10 μm, which means that this material is suitable for nasal application, because regulatory guidelines recommend fine microparticles between 5–10 μm.

The SEM pictures of the raw substances (Fig.1a) show the large, dimensional particles, with a smooth surface for the PHCl particles (A) and a rough surface for the M particles (B).

Table 2. The particle size distributions of the dried samples

Samples	D 0.1 (μm)	D 0.5 (μm)	D 0.9 (μm)
PHCl	8.5	38.4	137.9
PHCl-spd	4.1	18.9	145.4
PHCl+M-spd	10.0	67.3	275.2
PHCl-mcomp	3.1	5.7	10.0

Figure 1b reveals that the spray-drying method led to smaller particles, reflecting the results of the particle size analysis. The particles with (B) or without mannitol (A) have irregular shapes and uneven surfaces. The microcomposites (C) presented the best morphological characters: an ideal size (5–10 μm), a roundshape, and a smooth, flat surface, appropriate for nasal application. The morphology and size could be important by the application (i.e flowability) of the powder sample and by the mucoadhesion on the nasal surface. With nasal breathing, nearly all particles with a size of 10–20 μm are deposited on the nasal mucosa, those less than 2 μm pass through the nasal cavity and deposit in the lungs. If drugs are introduced as soluble particles they may readily pass into the nasal lining secretions and then be absorbed into the blood. The particles with (B) or without mannitol (A), have irregular shapes and uneven surfaces.

3. 2. Structural Analysis

PHCl exists in three different crystalline forms, denoted as forms I, II and III, with decreasing melting temperatures, respectively. The commercial product used was modification II.[26]

DSC was utilized to investigate the structure and physico-chemical characteristics of PHCl in the raw form and of the obtained microparticles. Figure 2 depicts the DSC curve of the raw PHCl, which shows one endothermic peak at 163.58 °C, corresponding to the melting point

a) b)

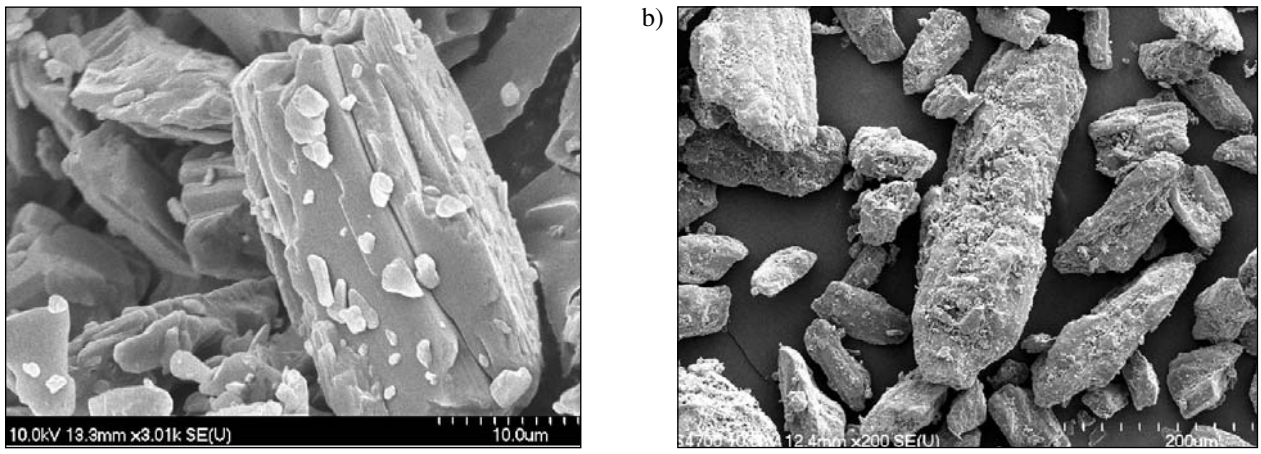

Figure 1a. SEM pictures of raw PHCl (a) and β-D-mannitol (b)

