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Natural gum-type biopolymers as potential modified nonpolar drug release systems

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ABSTRACT

In this work, the relationship between surface properties and drug release mechanism from binary composition tablets formed by quetiapine fumarate and biopolymer materials was studied. The biopolymers correspond to xanthan and tragacanth gums, which are projected as modified drug release systems. The surface studies were carried out by the sessile drop method, while the surface free energy (SFE) was determinate through Young-Dupree and OWRK semi-empirical models. On the other hand, the drug release studies were performed by *in vitro* dissolution tests, where the data were analyzed through kinetic models of zero order, first order, Higuchi, and Korsmeyer-Peppas. The results showed that depending on the type and the proportion of biopolymer, surface properties, and the drug release processes are significantly affected, wherein tragacanth gum present a usual erosion mechanism, while xanthan gum describes a swelling mechanism that controls the release of the drug.

1. Introduction

Currently there is an interest in the search for polymer materials that could be used in the pharmaceutical field as modified drug release systems and mainly in those drugs that are described by complex pharmacokinetics characteristics (DeVane & Nemeroff, 2001; Liechty, Kryscio, Slaughter, & Peppas, 2010; Peppas, 2013) such as quetiapine fumarate (Nemeroff, Kinkead, & Goldstein, 2002), which is an antipsychotic drug with some biopharmaceutical features, since (i) it presents a poor aqueous solubility and (ii) to generate its pharmacological effect, it must pass through the blood-brain barrier (DeVane & Nemeroff, 2001). Therefore, this situation entails a continuous challenge in the design and develops of better pharmaceutical dosage forms for this drug, as well as other of this type (Katzman et al., 2011). In this way, pre-formulation studies focused on providing new information about the performance of new formulation ingredients or new alternatives, correspond to an interesting strategy in design and development of this class of products (Bharate & Vishwakarma, 2013; Madan, 1985). Although, there are many reports of strategies to improve the aqueous solubility of nonpolar drugs or to facilitate passage through the biological membranes, those studies are focused on the development of modified release systems from compressed pharmaceutical dosage form for this drug using biopolymers such as xanthan (Benny, Gunasekar, & Ponnusami, 2014) and tragacanth gum (Nur, Ramchandran, & Vasiljevic, 2016). In relation to these biopolymeric gums, there are several interesting features that project them as potential excipients in this kind of formulations, such as biocompatibility, low cost as raw material, high acceptance in pharmaceutical industry, but above all, the ability to perform as modified release systems by swelling mechanisms (Benny et al., 2014). At this point, it is very interesting to notice that some polymeric materials with potential to be used as compressed matrix systems for modified drug release has remarkable surface properties, which could be known through the contact angle evaluation and the application of surface free energy studies (Yarce, Pineda, Correa, & Salamanca, 2016). For this reason, our research focused on studying the surface characteristics in solid state and *in vitro* drug release mechanisms from tablets blend-performed with quetiapine fumarate and natural gums (tragacanth and xanthan gum) and thus, to present those biopolymeric materials as likely matrix excipient for modified drug delivery systems.

2. Materials and methods

2.1. Materials

The biopolymer materials used were: xanthan gum with M_n of 2000 KDa–16,000 KDa and tragacanth gum with M_n 840 KDa (Sigma-Aldrich, St. Louis, MO, USA). The model drug was quetiapine fumarate

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with molecular formula $C_{42}H_{50}N_6O_4S_2{\cdot}C_4H_4O_4$ and molecular weight 883.11 g/mol (Ipca Laboratories Ltd, India) used as received. The reagents used for the preparation of the dissolution media were: KOH, KCl, KH_2PO_4, and K_2HPO_4 (Merck KGaA, Darmstadt, Germany). Water Type II obtained from a purification system (Millipore Elix essential, Merck KGaA, Darmstadt, Germany) was used for the preparation of the test solutions, with values of pH and conductivity of 5.5 and 1 μS/cm, respectively. For contact angle measurements, reference liquids were used: ultra-pure water type I obtained from a purification system (Arium pro Sartorius Stedim biotechnology VF, Göttingen, Germany), with a conductivity value of 0.056 μS/cm, Isopropanol (LiChrosolv, Merck KGaA, Darmstadt, Germany) and ethyleneglycol (Merck KGaA, Darmstadt, Germany). The reference extended-release system was Seroquel XR Quetiapine (AstraZeneca, Delaware, USA).

2.1.1. Preparation of buffer solutions

The buffer solutions with pH values of 1.2 and pH 7.4 and ionic strength of 0.15 M were prepared from mixtures of HCl/KCl, and KH_2PO_4/K_2HPO_4, respectively. KCl was used to adjust the ionic strength. This buffer solutions are important due to pH 1.2 is useful for simulation of *in-vivo* gastric conditions, while pH 7.4 is uses for enteric conditions simulation.

2.2. Methods

2.2.1. Granulometric characterization of powder raw materials

The mean granular diameter of the biopolymeric gums was obtained using a sieving system by tapping Ro-Tap RX-29 (wsTyler, Mentor, OH USA). On the other hand, the percentage of compressibility was determined from the Carr index using a density meter (Logan Tap −2S), while the flowability degree was determined from the angle of repose using a fixed funnel method.

