Drug Delivery by Buccal/Sublingual Microenvironmental pH Modification

Subjects: Pharmacology & Pharmacy

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Many drug candidates are poorly water-soluble. Microenvironmental pH (pH_M) modification in buccal/sublingual dosage forms has attracted increasing interest as a promising pharmaceutical strategy to enhance the oral mucosal absorption of drugs with pH-dependent solubility. Optimizing drug absorption at the oral mucosa using pH_M modification is considered to be a compromise between drug solubility and drug lipophilicity (Log D)/permeation. To create a desired pH_M around formulations during the dissolution process, a suitable amount of pH modifiers should be added in the formulations, and the appropriate methods of pH_M measurement are required.

Keywords: microenvironmental pH modification ; buccal/sublingual dosage form ; solubility

1. Introduction

Buccal/Sublingual administration is an attractive route to achieve systemic drug delivery. It offers advantages such as circumventing the hepatic first-pass metabolism and chemical/biological drug degradation associated with oral administration, the quick onset of drug action, ease of administration and relatively high level of patient compliance [1][2][3][4]. In general, formulations such as mucoadhesive films, patches, tablets, gels, etc., have been employed for buccal/sublingual drug delivery, which could increase the contact time between drugs and the oral mucosa. Among the various physicochemical properties of the drug candidates, aqueous solubility and lipophilicity (Log D)/permeation are two crucial factors affecting drug absorption at the oral mucosa. A good drug candidate should be soluble in human saliva, and possess enough lipophilicity to permeate the epithelium at the oral mucosa [3]. However, it is estimated that over 40% of drugs on the market are poorly water-soluble [5], which could lead to a slow drug release. Generally, poorly water-soluble drugs are weakly ionizable drugs, which might have pH-dependent solubility and/or pH-dependent lipophilicity (Log D)/permeation. Therefore, pH plays a crucial role in the absorption of those drugs in the oral cavity.

Microenvironmental pH (pH_M) modification is widely used in oral solid dosage forms to increase the dissolution of poorly water-soluble drugs with pH-dependent solubility in the gastrointestinal (GI) tract, and this approach creates a microenvironment with an ideal pH level in the vicinity and inside the solid dosage forms by adding pH modifiers to the formulations [6][7][8][9]. It has been demonstrated that pH_M modification is an effective way to increase drug dissolution and enhance drug absorption in the GI tract [7][10][11][12]. Typically, the pH rapidly changes from highly acidic in the stomach to neutral in the small intestine. Under fasted-state conditions, the gastric pH range is between 1.7 and 4.7, and the pH in the small intestine slightly increases from 5.9 in the proximal parts to 7.8 in distal parts for the human subjects [13]. The physiological environment for drug dissolution in the oral cavity is different compared to that in the GI tract. The pH range for unstimulated human saliva is 6.2 to 7.6 and the average salivary pH is 6.8 [14][15]. The neutral pH environment, without dramatic shifts, is beneficial to create a desired pH_M. Additionally, the limited volume (average 0.8 to 1.1 mL) and the low secretion rate of human saliva (0.35 to 2.00 mL/min) [16][17] could lead to a slow release of the pH modifiers from the formulations and, hence, to maintaining the ideal pH_M. Therefore, the oral cavity provides a suitable physiological environment for pH_M modifications. pH_M might not only affect drug release from formulations, but also drug permeation across the oral mucosa. Generally, pH modifiers could modulate pH_M both in and in the vicinity of the buccal/sublingual formulations and affect the drug ionization, and thereby influence the drug permeation across the oral mucosa. Thus, pH_M modification in buccal/sublingual dosage forms might be an effective strategy to enhance the absorption of drugs with pH-dependent solubility or/and permeation.

2. Concept of Microenvironmental pH (pH_M) Modification in the Buccal/Sublingual Dosage Forms

2.1. Theory: pH-Dependent Dissolution and Permeation

Drug dissolution/release from buccal/sublingual formulations is one of the crucial factors affecting drug absorption at the oral mucosa. The relationship between the pH, drug solubility and dissolution rate has been elucidated using the Nernst-Noyes-Whitney equation [18] (Equation (1)) and the “solubility-pH” equations (take monoacidic drugs and monobasic drugs as examples) [19][20] (Equations (2) and (3)), as described below:

$$\frac{dC}{dt} = \frac{DS}{Vh}\left(C\mathrm{s} - C_b\right) \quad (1)$$

where $\frac{dC}{dt}$ is the dissolution rate, *D* is the diffusion coefficient, *S* is the surface area of solid exposed, *V* is the volume of dissolution media, *h* is the thickness of the diffusion layer, C_s is the concentration (saturated) of drug at the solid surface and C_b is the concentration of drug in the bulk medium.