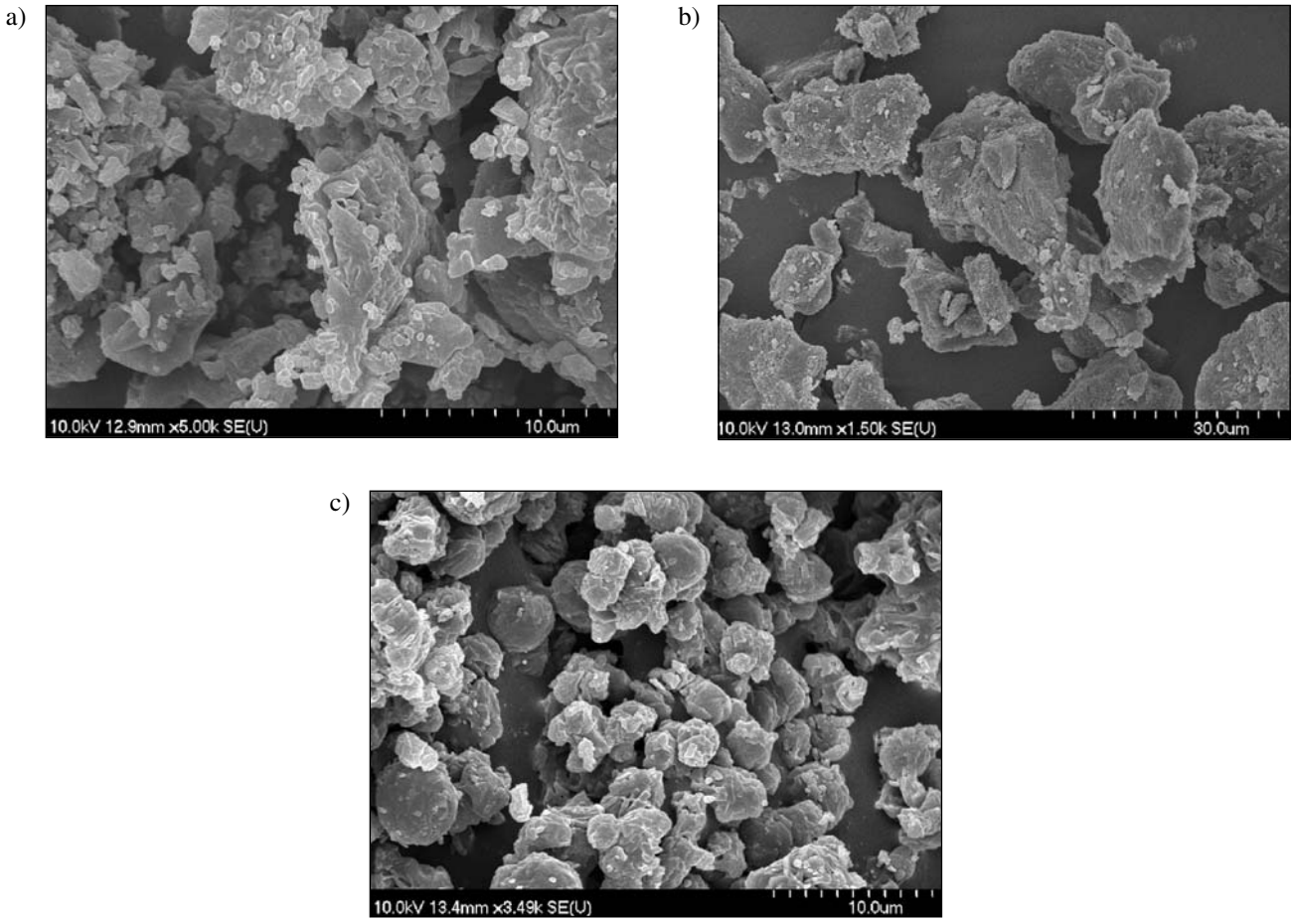

Figure 1b. Morphology by SEM of PHCl-spd (a), PHCl+M-spd (b) and PHCl-mcomp (c)

