Expert Opinion

Dissolution-modulating mechanism of pH modifiers in solid dispersion containing weakly acidic or basic drugs with poor water solubility

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Importance of the field: Although the solid dispersion method has been known to increase the dissolution rate of poorly water-soluble drugs by dispersing them in hydrophilic carriers, one obstacle of the solid dispersion method is its limited solubilization capacity, especially for pH-dependent soluble drugs.

Areas covered in this review: pH-modified solid dispersion, in which pH modifiers are incorporated, may be a useful method for increasing the dissolution rate of weakly acidic or basic drugs. Sufficient research, including the most recent reports, was undertaken in this review.

What the reader will gain: How could the inclusion of the pH the pH modifiers in the solid dispersion system change drug structural behaviors, molecular interactions, microenvironmental pH, and/or release rate of pH modifiers, relating with the enhanced dissolution of weakly acidic or weakly basic drugs with poor water solubility? These questions have been investigated to determine the dissolution-modulating mechanism of pH modifiers in solid dispersion containing weakly acidic or basic drugs.

Take home message: It is believed that step-by-step mechanistic approaches could provide the ultimate solution for solubilizing several poorly water-soluble drugs with pH-dependent solubility from a solid dispersion system, as well as provide ideas for developing future dosage systems.

Keywords: dissolution-modulating mechanism, microenvironmental pH modulation, molecular interactions, pH-modified solid dispersion, structural behaviors, weakly acidic or basic drugs

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1. Introduction

Several recent drug candidates have poor water-solubility, which is associated with a variety of inadequate properties, including rate-limiting dissolution, slow absorption and low bioavailability. Therefore, attempts to improve solubilization of poorly soluble drugs are very important and continuing in pharmaceutical science and technology. One common approach is the formation of a solid dispersion (SD) system, a solid product consisting of at least two different components, generally a hydrophilic polymer and a hydrophobic drug. The drug can be dispersed molecularly to form an amorphous structure with reduced particle size for better wettability to enhance drug dissolution [1-5]. However, the solubilization capacity of SD systems may be limited by the carrier, by recrystallization, or by spring-like precipitation on exposure to an

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Article highlights.

- A conventional solid dispersion approach occasionally leads to unexpected results to enhance drug solubility, especially for pH-dependent water-insoluble drugs, and hence leads to a way to overcome this limitation using pH-modified solid dispersion.
- The fact that the inclusion of an alkalizer or acidifier into a solid dispersion containing weakly acidic drug or weakly basic drug, respectively, creates a corresponding basic or acidic microenvironment for facilitating the enhancement of drug dissolution has been attributed to the release rate of pH modifier from solid dispersion.
- Determination of microenvironmental pH and concentration of pH modifiers is crucial to evaluate the capability of maintaining pH modifiers in the dosage form, especially that a specified method for both imaging and quantification has been highly acclaimed for investigation.
- The incorporation of a pH modifier with a carrier of solid dispersion promotes the amorphous formation of drug structure and induces the possibility of some molecular interaction among functional groups of drug and pH modifier, contributing to the control of microenvironmental pH and the enhancement of drug dissolution in such pH-modified solid dispersions.
- Selection of a suitable acidifier or alkalizer is not based simply on the corresponding type of drug, a weakly basic drug or weakly acidic drug, but preferably depends on the specific pH-solubility profile of drug and pH modifier in order to obtain an effective pH-modified solid dispersion for enhancing drug dissolution.

This box summarizes key points contained in the article.

aqueous solution [6-9]. A non-emulsifying or emulsifying SD system depending on the polymer and an extra agent, such as a surfactant, can be used to solubilize the drug. In some cases, a secondary polymer can be simultaneously combined and incorporated in SD systems to limit precipitation in solution for complete solubilization of poorly water-soluble drugs [9]. Moreover, the properties of a SD are greatly affected by factors such as the mutual compatibility of the components or the uniformity of drug distribution in the system.