$$C_{\mathrm{s}} = C_{\mathrm{S0}}\left[1 + 10^{\,\mathrm{pH}\,-\mathrm{p}Ka}\right]\left(\mathrm{for}\ \ \mathrm{monoacidic}\ \ \mathrm{drugs}\right) \quad (2)$$

$$C_{\mathrm{s}} = C_{\mathrm{S0}}\left[1 + 10^{\,\mathrm{p}Ka\,-\mathrm{pH}}\right]\left(\mathrm{for}\ \ \mathrm{monobasic}\ \ \mathrm{drugs}\right) \quad (3)$$

where C_s is the drug solubility at a given pH and C_{S0} is the intrinsic solubility of the drug.

According to the “Solubility-pH” equations, a slight shift in the pH might lead to a significant change in the drug solubility. Theoretically, decreasing the pH could improve the solubility of a weakly basic drug by increasing the concentration of ionized drug in the solution. When most of the dissolved drug substance remains in its ionized form, a further decrease in the pH has little effect on its solubility, and the drug solubility approaches a plateau level in the pH-solubility profile. A suitable pH level at the surface of a solid formulation exposed to dissolution media could increase the local drug concentration (C_s) and, consequently, enhance the drug dissolution and release (dCdt
) from the solid formulation.

The mechanism of drug transport across the oral epithelium is similar to that across the other epithelia in the human body. Generally, both the transcellular and paracellular pathways are involved in this process [3][21][22][23][24]. For the drugs transported mainly via the transcellular route, drug permeation across the oral mucosa might be affected by the pH at the oral mucosa. According to the pH-partition theory, the neutral forms of drugs are more permeable (lipophilic) than the ionized species; therefore, a pH shift not only affects the dissociation of weakly ionizable drugs, but also the drug permeation across biological membranes (**Figure 1**) [25][26].

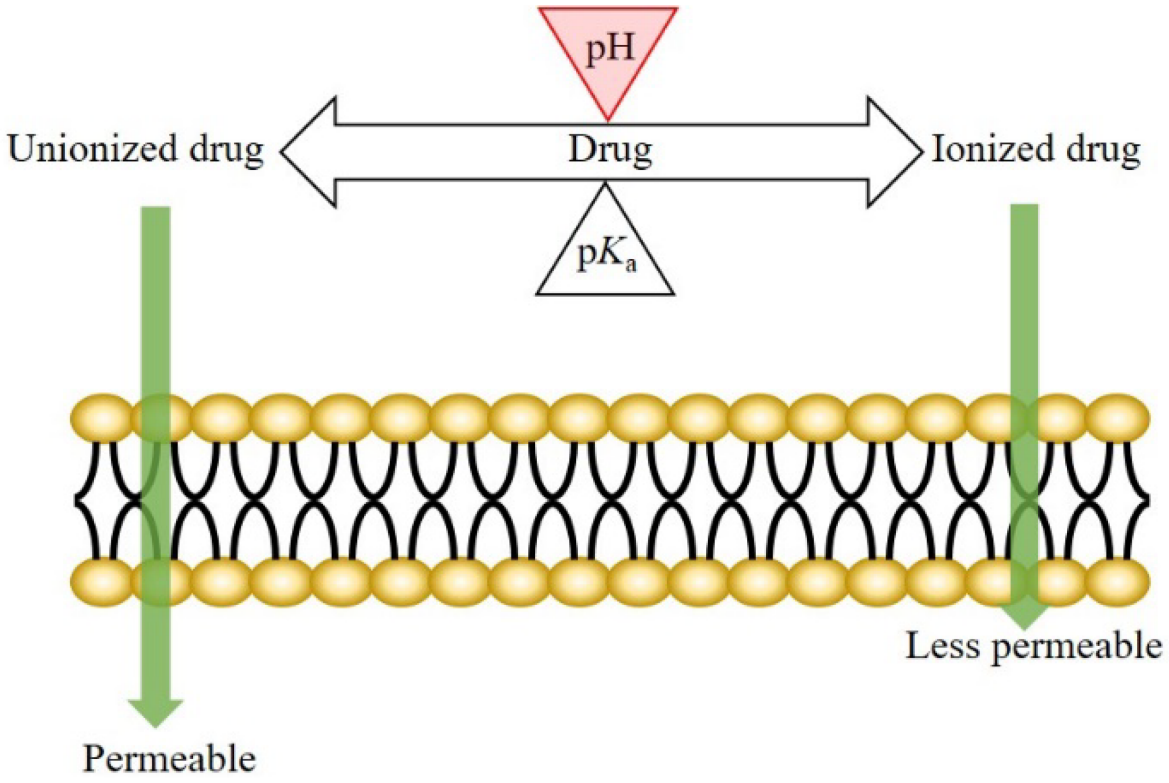

Figure 1. Illustration of pH-partition theory.