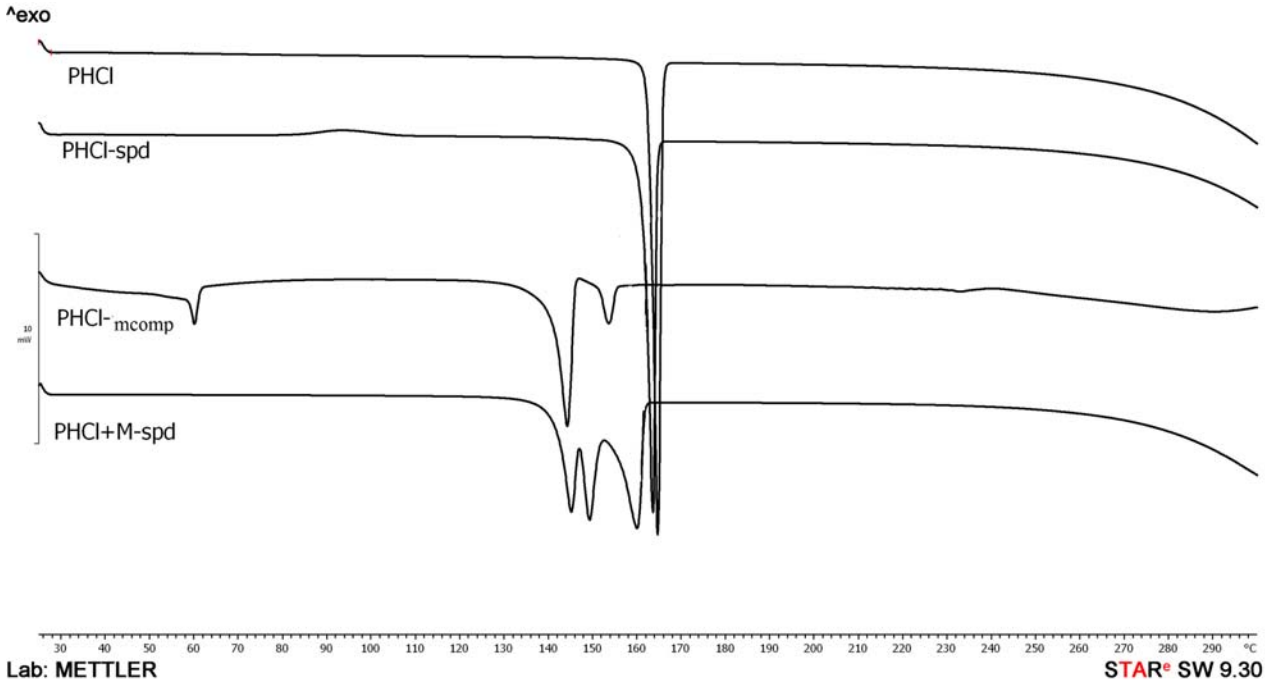

Figure 2. DSC curves of propranolol hydrochloride and the prepared samples

of polymorphic modification II (Table 3). DSC analysis of PHCl-spd yielded nearly the same curve as before, and hence the spray-drying did not affect the crystal structure of the drug. In the presence of the excipients, β-D-M was present as its α and δ modifications. In this formulation, the melting point of PHCl was lower. It is presumed that the drug dissolved in the melted excipients (Table 3.).

Table 3. Thermoanalytical data of the samples

Samples	Integral (mJ)	Normalized ($J\ g^{-1}$)	Peak (°C)
PHCl	–542.28	–123.24	163.58
PHCl-spd	–479.92	–113.72	162.72
PHCl+M-spd	–264.34	–55.77	159.77
PHCl-mcomp	–64.76	–14.76	153.47

The polymorphic forms of PHCl were readily distinguished through their IR absorption bands in the interval 3600– 650 cm^{-1}. The specific major bands of PHCl form II are the peak at 1267.1 cm^{-1} due to the aryl alkyl ether at and the peak at 771.42 cm^{-1} due to α-substitued naphthalene.[27]

The FT-IR spectrum of PHCl and the samples are shown in Figure 3. It may be seen that the maxima in the PHCl spectra do not differ significantly from the maxima for the samples studied. The FT-IR spectra of PHCl-spd and PHCl exhibit the same peaks corresponding to the major functional groups in PHCl. Thus the spray-drying procedure did not influence the structure of the drug. The spectra of PHCl-mcomp and PHCl+M-spd do differ slightly, because of the present of excipients but no major interaction was observed between the drug and M or the other substances used in the microcomposite.