2.2.2. Thermal characterization of polymer-drug blends

The model drug, the polymeric materials and their respective blends in 1:1 mass proportions were analyzed in a Q2000 differential scanning calorimeter (DSC; TA Instruments, New Castle, DE, USA) calibrated with indium T_f = 155.78 °C ΔH_f = 28.71 J/g. DSC analysis was carried out using three heating-cooling cycles from 10 °C (283.15 K) to 200 °C (523.15 K) with a heating rate of 10 °C/min.

2.2.3. Preparation of the binary composition tablets

The tablets were made using a homemade tableting machine with ¼ in. stainless steel flat punches. For each tablet, 345 mg of quetiapine fumarate were mixed with different proportions of the gums, corresponding to 0, 25 and 40% w/w. A compression force of 400 psi applied for 10 s was used to evaluate different properties as follows. The hardness of each tablet was then determined in triplicate using a durometer (Logan HDT-400), while the disintegration time was measured by an automated disintegrator (Logan USP DST-3) in water type II at 37 °C. Additionally, the friability for each compressed system was measured using a friability tester (Logan FAB-2S).

2.2.4. Surface characterization of binary composition tablets

2.2.4.1. Analysis of surface roughness of the tablets. Determining the roughness degree for each tablet was carried out by the micro-display high magnification technique, using a micro-stereoscope (Nikon SMZ1500, Nikon Industries Inc., Melville, NY, USA). The "surface roughness" was estimated with the NIS-Elements Advanced Research software (Nikon Industries Inc., Melville, NY, USA). For this analysis, the methodology was performed according to previous work (Yarce, Echeverri, Palacio, Rivera, & Salamanca, 2017). All tests were carried out under homogeneous conditions of incident light intensity, temperature, and relative humidity. Finally, the relative roughness index ($I_{R/A}$) indicates the surface roughness of the tablets and it is defined as:

$$I_{R/A} = \frac{\left(\frac{ANR}{R}\right)}{ANR} = \frac{1}{R} \quad (1)$$

where ANR is the not roughened area of the image and R is the roughness factor, both parameters given by the software through a correlation between the dark and light zones over the tablets surface. When $I_{R/A} \leq 1.20$, it is established that the surface tends to be rough, while $I_{R/A} \geq 1.30$ suggests that the surface is smooth. Furthermore, values between 1.20 and 1.30 set an intermediate state between the smooth and rough surface

2.2.4.2. Contact angle measurements. Static contact angle determination was performed on the surfaces of each tablet prepared with quetiapine and biopolymer material immediately after their manufacturing. For each system, the sessile drop method was carried out using a contact angle meter (OCA15EC Dataphysics Instruments, Filderstadt, Germany) with software controller (SCA20 version 4.5.14). The data capture was recorded in IDS video camera, where the information obtained was taken in a range of 400–800 frames as a reference point. Moreover, the contact angle capture point was defined when the reflection of the incident drop light disappeared completely (approximately 1seg, since its exit from the dispensing system). A fixed height for dropping of 1 cm was taken. The drop volumes were found in a range of 0.005–0.015 mL. Each measurement was performed at 22 ± 1 °C temperature and at a relative humidity of 60 ± 5%, determined with a digital Thermo hygrometer (HTC-1, Thomson Co). The contact angle was measured by triplicates on the surface of the tablets. In addition, notice that hysteresis analysis of the contact angle is not performed, since the tablet surfaces show a liquid absorption phenomenon due to their porosity. However, to evidence this situation, the determination of absorption rate is performed. The reported data corresponds to the average of triplicate measurements.

2.2.4.3. Surface free energy determination (SEF). The determination of the adhesion work (W_{adh}) given at the interface of quetiapine-gum tablets was determined by the Young-Dupree model, while the surface free energy of the tablets (γ_{SV}) was determined from of the Owens, Wend, Rable and Kalble (OWRK) model (Yarce et al., 2016). In the case of Young-Dupree, ultra-pure water was used as reference liquid, whereas for the OWRK model, fluids of increasing polarity corresponding to isopropanol, ethylene glycol and water were used.

2.2.4.4. Water absorption rate by tablet surface. The rate of surface water absorption on tablets of quetiapine-gums was determined by changing the contact angle as a function of the elapsed time or age of the drop from the test liquid on the solid surface. This measure was carried out using the tracking function of the non-static contact angle provided by Dataphisycs OCA20 software. The data were initially plotted from the software as contact angle vs drop age; subsequently, the areas under the curve were plotted against the percentage of polymer added. For the above, GraphPad Prism software 6 was used. Each test was carried out to the point where the instrument did not perform any detection in the variation of the contact angle, either because all the liquid was absorbed on the surface of the tablet or because of a process of deformation of the flat surface of the tablet, due to processes of swelling or erosion.

2.2.5. In vitro dissolution studies

The dissolution study was carried out for each mixing system between quetiapine-gums, using the method of the pallets in a previously calibrated dissolutor (apparatus II, Vision G2 Classic 6-Hanson, Chatsworth, CA, USA). The speed of the palette was 100 rpm at a temperature 37 °C ± 0.5 °C. The volume of the gastric and plasma conditions simulating media (pH 1.2 and pH 7.4 buffer solutions with the ionic strength of 1.5 M, respectively) were 900 mL. Each dissolution test was performed for a different time depending on the type of gum,