2.2. pH_{max} Concept

A pH_{max} concept defined as the pH value at which a given drug has a maximal aqueous solubility and the sum of its ionized species and unionized species in solution is at a maximum [27]. Modulating the saliva pH at the sublingual mucosa to the pH_{max} by adding buffering agents in sublingual formulations was expected to lead to a maximal potential absorption. The pH_{max} concept was proven to be valuable in the case of a propranolol sublingual tablet with buffering agents, which achieved a higher absorption in human subjects than the conventional non-buffered tablet. However, previous studies regarding the metroprolol buccal tablet and gel did not support the pH_{max} concept. A specific pH level (rather than pH_{max}) also led to the highest buccal absorption of metroprolol [28][29].

2.3. Microenvironmental pH Modification in Buccal/Sublingual Dosage Forms

The aim of pH_M modification is to enhance the absorption of a given drug by influencing its solubility and permeability. Upon pH_M modification in buccal/sublingual dosage forms, a small space exists between the formulation and the mucous membrane when the formulation is attached the oral mucosa. Typically, a drug must have a sufficient aqueous solubility to be released from the formulation and dissolved in the space, before permeating through the membrane of the oral mucosa. The pH of the space and the pH inside the formulation could be modified by adding pH modifiers into the formulation, which might affect the drug release (caused by the changes in drug solubility), drug solubility in the space and drug permeation across the mucosa by influencing the drug dissociation (**Figure 2**). In general, the drug, pH modifier and mucoadhesive polymer are the main components of the pH_M modifying buccal/sublingual formulations.

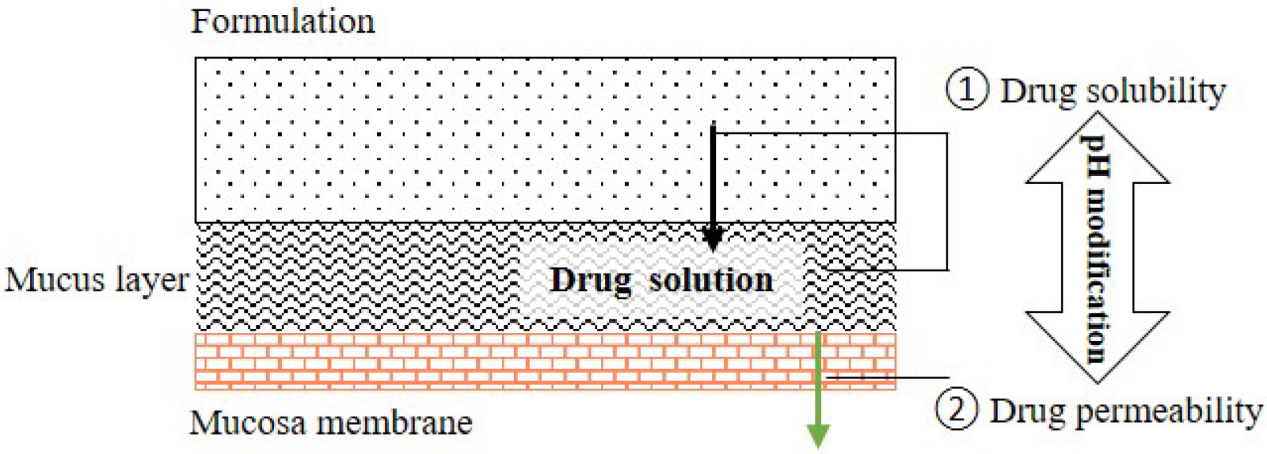

Figure 2. Schematic drawing of drug permeation across oral mucosa from the buccal/sublingual formulation.