X-ray powder diffraction curves are presented in Figure 4. The results obtained after processing the Powder Diffraction File (PDF) database indicated that the maxima and their intensities in the curves of the size-modified particles were not changed in comparison with the curve of the starting PHCl. The XRPD curves of the product microparticles contain characteristic peaks of raw PHCl, which display similar X-ray diffraction peaks, but at lower intensity.

The characteristic peaks of PHCl appear at diffraction angles 2θ of 12.510° and 17.195°.

To summarize the structural characterizations, the drug and the excipients were in dissolved form before the drying procedure. After the spray-drying procedure, the recrystallization of the PHCl and M was detected. The drug was present in stable crystalline form II. The M was transformed to the α and δ modifications. The three polymorphic forms of M exhibit unique peaks including; alpha (9.57° and 13.79 °), beta (10.56°, relatively intense peak at 14.71°) and delta (extremely intense peak at 9.74° then no peaks until 14.66°).[28]

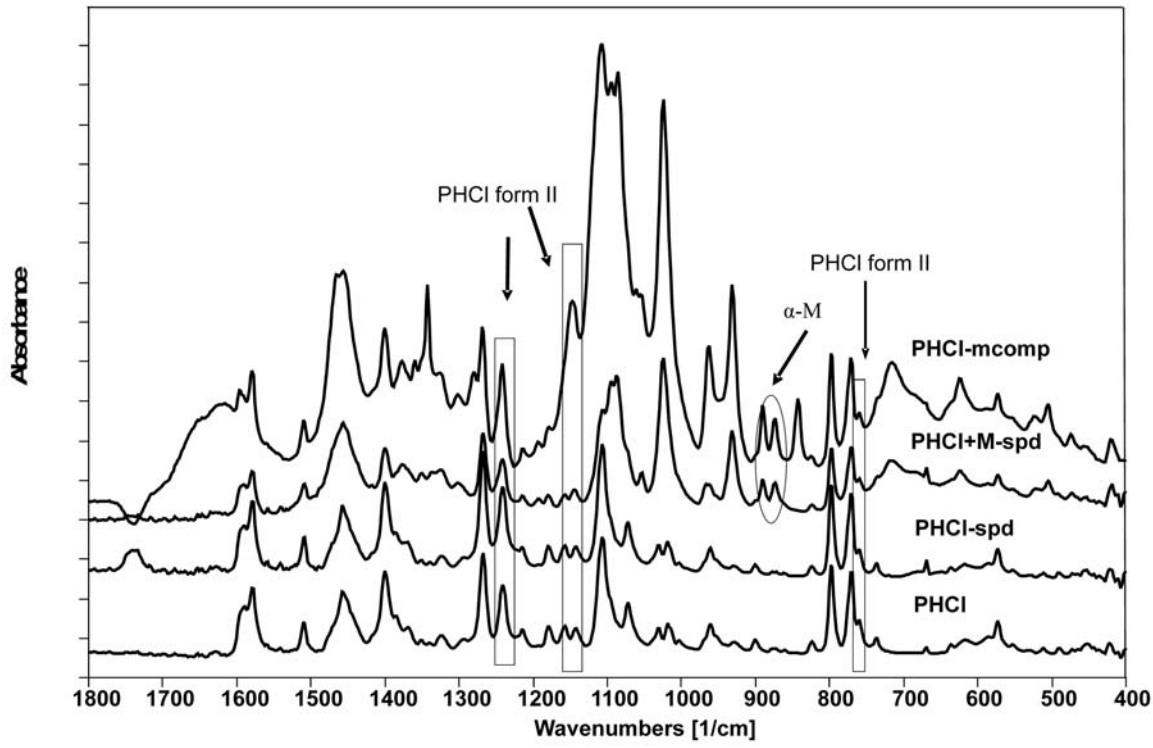

Figure 3. FT-IR spectra of PHCl and the samples

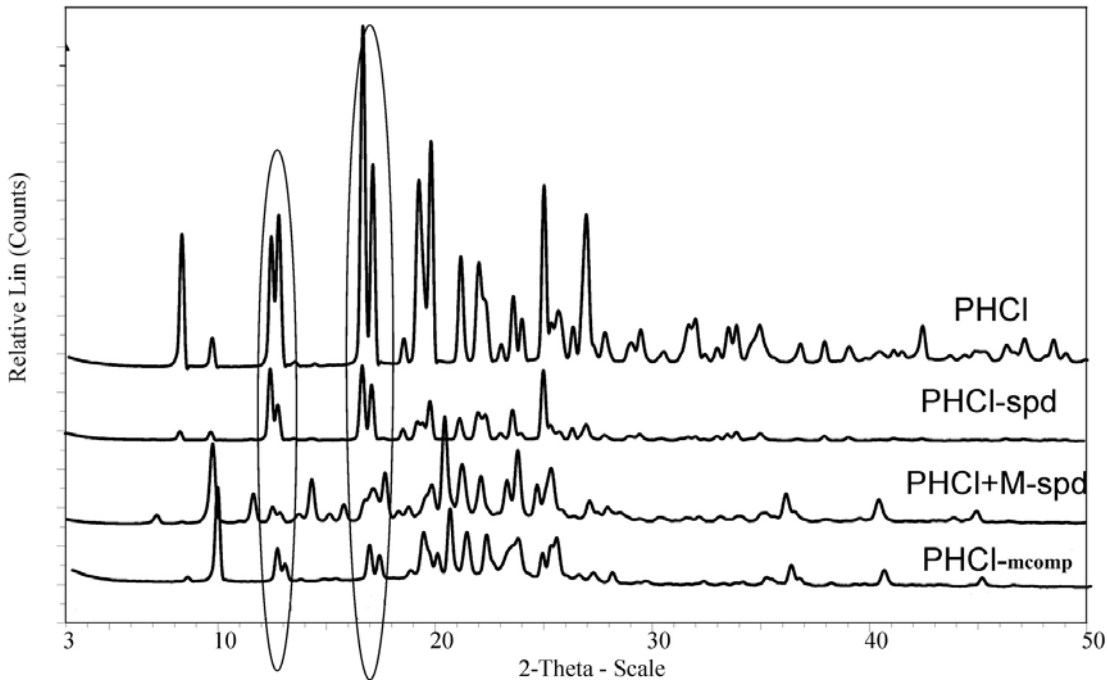

Figure 4. XRPD spectra of PHCl and the microparticles obtained

4. Conclusions

According to regulatory guidelines, the physicochemical properties of PHCl preformulated by a spray-drying procedure are suitable for dry powder nasal application where the critical parameter is the particle size (> 5 μm). This formulation of microcomposites containing mucoadhesive Na-HA (ideal biomaterial for pharmaceutical applications due to its advantages as concerns biocompatibility, biodegradability and viscoelasticity), using