TASTE MASKING OF ROXITHROMYCIN BY SPRAY DRYING TECHNIQUE

KRZYSZTOF SOLLOHUB1, MARTYNA JANCZYK2, ANNA KUTYLA1, HANNA WOSICKA3, PATRYCJA CIOSEK2 and KRZYSZTOF CAL1,*

1 Department of Pharmaceutical Technology, Medical University of Gdansk, Hallera 107, 80-416 Gdańsk, Poland
2 Department of Microbioanalytics, Warsaw University of Technology, Noakowskiego 3, 00-664 Warszawa, Poland
3 Department of Pharmaceutical Technology, Poznan University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań, Poland

Abstract: The spray drying technique was used to obtain the roxithromycin containing microcapsules with high taste masking efficiency. Eudragit L30D-55 was chosen as a barrier coating. The taste was evaluated by an electronic tongue, and taste-masking effect in water lasted at least several dozen hours.

Keywords: roxithromycin, spray drying, taste masking

Oral liquid dosage forms are formulations of choice in pediatric use, in general due to disability to swallow tablets by patients up to 8–10 years old (1, 2). Most of commercial liquid preparations contain artificial sweeteners (saccharin, aspartame) and flavor mixes to cover the bitter taste of active pharmaceutical ingredient (API). Due to poor effects of this method and risk of toxic and allergic reactions, European Medicines Agency strongly suggests withdrawing of artificial flavors and sweeteners from dosage forms, especially those intended for children and recommends other ways for masking the taste in such preparations (3, 4). In theory, complete isolation of impalatable API should prevent the contact with the taste buds. Barrier coating is widely used in solid oral dosage forms (e.g., tablets), but it is rather difficult to achieve good isolation of API in oral suspensions; however, it can be performed by appropriate coating or microencapsulation of API or particles containing API, which next can be dispersed in aqueous phase.

Roxithromycin is a semi-synthetic macrolide antibiotic derivative of erythromycin A. It is not registered yet in the USA but widely used in the European Union. Roxithromycin is available only in a small number of pediatric commercial preparations – oral suspensions or tablets designed for the preparation of an oral suspension ex tempore, but they contain flavors and do not exhibit satisfactory taste masking of roxithromycin (5).

The aim of this study was to obtain microencapsulated roxithromycin with highly efficient taste-masking effect of this bitter drug. As a powerful tool for particle engineering, the spray drying technique was chosen for roxithromycin microencapsulation, and Eudragit L30D-55 (methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%) was used to form a taste-masking coat (6, 7). The taste of formulated microcapsules was evaluated by the electronic tongue (8, 9).

Electronic tongue sensor arrays are state-of-the-art tools, which can be used for instrumental taste evaluation of pharmaceuticals. Up to date the only method approved for taste estimation is human taste panel, which suffers from ethical (especially in children), safety and economical concerns. Studies of electronic tongues development and validation in pharmaceutical sciences are subject of great interest nowadays (9–12).

EXPERIMENTAL

Materials
Roxithromycin was donated by Polfa Pabianice (Pabianice, Poland), and Eudragit L30D-55 (Evonik Rohm GmbH, Darmstadt, Germany)

* Corresponding author: e-mail: kcal@wp.pl
was donated by Polconsult (Warszawa, Poland). All materials used were of European Pharmacopoeia grade.

**Preparation of microencapsulated roxithromycin**

The polymer dispersion was diluted with water using a magnetic stirrer, and then roxithromycin was dispersed in the amount of about 13% of the dispersion’s solid content. After 0.5 h of gentle stirring, dispersion was spray dried. This process was performed using laboratory spray drier Buchi B-290 (Buchi, Flawil, Switzerland) equipped with standard 0.7 mm nozzle. The pressure of compressed air was 0.7 MPa, aspiration setting was 100%, and the feed was pumped with the rate of 7.5 mL/min. The mixture was spray dried in relatively low temperature (inlet and outlet temperatures: 70 and 45°C, respectively) due to formation of deposit of the polymer on spray drier chamber and polymeric lint formation on nozzle orifice. Such conditions and composition of the formulation were chosen during preliminary studies, and were focused on the best yield after drying.