3. Properties of Saliva Associated with pH Modification

The main functions of saliva are to maintain oral health and help to build and maintain the health of hard and soft tissues. Approximately 99% of saliva is water, and the other 1% consists of a variety of electrolytes and proteins [30][31]. Regarding buccal/sublingual drug delivery, saliva provides a water-rich environment that facilitates in the drug dissolution and release from buccal/sublingual formulations before the drugs permeate through the membrane of oral mucosa [32]. To achieve a successful pH_M modification in buccal/sublingual formulations, some properties of saliva should be taken into consideration during the formulation design.

3.1. pH and Buffer Capacity of Saliva

Human saliva has been reported to have a pH range of 6.2–7.6 [14]. The composition of saliva secreted from different regions differs, leading to different saliva pH. The pH in the palate, the floor of the mouth, the buccal mucosa and the tongue, in humans, have been reported to be 7.3, 6.5, 6.3 and 6.8, respectively [33]. The flow of saliva with a buffer capacity resisting pH shift could remove acidic and basic foods on the oral mucosa, maintaining the pH in the oral cavity near neutrality in a long term. The bicarbonate, the phosphate and the protein buffer systems in the whole saliva are the major systems contributing to the buffer capacity, and their concentration and buffer capacity are dependent on the secretion rate of saliva [34][35][36].

3.2. Secretion Rate of Saliva and Thickness of Salivary Film

Saliva is a complex mixture secreted by salivary glands. There are three pairs of major glands: the parotid, submandibular and sublingual glands, and numerous minor salivary glands [37]. Salivary secretion continues throughout the day, with an average total volume of 500–600 mL. Previous studies have reported that the mean flow rate of unstimulated human saliva and stimulated human saliva is 0.35 mL/min and 2 mL/min, respectively [16][38].

4. Drug Candidate and pH Modifier for Buccal/Sublingual Dosage Forms

4.1. Drug Candidate

The low drug loading capacity of buccal/sublingual formulations and the limited absorption area in the oral cavity are two main limitations for buccal/sublingual drug delivery. Thus, drug candidates should be high potency to achieve successful therapeutic efficacy. In addition, suitable drug candidates must not cause local irritation and toxicity at oral mucosa. Regarding physicochemical properties, high lipophilicity (log P (octanol/water) > 2), fairly good water-solubility and small molecular size (less than 800 Da) are typically considered as ideal parameters for drug candidates, as described previously [3]. The extent of different drug transport pathways across the epithelium depends on the drug physicochemical properties [39][40]. Typically, drug candidates with high lipophilicity can move across the lipid-rich epithelial cell membrane with relative ease. Fairly good water solubility allows for the fast drug release of buccal/sublingual formulations and drug diffusion across the hydrophilic cytoplasm of cells and paracellular passage. Macromolecules can be delivered via the oral mucosa, e.g., buccal insulin spray (Generex Oral-lyn®) was approved by Food and Drug Administration (FDA) for the treatment of patients under the Investigational New Drug (IND) program [41][42][43]. However, the number of marketed buccal/sublingual macromolecules is very small.

However, over 40% of marketed drugs and approximately 90% of drug candidates are reported to be poorly water-soluble [5], and most of them are weakly ionizable drugs, indicating that their solubility and/or permeability across the lipid-rich epithelium are pH-dependent [44][45][46][47]. Typically, the ionic form of a drug is more water soluble than its non-ionic form. A change in the pH might influence the ratio of the ionized form of the dissolved drug, according to the Henderson-Hasselbach equation (Equation (4)) [48]. When the difference in the water solubility (and/or lipophilicity) between the two forms is big enough, a slight pH change might have a significant effect on the drug solubility. Therefore, drug candidates suitable for pH_M modification should have pH-dependent solubility and/or pH-dependent lipophilicity and be poorly soluble at physiological pH in the oral cavity.

4.2. pH Modifier

There are a few concerns about the excipients used in pharmaceutical formulations. A pH modifier can only be considered as a pharmaceutical excipient if it has been demonstrated to be safe for human beings. So far, various pH modifiers have been applied in the food and pharmaceutical industries. The Generally Recognized as Safe (GRAS) list of the FDA lists some safe pH modifiers that have been added to food. In addition, various pH modifiers recommended for oral liquids have been collected in the United States Pharmacopeia (USP). However, the specific pH modifiers for buccal/sublingual formulations were not referenced. The pH modifiers collected in the USP [49] and their maximum potency per unit dose

used in solid oral and buccal/sublingual formulations in the database of Inactive Ingredient Search for Approved Drug Products Search, provided by the FDA [50]. The pH modifiers can be divided into three categories: acidifying agents, alkalizing agents and buffering agents. Currently, only a few pH modifiers, were applied in the commercial buccal/sublingual formulations approved by the FDA. pH modifiers demonstrated without local irritation and toxicity to oral mucosa could also be potential choices for the buccal/sublingual dosage forms.