PEG (a solubilizer and stabilizer) and M (to achieve a uniform particle size and to prevent the aggregation) resulted in acceptable morphology for intranasal administration. The results obtained with the different analytical methods used (DSC, FT-IR and XRPD) indicated that the PHCl has a physically stable crystalline form in the samples.

5. Acknowledgement

This research was supported by the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 National Excellence Program.

6. References

1. CR. Behl, HK. Pimplaskar, AP. Sileno, J. De Meireles, VD. Romeo, *Adv. Drug Deliv. Rev*. **1998**, *29 (1)*, 89–116.
2. CR. Behl, HK. Pimplaskar, AP. Sileno, WJ. Xia, WJ. Gries, J. De Meireles, VD. Romeo, *Adv. Drug Deliv. Rev.* **1998**, *29 (1-2)*, 117–133.
3. HR. Constantino, L. Illum, G. Brandt, PH. Johnson, SC. Quay, *Int. J. Pharm*. **2007,** *337*, 1–24.
4. Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (FDA, USA, July 2002). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf
5. Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (FDA, USA, April 2003). http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3609b1l.pdf
6. Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf
7. H. Critchley, SS. Davis, NF. Farraj, L. Illum, *J Pharm. Pharmacol*. **1994**, *46*, 651–656.
8. E. Gavini, AB. Hegge, G. Rassu, V. Sanna, C. Testa, G. Pirisino, J. Karlsen, P. Giunchedi, *Int. J. Pharm.* **2006**, 307, 9–15.
9. Y. Huh, HJ. Cho, IS. Yoon, MK. Choi, JS. Kim, E. Oh, SJ. Chung, CK. Shim, DD. Kim, *Eur. J. Pharm. Sci.* **2010**, *40(1)*, 9–15.
10. LM. Benedetti, EM. Topp, VJ. Stella, *J. Control Release*. **1990**, *13*, 33–41.
11. C. Callens, JP. Remon, *J. Control Release*. **2000**, *66*, 215–220.