Unfortunately, the conventional SD approach is not a satisfactory remedy for all poorly water-soluble drugs. Generally, poorly water-soluble drugs are weakly acidic or basic compounds and, hence, show pH-dependent solubility. For this reason, modulation of pH in dosage forms, known as 'microenvironmental pH' (pH_M), is a promising way to modify the release rate of several pH-dependent and ionizable drugs [10-16]. The pH_M can be defined as the pH of the saturated solution in the immediate vicinity of the drug particles and has been used to modify the dissolution of ionizable drugs from pharmaceutical formulations in a predictable manner [9,17,18]. For a weakly basic drug that is deprotonated and non-ionized in intestinal fluid, an acidifier is commonly used to enhance the drug dissolution rate by decreasing the pH_M of the dosage forms [9,11,12,14,15]. On the other hand, an alkalizer is a suitable pH modifier to increase the pH_M of a solid dosage form containing a weakly acidic drug [13,16]. However, in reality, this rule is not applicable in every case. For example, an acidifier is not as effective as an alkalizer for enhancing the dissolution of a drug such as telmisartan, which is poorly soluble in intestinal fluid [18]. Hence, the optimal choice is dependent on the specific drug and can be screened in a preliminary solubility study. Normally, pH modifiers are introduced into the system by wet granulation to form a controlled-release matrix or SD preparation. The enhancement of the dissolution rate is probably rather dependent on each preparation method because of the different dissolution-modulating mechanisms. The mechanism of pH modifiers in controlling pH can be investigated by observation of color changes of some pH indicators contained in solid dosage forms or by quantifiable methods such as pH_M determination or examination of pH modifier release. In addition to altering the pH_M to an optimal pH for controlled solubility, pH modifiers affect drug structural behaviors in solid dosage forms by promoting the hydrophilic polymer to reduce drug crystallinity if drug is present in a crystalline form or by preventing the recrystallization of an amorphous SD system [10]. The intermolecular interaction mediating the changes in release rate of pH-dependent drugs from SD is also important in elucidating the effect of these pH modifier-bearing SDs [9,18]. Understanding the pharmaceutical mechanisms of pH modifiers in SD systems, including the correlation between potential changes in drug crystallinity, pH_M control, release rate of pH modifiers and the enhanced dissolution of poorly water-soluble drugs, is essential for detailed investigation of pharmaceutical strategies. Therefore, this review aims to give readers a deeper insight of the dissolution-modulating mechanisms of pH modifiers in SD containing a weakly basic or acidic drug. Moreover, different from many reports outlining the pH modifier's role as a stabilizer [19-21], this review gives the whole scope on the role of pH modifiers in enhancing the dissolution rate of poorly water-soluble drugs in pH-modified SD systems together with the investigation of the mechanism and characterization of the systems.

2. pH_M and dissolution behaviors

The dissolution rate of a drug from a SD has been explained through a large number of studies and is affected by mechanisms such as enhanced wettability, particle size reduction, reduced agglomeration and amorphous structure, which lead to increased solubility and dissolution [22-25]. The dissolution of a solid composed of more than two components is more complex than that of a pure solid. The components, which are intimately mixed in SD, mutually affect each other's dissolution rate. Approximately 50 years ago, Higuchi investigated a uniform mixture of two dissolving compounds, both in the crystalline state [26]. One of the compounds dissolved faster (normally the polymer), resulting in a porous layer of the other compound (normally the poorly water-soluble drug). He assumed that the concentration of

a drug was equal to its solubility in the porous layer, which implies that no supersaturation of drug occurred in the liquid compartment of the porous layer. It is unlikely that drug from amorphous SDs will be supersaturated during dissolution of a SD. The degree of supersaturation can increase with time, especially when the polymer dissolves rapidly. On the other hand, it is impossible to obtain accelerated dissolution without supersaturation, especially from a non-disintegrating SD tablet. Another complication is that crystallization of the poorly water-soluble drug at the tablet surface can occur as a result of this supersaturation and thus influence the dissolution behavior of SDs [27-30]. No matter which of the above occurs, both supersaturation and crystallization kinetics will affect the time needed to reach steady-state dissolution.

The dissolution of a solid is commonly explained by the Noyes–Whitney equation, in which the dissolution rate is proportional to the difference of chemical potentials between bulk concentration and concentration at the dissolving interface:

$$dC/dT = kS(C_s - C_t) \quad (1)$$

where dC/dT is the dissolution rate (concentration with respect to time), k is the dissolution rate constant, S is the surface area available for dissolution, C_s is the concentration of the drug in the immediate proximity of the dissolving particle, that is, the saturation solubility of the compound in the dissolution medium, and C_t is the concentration of the drug in the bulk fluid. The equation describes the relationship between dissolution rate and solubility. It also reflects the effect of dissolution pH on the dissolution rate of a drug with pH-dependent solubility. An appropriate value for C_s is solubility of the drug in the diffusion layer at the surface of the dissolving particle rather than in the bulk medium [4,31,32]. Dissolution behaviors of the drug substance only abide by the Noyes–Whitney equation once the saturation solubility at the surface of the particles, considered the microenvironment solubility depending on the self-buffering effect, is used in the calculations.

Therefore, introducing a pH modifier into a SD has been considered a likely solution for a weakly acidic or basic drug. For example, the addition of acidifiers into weak base-containing SDs can, in theory, recover the release rate of drug by maintaining an acidic microenvironment, facilitating solubilization of the solid dosage form, and preventing conversion of the more ionizable drug to a less soluble base owing to penetration of intestinal juices. The increased solubility can lessen or even exclude supersaturation and therefore hinder crystallization in the microenvironment of the dissolving dosage form.