5. Methods for Microenvironmental pH Measurement

5.1. pH Electrode Approach

The most common method to determine the pH_M is the pH electrode approach. As the previous studies described [51][52][53][54][55][56][57], formulations (e.g., tablets, film and patch) were allowed to swell in a limited volume of buffer solution (at neutral pH) at room temperature for a certain period. Subsequently, the pH on the surface of the formulations was determined using a pH electrode. Mucoadhesive buccal films containing ornidazole were allowed to swell in 4 mL of phosphate buffer (pH 6.8 ± 0.1) at room temperature for 120 min and the surface pH was measured using an electrode pH meter [52].

5.2. Computer-Enhanced Color Images Method

To gain more information on the pH_M change during the dissolving process of the fentanyl tablet, a computer-enhanced color images (of pH paper) method was used to record the pH_M as it varied over the surface of the swelling tablet [58]. The schematic view of the setup and the computer-enhanced color images of pH paper are shown in **Figure 3**. A piece of pH paper was placed over a tablet. The tablet with the pH paper was held between two microscope slides, and a small volume of deionized water was applied to the pH paper. The tablet was rapidly wetted by the water that permeated the pH paper. As the tablet swelled, the pH paper was digitally photographed at different time intervals. The pH over the distinct regions of the tablet surface were then determined from the digital images and in comparison to the reference pH standards. The pH_M decreased from 7.0 to 5.0, and then gradually increased to around 6.0 during the first 5 min of the dissolving process [58].

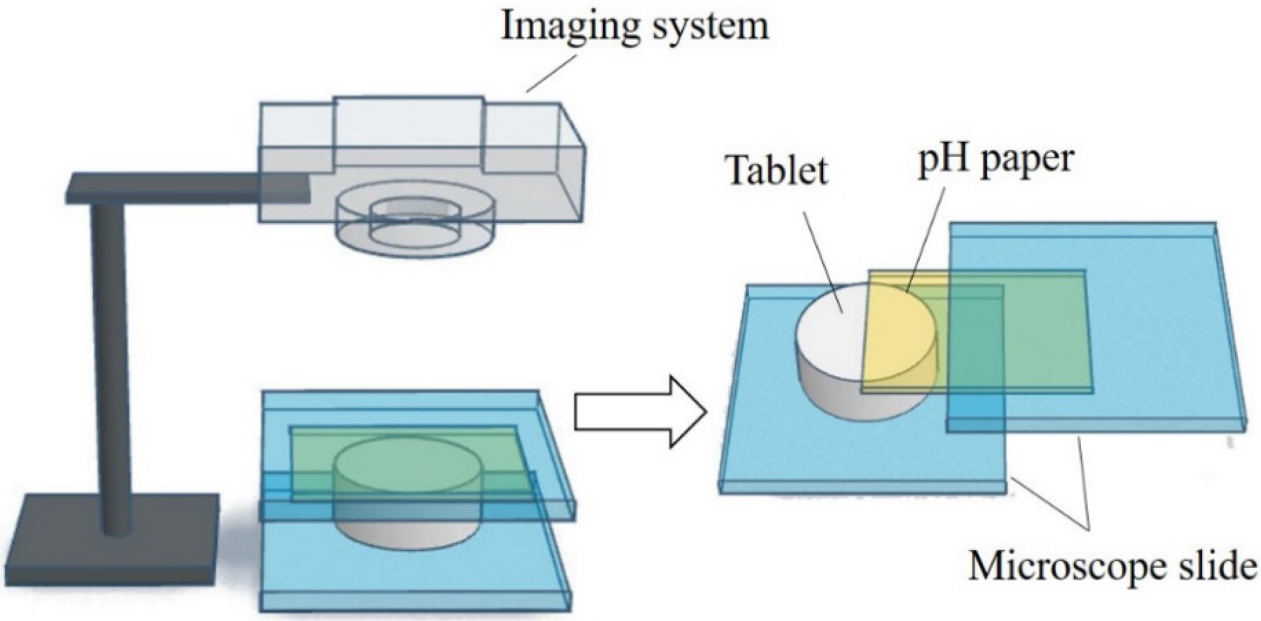

Figure 3. Schematic view of the setup of the computer-enhanced color images method.

