Colloids and Surfaces A: Physicochem. Eng. Aspects 441 (2014) 716–724

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

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

A strategy to estimate the intrinsic flux of a poorly water soluble substance for comparison with its release from lipid-core nanocapsules

Luana A. Fiel[a,*], Karina Paese[a], Marília Rizzi[b], Sílvia S. Guterres[a], Adriana R. Pohlmann[a,b]

[a] Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

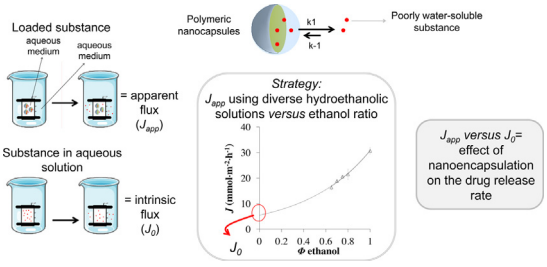
[b] Departamento de Química Orgânica and Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

HIGHLIGHTS

- Strategy to estimate intrinsic dialysis flux (J_0) of lipophilic substance in water.
- Correlates the apparent flux against hydroethanolic mediums with the ethanol ratio.
- Comparison of the J_0 with the release flux from LNCs without further interferences.
- Evaluation of the nanoencapsulation effect on the lipophilic substance release rate.

GRAPHICAL ABSTRACT

A strategy was developed to estimate the intrinsic dialysis flux of poorly water soluble substance in aqueous solution allowing the evaluation of the effect of nanoencapsulation on the release rate of a lipophilic substance.



ARTICLE INFO

Article history:
Received 5 August 2013
Received in revised form 1 October 2013
Accepted 17 October 2013
Available online 27 October 2013

Keywords:
Colloidal aqueous solution
Lipophilic substance
Intrinsic flux in water
Dynamic dialysis

ABSTRACT

In studies on the release of drugs, antioxidants, vitamins, etc., from submicrometric particles, the released portion cannot be separated from that which remains entrapped in the carrier using conventional filtration methods due to the membrane cut-off. Thus, other methods, for example, ultrafiltration–centrifugation or dialysis with dialysis bags, which enable this separation are used. However, as the substances vehiculated in colloidal aqueous solutions are usually poorly water soluble substances, it is not easy to obtain their intrinsic flux (J_0) value in aqueous solution. In this context, our objective was to develop a strategy to obtain the J_0 value of a poorly water soluble substance dialysate from an aqueous solution aiming to compare it with its apparent flux (J_{app}) from an aqueous colloidal system allowing the evaluation of the effect of nanoencapsulation on the release rate of a lipophilic substance. Different hydroethanolic solutions of a poorly water soluble substance (benzophenone-3 (BZ3)) were dialyzed against hydroethanolic media using dynamic dialysis with bags. The J_{app} value of BZ3 in each system was plotted as a function of the proportion of organic solvent and the exponential mathematical

Abbreviations: *a*, a constant which incorporates structural and geometric characteristics of the pharmaceutical form; *A*, the active substance percentage dialyzed at time *t* in burst release stage; *B*, the active substance percentage dialyzed at time *t* in continuous release stage; BZ3, benzophenone-3; BZ3-LNC, Benzophenone-3-loaded lipid-core polymeric nanocapsules; *C*, percentage of BZ3 dialyzed at time *t*; C_0, the total content of active substance (in percentage); CCT, caprylic/capric triglyceride; $d_{4,3}$, volume-weighted mean diameter; DLS, dynamic light scattering; GPC, gel permeation chromatography; h, hours; HPLC, high performance liquid chromatography; *J*, flux/flow values; J_0, intrinsic flux/flow value; J_{app}, apparent flux/flow value; *k*, k_1 and k_2, kinetics rate constants; LNC, lipid-core polymeric nanocapsules; M_∞, amount of active substance in infinite time; min, minutes; MSC, model selection criteria; *n*, release exponent; NC, polymeric nanocapsules; PCL, poly(e-caprolactone); *PDI*, *polydispersity index*; *r*, correlation coefficient; rpm, rotations per minute; SD, standard deviation; SEM, scanning electron microscopy; SPAN, polydispersity; *t*, time; UV, ultraviolet light; ϕ, proportion of organic solvent.

* Corresponding author at: Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves, 9500, PBOX 15003, CEP 91501-970, Porto Alegre, RS, Brazil. Tel.: +55 51 33086285; fax: +55 51 33087304.
E-mail address: luanafiel@yahoo.com.br (L.A. Fiel).

0927-7757/$ – see front matter
http://dx.doi.org/10.1016/j.colsurfa.2013.10.036

equation of this relation was used to calculate the J_0 value of the substance in aqueous solution. BZ3-loaded lipid-core nanocapsule suspensions (BZ3-LNC) were used as a model for colloidal nanocarriers. The J_{app} value obtained for the release from the BZ3-LNC suspension was around 14-fold lower than the J_0 value, indicating that the encapsulation of BZ3 into the LNC system was able to slows its diffusion. The strategy developed allows the use of the J_0 values of poorly water soluble substances in aqueous solutions to verify whether the nanoencapsulation can prolong, for example, the substance delivery on the biological environment.

