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A dynamic system for the simulation of fasting luminal pH-gradients using hydrogen carbonate buffers for dissolution testing of ionisable compounds

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ABSTRACT

The hydrogen carbonate buffer is considered as the most biorelevant buffer system for the simulation of intestinal conditions and covers the physiological pH range of the luminal fluids from pH 5.5 to about pH 8.4. The pH value of a hydrogen carbonate buffer is the result of a complex and dynamic interplay of the concentration of hydrogen carbonate ions, carbonic acid, the concentration of dissolved and solvated carbon dioxide and its partial pressure above the solution. The complex equilibrium between the different ions results in a thermodynamic instability of hydrogen carbonate solutions. In order to use hydrogen carbonate buffers with pH gradients in the physiological range and with the dynamics observed in vivo without changing the ionic strength of the solution, we developed a device (pHysio-grad®) that provides both acidification of the dissolution medium by microcomputer controlled carbon dioxide influx and alkalisation by degassing. This enables a continuous pH control and adjustment during dissolution of ionisable compounds. The results of the pH adjustment indicate that the system can compensate even rapid pH changes after addition of a basic or acidic moiety in amounts corresponding up to 90% of the overall buffer capacity. The results of the dissolution tests performed for a model formulation containing ionizable compounds (Nexium 20 mg mups) indicate that both the simulated fasting intraluminal pH-profiles and the buffer species can significantly affect the dissolution process by changing the lag time prior to initial drug release and the release rate of the model compound. A prediction of the in vivo release behaviour of this formulation is thus most likely strongly related to the test conditions such as pH and buffer species.

1. Introduction

The pH values of the luminal fluids in the human intestines range from pH 5 to pH 8.4 and depend on the location and the prandial conditions (Diakidou et al., 2009; Vertzoni et al., 2004). The intraluminal contents are mainly buffered by hydrogen carbonate (HCO_3^-) ions. These are secreted by the pancreas and intestinal epithelial cells. Further constituents in the GI lumen that are also contributing to pH and buffer capacity of the intraluminal fluids are bile salts, proteins, carbohydrates and other food components (Kalantzi et al., 2006; McConnell et al., 2008; Persson et al., 2005; Repishti et al., 2001). However, their contribution to the buffering properties of the intraluminal contents is variable and often limited. Therefore, the hydrogen carbonate buffer may be considered being the most biorelevant buffer system for the simulation of intestinal conditions and reflecting an integral element of the ionic composition and buffer capacity of small intestinal fluids (Fadda et al., 2009; Liu et al., 2011). Thus, the application of the hydrogen carbonate buffer system is essential for a realistic simulation of intestinal conditions, particularly, if it is the aim to predict drug release from immediate release (IR) solid oral dosage forms containing ionisable drugs and/or excipients. Several studies suggested that the dissolution of such formulations can be significantly altered by the ionic composition, total ion concentration and buffer capacity of the dissolution media (Bodmeier et al., 1996; Wagner and McGinity, 2002; Wagner and Gruetzmann, 2005). Furthermore, it has been demonstrated that for dissolution testing of dosage forms containing ionisable compounds hydrogen carbonate buffers are often more discriminative than compendial phosphate buffers (Fadda et al., 2009; Liu et al., 2011). For this reason, in various cases they may enable a better prediction of in vivo drug release based on in vitro results.

Besides IR formulations containing ionisable drugs (e.g. weak acids) and/or excipients also for examining enteric coated formulations as well as formulations comprising ionic polymers the choice

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of an adequate buffer system is crucial for the predictive power of the dissolution experiment. As a result of the instability of the hydrogen carbonate buffer, in the last decades this buffer system was scarcely used in in vitro experiments. Thus, to date there is a lack of data indicating the importance of adequately simulating the ion composition of intraluminal fluids with respect to obtaining in vitro in vivo correlations (IVIVCs). Moreover, it should be kept in mind that the identity of anions of buffering species used for simulating the pH-gradients might be crucial for cationic excipients as well as weakly alkaline APIs and is also likely for APIs which are scavengers of free radicals (Vertzoni et al., 2004). To date there is a lack of convincing comparisons vitro vs. in vivo on the importance of using bicarbonates especially in addition to other luminal components for achieving biorelevance in the fasted state. Therefore, the ultimate usefulness of bicarbonates for the biorelevant simulation of the fasting conditions cannot be stated. However, for various test formulations it has been demonstrated that by using hydrogen carbonate buffers a more realistic estimation of the in vivo drug release characteristics can be achieved (Fadda et al., 2009; Ibekwe et al., 2008, 2006; Liu et al., 2011; McConnell et al., 2008; McNamara et al., 2003; Sheng et al., 2009). Nevertheless, despite these convincing results, the use of hydrogen carbonate buffers did not become a common standard for the dissolution testing as well as investigation of interactions of luminal components with ionisable excipients as well as the determination of the drug stability under simulated fasting luminal conditions. The reason thereof is that, since to date, when using this buffer system, it was not possible to guarantee a constant media pH and composition over the entire dissolution experiment.