5.3. UV/Vis Imaging Method

In a previous works, an UV/Vis imaging method with an agarose hydrogel mimicking the fluid on the surface of the buccal mucosa was constructed. The effect of the malic acid dose on the pH_M during the initial dissolution of the buccal films, and the information related to film the swelling and possible drug precipitation in the films were monitored using this method [59]. The agarose hydrogel contained agarose (0.5% *w*/*v*), bromothymol blue (pH indicator, 6.29×10^{-5} M) and a buffer solution, simulating the human saliva pH and buffer capacity. A buccal film was attached on the agarose hydrogel, and the absorbance change of the pH indicator in the hydrogel at a wavelength of 610 nm was monitored during the swelling of the film. To relate the absorbance of bromothymol blue to the pH in the hydrogel, an absorbance-pH profile was

constructed as a calibration curve. Based on the calibration curve, the pH during the swelling of the buccal film could be measured.

6. Microenvironmental pH (pH_M) Modification Methods

6.1. Microenvironmental pH Modification Using Acidifying/Alkalizing Agents

The most direct and effective way to change the pH_M is to add acids or bases into the formulations. The pH_M change might compromise the drug release from the formulations and the drug permeation, hence improving the drug absorption at the oral mucosa. Suitable pH shifts might increase the drug solubilities, despite them being poorly soluble in human saliva at the physiological pH. Previous studies have shown that the addition of organic acids leads to a significant increase in the dissolution of dapoxetine hydrochloride (DPX) particles in phosphate buffer at pH 6.8 (37 ± 0.5 °C) due to the pH-dependent solubility of DPX and the low pH_M around the drug particles [60][61]. In addition, the enhanced pharmacokinetic performance of DPX via the buccal films with organic acids in male Wistar rats was observed compared to that of the marketed DPX oral tablet (Priligy®) [61].

6.2. Microenvironmental pH Modification Using Buffering Agents

The pH_M in the vicinity of formulations at the oral mucosa is generally affected by the release of the ingredients (particularly the acidic and basic ingredients) from the formulations. The pH_M changes over time, along with the ingredients released upon dissolution. To maintain the suitable pH_M and achieve optimal drug absorption at the oral mucosa, buffer agents are incorporated in formulations. The addition of buffering agents can form a buffer system in and around the matrix of the formulations and prevent the pH_M from changing. This method was demonstrated to be effective in some cases. Phosphate buffer and borate buffer were used in methylcellulose-based gels to create pH_M 7.4, 8.5, 9.0 and 9.5 for the buccal delivery of metoprolol in Göttingen minipigs in a previous study. A higher buccal absorption of metoprolol from the gels was observed at higher pH values, and the absolute bioavailability of metoprolol via buccal dosing was significantly higher compared to that via oral administration [29]. In the study, the metoprolol release from the gels might be similar, and the pH has little effect on metoprolol release, because the concentration of methylcellulose used in the gels was the same (1%, *w*/*v*) and metoprolol had already been dissolved in the gels. Metoprolol permeability across the buccal mucosa is the rate-limit step for the buccal absorption of metoprolol. Furthermore, metoprolol with pK_a 9.56 [62] has a pH-dependent lipophilicity and permeability in vitro and ex vivo [29][63]. Thus, the pH has a crucial influence on the buccal absorption of metoprolol incorporated in gels.

6.3. Microenvironmental pH Modification Using Effervescence

Formulations with effervescence generally contain an alkaline agent (e.g., sodium carbonate and sodium bicarbonate) and an acid that is capable of inducing the effervescence reaction during the dissolution [64]. The carbonic acid produced from the chemical reaction could decrease the pH_M and rapidly convert to water and carbon dioxide. The tablet using an effervescence reaction (containing citric acid and bicarbonate) was employed to enhance the absorption of fentanyl at the buccal mucosa [58][65][66]. A dynamic shift in the pH_M (pH was decreased and subsequently be increased) occurred in the microenvironment between the tablet and the buccal mucosa, and the pH_M shift might be the main factor for the enhanced buccal absorption of fentanyl. The initial decrease in the pH, caused by the carbonic acid and release of citric acid from the tablet, facilitated the release of fentanyl from the tablet. The pH subsequently increased due to the dissociation of carbonic acid (into CO_2 and water) and the dissipation of the CO_2, which favored the formation of unionized fentanyl. The unionized fentanyl can move across the lipid-rich oral mucosal membrane with greater ease than the ionized fentanyl [58][65][66].

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