**Evaluation of microencapsulated roxithromycin**

The bulk roxithromycin and obtained roxithromycin containing microcapsules were visualized by scanning electron microscopy (SEM), using Carl Zeiss EVO 40 apparatus (Jena, Germany). Prior to being examined for taste-masking effect, the pure and the microencapsulated roxithromycin were dispersed in water to obtain commonly in vivo used concentrations. Each dispersion was prepared five times and immediately measured for 10 min in random order. The sensor array used was formed by eight types of ion-selective electrodes. The composition of the sensor array was selected based on previous experiences (9). Chemical images of investigated samples were obtained using steady-state responses of sensors – each sample was characterized by 16 variables. Data matrix was processed by Principal Component Analysis (PCA). All calculations and data analysis was performed in MatLab (The MathWorks, Inc., Natick, USA) and Origin (Microcal Software, Inc, Northampton, USA) software.

**RESULTS AND DISCUSSION**

In the studies, Eudragit L30D-50 was used due to creating continuous, thick, and stable coating, which could isolate roxithromycin from the taste buds and aqueous environment in the final drug form. The formulation subjected to spray drying was fully aqueous and binary to simplify taste-masking mechanism and to check if Eudragit L30D-55 is suitable for this purpose. Roxithromycin was not dissolved in the feed to omit changes in crystal form. The SEM micrograph of bulk roxithromycin is showed in Figure 1, and microencapsulated roxithromycin is presented in Figure 2, where the coating of roxithromycin is easily visible. The spheres in the background in Figure 2 originate from the excess of polymer.

One of the most important issues in the taste-masking coating is the choice of appropriate poly-
mer. Polymers insoluble in aqueous environment, like ethylcellulose, cannot be used for masking the taste in unmodified release drug forms, because they prolong dissolution time and the drug substance can diffuse outside the microcapsules to the aqueous phase during shelf life of e.g., suspension. Methacrylate polymer used in this study dissolves at pH > 5.5 and in the presence of alkali ions. It means

Figure 3. Taste clusters of pure and microencapsulated roxithromycin visualized on 2D (A) and 3D (B) PCA plots; ROX – pure roxithromycin, ROX-EUD – microencapsulated roxithromycin; PC1, PC2 or PC1, PC2, PC3 – the first two or three principal components, respectively.
that microcapsules suspended in pure water or in slightly acidic environment will be stable. The enteric solubility of the polymer used is particularly important for roxithromycin because this API in the enteric-coated form demonstrated better stability in vivo and better bioavailability than that in the non-modified release oral suspension (13).

Examined by the electronic tongue for the taste masking effect, microencapsulated roxithromycin forms one cluster, which is easily separable from the cluster for pure roxithromycin (Figure 3). Chemical images prepared with the use of sensor array were processed by PCA, which is a linear feature-extraction technique enabling to find new directions in the pattern space, so that they could explain the maximum amount of variance in the data set as possible. Usually the first two or three Principal Components (PC1, PC2, PC3) are sufficient to transfer the majority of the variation of the samples, and are used to visualize the similarity and differences of their chemical images on 2D/3D PCA plots. The results showed in Figure 3 prove that the electronic tongue was able to distinguish pure drug from the microencapsulated one. The taste masking effect of Eudragit L30D-55 coating was measured and observed for at least several dozen hours, but for microcapsules dispersed in phosphate buffer pH 6.8 the taste-masking effect of coating disappears between 10 and 20 min.

CONCLUSIONS

The presented results serve as the evidence for the possibility of roxithromycin microencapsulation in order to mask its bitter taste in one-stage, easily scalable up spray drying process. Due to PCA analysis of the results from the electronic tongue, it was possible to distinguish roxithromycin samples by the presence of taste masking substance criterion/standard, i.e., chemical images obtained by the measurements of pure roxithromycin and roxithromycin microencapsulated with taste-masking coating were significantly different. Further studies are required to optimize the feed and spray-drying parameters, to study the dissolution profiles and the stability of the obtained microcapsules, both in aqueous environment and/or in dry dosage forms.

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REFERENCES


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