1. Introduction

The incorporation of drugs into formulations can modify their behavior in a biological environment [1–3]. Therefore, when using a carrier/vehicle, it is of great importance to study the release rate of the drug from this matrix. Release studies can be performed to verify the location of the drug entrapped in the carrier [4,5], to predict and/or correlate the drug release behavior *in vivo* [6], especially for short-acting oil depots, and also for the quality control of formulations [7]. Nanotechnology related to drug delivery has been applied as a strategy to improve therapeutics or cosmeceutics since the desired effect of the entrapped substances can be achieved with low doses and the duration of action can be increased, which can increase the time between administrations [3,8].

In studies on the release of drugs, antioxidants, vitamins, etc., from submicrometric particles, the separation of the released drug from that still entrapped to the carrier is not possible macroscopically. Thus, it is necessary to use methods which enable this separation such as direct filtration [9], ultrafiltration–centrifugation [10,11], low pressure ultrafiltration [12,13] and dynamic dialysis with permeation cells [14,15] or with dialysis bags [5,16–20]. Direct filtration, ultrafiltration–centrifugation and low pressure ultrafiltration are techniques in which first the medium containing the drug loaded-colloid is diluted under sink conditions and then the medium is sampled followed by the use of a separation technique. For all this techniques it is important to ensure that no drug–membrane interactions occur. Direct filtration and ultrafiltration–centrifugation are associated with the problem of possible changes in the profile of the drug release from the carrier caused by the application of external forces to the system. The centrifugal force, for example, can induce the drug release and also may cause disintegration of the carrier. The low pressure ultrafiltration is a very interesting technique where the separation between the colloid and the drug is performed under low pressure reducing the chances of inducing drug release and disruption of the carrier. However, this technique has the problem of needing a fast flow of filtration that does not interfere in the real time of release profile. It is also important to mention that is necessary to have especial equipment for performing the separation procedure by low pressure ultrafiltration. On the other hand, dynamic dialysis using permeation cells, such as Franz cells, or with dialysis bags are techniques in which the separation of the medium containing the nanocarrier loaded with the drug from the acceptor phase, which will receive the released drug, is carried out using a semi-permeable membrane. The drug, after being released, diffuses across the membrane toward the acceptor phase, which ensures separation of the released portion of the drug from the loaded portion. When using dynamic dialysis, it is necessary to pay attention in the sink condition for the drug and also to the possibility of drug–membrane interactions [21]. If the sink condition is maintained and the drug–membrane interactions are low enough to do not interpose the drug flow, dynamic dialysis is a less invasive technique compared to the others since no strong external force is used for the separation of the drug released from the carrier. Dynamic dialysis using permeation cell is generally used for evaluating the release profile of drug loaded-colloids intended for topical use while dynamic dialysis with bags is used in the most variety of applications.

Polymeric nanocapsules (NCs) and lipid-core polymeric nanocapsules (LNCs) are nanostructured devices in which a polymeric wall surrounds an oily core, which present high efficiency for loading substances with low water solubility [22,23]. LNCs differ from NCs since they have a solid lipid dispersed in a liquid lipid oily core [24–26]. The solid lipid–liquid lipid dispersion as an oily core can change the release rate and the mechanical properties of the particles [27,28]. Researchers who have evaluated the release rate of drugs from NCs or LNCs have, in general, used the dialysis bag method, mentioned above, to separate the released drug from the nanocarrier [5,17,18]. To verify the effect of the nanoencapsulation on the drug release rate, these studies usually compare the apparent flux (J_{app}) of the passage of the drug through the dialysis membrane from samples where it is encapsulated in the nanoparticle with that of samples of the drug in hydroethanolic [5,17,18] or micellar solutions [5] or even in suspensions [29]. However, in the case of hydroethanolic solution, the solubility of the drug can decrease during the dialysis experiment as the membrane is also permeable to the solvent. In the case of a micellar solution there is also the problem associated with a structured system, *i.e.* the micelles of the surfactant, where the passage of the particulates through the membrane can affect the results [5]. Thus, evaluating the release rate of drugs from nanocarriers in the aqueous medium (considering a biological medium) presents a challenge, that is, how to evaluate the effect of nanoencapsulation on the drug release rate, based on the flux through the dialysis membrane, if the free substance has low solubility in water, inhibiting a comparison with the intrinsic flux (J_0) of the substance in aqueous solution.

In this context, our objective was to develop a strategy to obtain the J_0 of a lipophilic substance dialysate from an aqueous solution and compare it with its J_{app} from an aqueous colloidal system. With this approach we performed dialysis experiments on hydroethanolic solutions containing a poorly water soluble substance and correlated the J_{app} of the substance from each hydroethanolic solution with the proportion of ethanol. The intrinsic dialysis flux (J_0) of the substance in aqueous solution was estimated from this correlation. Finally, the estimated value was compared with that obtained during the release of this substance from a nanocarrier. Dynamic dialysis with bags was used for this procedure. LNC formulations and benzophenone-3 (BZ3), a chemical sunscreen, were used as models for nanocarriers and a poorly water soluble substance, respectively.

2. Experimental

2.1. Materials

Poly(ε-caprolactone) (MW = 65,000 g mol^{-1}) and sorbitan monostearate (Span 60) were purchased from Sigma–Aldrich (Strasbourg, France). Polysorbate 80, caprylic/capric triglyceride (CCT) and benzophenone-3 (BZ3) were obtained from Delaware