12. KP. Chowdary, YS. Rao, *Biol. Pharm. Bull*. **2004**, *27*, 1717–1724.
13. A. Pomázi, R. Ambrus, P. Sipos, P. Szabó-Révész, *J Pharm Biomed Anal*. **2011**, 56, 183–190.
14. YH. Liao, SA. Jones, B. Forbes, GP. Martin, MB. Brown, *Drug Deliv*. **2005**, 12, 327–342.
15. PR. Nassab, R. Rajkó, P. Szabó-Révész, *J Pharm Biomed Anal.* **2006**, 41, 1191–1197.
16. GB. Prestwich, KP. Vercruysse, *Pharm Sci Technol Today*. **1998**, *1*, 42–43.
17. V. Zabaleta, MA. Campanero, JM. Irache, *J Pharm Biomed Anal*. **2007**, *44 (5)*, 1072–1078.
18. GSMJE Duchateau, J. Zuidema, WM Albers, FWHM. Merkus, *Int. J. Pharm.* **1986**, 34, 131–136.
19. A. Hussain, T. Foster, S. Hirai, T. Kashihara, R. Batenhorst, M. Jones, *J. Pharm. Sci*. **1980,** 69, 1240–1243.
20. A. Hussain, S. Hira, R. Bawarshi, *J. Pharm. Sci*. **1980,** 69, 1411–1413.
21. AJ. Landau, RT. Eberhardt, WH. Frishman, *Am Heart J.* **1994**, *127*, 1594–1599.
22. AJ. Landau, WH. Frishman, N. Alturk, M. Adjei-Pok, M. Fornasier-Bongo, S. Furi*, Am. J. Cardiol.* **1993**, *72*, 995–998.
23. GH. Ahmed, PJ. Stewart, IG. Tucker, *Aust. J. Hosp. Pharm.* **1988**, *18 (5)*, 312–318.
24. P. Modamio, CF. Lastra, O. Montejo, EL. Marifio, *Int. J. Pharm.* **1996,** 130 (1), 137–140.
25. Pharmacopeea Romana, X. ed, Medicala, Bucuresti, **1993**.
26. M. Bartolomei, P. Bertocchi, M. Cotta Ramusino, E. Ciranni Signoretti, *Thermochimica Acta*.**1998,** *321*, 43–52.
27. M. Bartolomei, P. Bertocchi, M. Cotta Ramusino, N. Santucci, L. Valvo, *J. Pharm. Biomed . Anal.* **1999,** *21*, 299–309.
28. W. L. Hulse, R. T. Forbes, M. C. Bonner, M. Getrost, *Int. J. Pharm*. **2009**, *382, 67–72*.

Povzetek

Uporaba formulacij na osnovi suhih zmesi prahov predstavlja zanimivo alternativo tako za doseganje učinkovitejše dostave in daljšega časa zadrževanja učinkovin v nosni votlini kot tudi za izboljšanje njihove stabilnosti ter obsega absorpcije. V okviru predformulacijskih študij je potrebno posebno pozornost nameniti zlasti velikosti delcev prahov in fizikalni stabilnosti formulacije. Prašek za nos smo izdelali z metodo sušenja z razprševanjem, pri čemer smo kot modelno učinkovino uporabili propranolol hidroklorid. Ustrezno velikost delcev učinkovine smo zagotovili z izborom parametrov metode ter uporabo več pomožnih snovi. Izdelanim delcem mikrometrskih velikosti smo določili velikost in morfološke lastnosti. Njihovo strukturo smo nadalje ovrednotili z uporabo diferenčne dinamične kalorimetrije, rentgenske praškovne difrakcije in infrardeče spektroskopije s Fourierovo transformacijo. Potrdili smo, da z opisano metodo lahko pripravimo praške za nos z ustrezno velikostjo delcev, ne da bi pri tem prišlo do polimorfnih modifikacij ali kemijske razgradnje.