In the small intestinal pH range of pH 5.5–8.3, hydrogen carbonate buffers are mainly composed of carbonic acid (H_2CO_3) and HCO_3^- ions. H_2CO_3 is a weak acid ($pK_a \sim 6.4$), which is spontaneously formed by the dissolution of its anhydride carbon dioxide (CO_2) in water (Fadda et al., 2009; Mooney et al., 1981a). The pH value of aqueous solutions of CO_2 ranges from pH 3.9 to pH 6.97. The buffer capacity of pure hydrogen carbonate solutions is pH dependent. Around the pK_a (~6.4) buffer capacity is highest, whereas the medium has almost no buffering capacity below pH 5.5 (Garbacz et al., 2013; Mooney et al., 1981a). In the presence of cations of strong electrolytes, such as alkaline metals, the concentration of hydrogen carbonate ions in the solution is increased. However, for the pH-adjustment in the pH range below the hydrolysis-pH of the HCO_3^- salts (about pH 8.4), additional carbonic acid has to be introduced into the solution, resulting in an increased capacity of the HCO_3^-/H_2CO_3 buffer system. Altogether, the pH of a given hydrogen carbonate buffer is a complex and dynamic interplay between the HCO_3^- concentration, the concentration of carbonic acid (H_2CO_3), the amount of dissolved and solvated carbon dioxide (CO_{2aq}, $CO_2 + H_2O$) and the partial pressure of gaseous CO_2 above the solution (Eq. (1)).

$$CO_2(gas) \underset{K_{los}}{\overset{K_{sol}}{\leftrightarrow}} CO_2(aq) + H_2O$$
$$CO_2(aq) + H_2O \overset{K_{hyd}}{\leftrightarrow} H_2CO_3 \overset{K_{diss}}{\leftrightarrow} H^+ + HCO_3^- \quad (1)$$

Eq. (1): The equilibrium equation of carbon dioxide solutions.

The K_{sol} term in Eq. (1) expresses the solvation of CO_2(gas) in the aqueous medium. According to Henry's law, at a given temperature the composition of a pure carbonic acid solution is determined solely by the partial pressure of the CO_2 purged into the dissolution medium ($P(CO_2)$) and is as high as 29.76 atm/mol/L at a temperature of 25 °C (Henry constant). For this reason, it can be assumed that the total concentration of solubilised carbon dioxide (CO_{2aq}) can be expressed by the following equation:

$$[CO_{2aq}] = K_{sol} P(CO_2) \quad (2)$$

Eq. (2): Solubility equilibrium of CO_2(gas).

Under normal conditions (25 °C, 1 bar) the equilibrium constants of carbonic acid are $K_{hyd} = 10^{-2.2}$ for the hydration and about $K_{diss} = 10^{-3.7}$ for the dissociation of CO_2. The overall constant for dissociation of carbonic acid (K_a) into hydrogen carbonate ranges from $10^{-6.4}$ to $10^{-6.0}$ s^{-1}. The CO_2 loss from the solution as result of spontaneous media degassing is expressed by the constant K_{los}, which depends on physical parameters such as temperature, agitation rate, volume/surface ratio of the dissolution media and the gas exchange at the media surface and therefore is specific for the selected test conditions.

The complex equilibrium between the different ions results in a thermodynamic instability of CO_2 solutions. In the case of commonly used hydrogen carbonate buffers, an uncontrolled increase of the media pH under dissolution test conditions is the consequence of spontaneous loss of carbon dioxide (CO_2) from the solution (Garbacz et al., 2013).

In order to maintain the media pH at the desired level, many efforts have been made to keep the hydrogen carbonate buffer system in an equilibrium state according to Eq. (1). In principal, the equilibrium can be maintained either by preventing CO_2 loss from the solution or by replacing evaporated CO_2. The CO_2 loss during a dissolution experiment can e.g. be minimised by using appropriate sealing devices for dissolution test setups or by covering aqueous dissolution media with organic layers, such as paraffin (Fadda et al., 2009). The media pH can also be maintained via quantitative substitution of the escaped CO_2 by controlled feeding of the solution with CO_2 gas using an automated system that enables feeding of appropriate amounts of CO_2(gas) into the solution and re-acidifies the buffer to the desired pH value (Garbacz et al., 2013).

At a first sight the thermodynamic instability of hydrogen carbonate buffers can be considered as a huge disadvantage. However, it offers the unique opportunity to use a physiological buffer system that in addition provides the possibility to simulate the dynamic intraluminal pH changes in the human small intestine. In order to do so, both processes, the acidification as well as the alkalisation of the buffer system require continuous and dynamic adjustment. It is well known, that the acidification of the commonly used hydrogen carbonate buffers is a rather fast process whereas the CO_2 loss occurs relatively slow and spontaneous (Garbacz et al., 2013). However, under dissolution test conditions the degassing process described by K_{loss} can be accelerated and controlled by purging the solution with an inert gas such as N_2. If this inert gas is introduced into the dissolution medium, it enlarges the surface available for gas exchange and increases the CO_2 evacuation rate, which results in a rapid increase in pH. During pH adjustment of hydrogen carbonate buffer media by using CO_2, neutral gases or mixtures thereof, the resulting pH changes come along with CO_2(gas) exchange between medium and environment (Eq. (3)). Since the charge of cations from strong bases such as K^+ or Na^+, which are commonly used as hydrogen carbonate salts, is compensated by HCO_3^- during acidification or OH^- resulting from water hydrolysis during alkalisation, in the case of solutions containing only monovalent ions the total ion concentration and so the conductivity and ionic strength should remain almost constant. Therefore, with a well-designed and controlled hydrogen carbonate buffer system, it should be possible to adequately simulate intraluminal pH conditions as well as the intraluminal ionic composition in an in vitro experiment.

$$HCO_3^- + H2O \overset{K_{diss}}{\leftrightarrow} H_2CO_3 + OH^-$$
$$H_2CO_3 \overset{K_{hyd}}{\leftrightarrow} CO_2 * H_2O \underset{K_{sol}}{\overset{K_{los}}{\leftrightarrow}} CO_2(gas) \quad (3)$$