Furthermore, if the formulation containing the pH modifier is designed in a swelling-controlled system, the dissolution behavior will be more complex and can be fitted to the semiempirical power law equation to describe a model transport and investigate the mechanism of drug release (excluding any delay in drug release and any lag time) [33,34]:

$$M_t/M_{\inf} = kt^n \quad \text{or} \quad \ln(M_t/M_{\inf}) = n\ln(t) + \ln(k) \quad (2)$$

where M_t and $M_{\inf}$ are the cumulative amounts of drug released at time t and the total drug released over an extended time period, respectively; k is a constant reflecting the structural and geometrical characteristics of the system; and n is the release exponent indicating the release mechanism. $n = 0.5$ when release is primarily diffusion controlled (Fickian release, $t^{1/2}$ dependence) and $n = 1$ when release is swelling controlled (case II transport, purely relaxation controlled). Other values of n between 0.5 and 1 indicate anomalous transport kinetics, a combined mechanism of pure diffusion and case II transport. Equation 2 can reveal whether or not the inclusion of a pH modifier increases drug release. Whereas the control formulation (drug and polymers, without pH modifiers) commonly expresses a zero-order release mechanism (purely relaxation controlled), the incorporation of pH modifiers normally results in anomalous release corresponding to coupled diffusion/polymer relaxation. Depending on the type of pH modifier, a higher pH modifier concentration tends to decrease slope n, whereas the release constant k increases, suggesting that increasing the pH modifier concentration increases drug diffusivity. Simultaneously, the exponent implies a negligible improvement in dissolution for pH modifier with low pH modulation as n goes above unity.

Last but not least, another important factor involved in the dissolution process is the release rate of the pH modifier, which reflects the corresponding drug release and follows the same laws as the active substance. The pH_M can be modulated for drug dissolution as long as the pH modifier is present inside the solid dosage form [17,35,36]. Thus, evaluation of pH modifier release behaviors is crucial for thoroughly understanding the drug release mechanism from such pH-modulating systems. The extent of pH_M maintenance in the solid dosage form is highly dependent on the solubility of the pH modifier [37]. pH modifiers that show high water solubility will dissolve immediately in the medium penetrating the dosage form, then rapidly diffuse out. Irrespective of how high the solubility is, the release profile of these pH modifiers in this case will be almost identical. As a result, the respective drug release does not improve greatly. By contrast, a pH modifier with low saturation solubility can stay inside the system in large amounts for an extended period to supply a certain pH for the poorly water-soluble drug. As most of the frequently used pH modifiers have higher solubility than the drug possessing the same pH-dependent solubility profile, the selection of an adequate pH modifier for a specific drug, as well as the design of the solid dosage form, is critical. Although some studies mentioned that the enhanced release in the system was affected in other ways, such as by the creation of a porous structure resulting from pH modifier release in the case of citric acid, these represent special, rather

than general, cases [17,38,39]. In such cases, the main contributor to enhanced drug release remains controversial: Siepe *et al.* [17] claimed that pH_M modulation is the main contributor, whereas Espinoza *et al.* [38] assumed that citric acid utilizes the effect of a hydrosoluble excipient rather than an acidic one, and faster drug release was therefore due to the increased porosity from the fast release of this pH modifier.

3. Evaluation of pH_M in a solid dosage form

pH_M modulation has been attempted in order to investigate several techniques to determine pH_M directly or indirectly. To quantify pH modifier release, samples were withdrawn from the dissolution medium at the same time as for drug analysis and then analyzed. High-performance liquid chromatography (HPLC) or UV spectroscopy was used to determine release of acidifiers or organic pH modifiers [14,17,40,41]. However, inorganic or ionizable pH modifiers were assayed indirectly by potentiometry (applicable to limited ions and requiring longer analysis time), atomic absorption spectroscopy (AAS), atomic emission spectroscopy (AES) or inductively coupled plasma (ICP) spectrometry (applicable to a wide variety of elements and saving analysis time). The results of these quantitative analyses reflect the capability of maintaining a sufficient amount of pH modifier to modulate pH_M of solid dosage forms. The ideal pH_M modulation occurs when the pH modifier release rate is similar to or slower than the drug release rate during the entire period of dissolution. For example, Siepe *et al.* [17] specified that the percentage of fumaric acid release was 71.6% after 4 h, indicating that 28.4% fumaric acid remained in the tablet, and the release rate of this acidifier was almost identical to that of the drug for the entire dissolution process; by contrast, citric acid and succinic acid were almost completely released after 4 h. One matter that requires attention is that pH modifier release may be simultaneously influenced by factors such as the design of the dosage form, pH modifier solubility, and the preparation method of SD. For example, incorporation of separately mixed pH modifier with a binary SD (drug and polymer only) results in less effective pH_M modulation than a ternary SD including the pH modifier [37]. Besides the possibility of loosening the molecular interaction, this physical mixture may cause a faster release of pH modifier.

Until recent years, the exact definition of pH_M was controversial. Therefore, in attempts to measure the pH_M of a solid dosage form, several techniques have been proposed to determine the pH on the surface or inside a solid dosage form or both. Two decades ago, Doherty and York utilized a modified dissolution apparatus, constant surface area disks, and a micro-pH probe to measure the pH at the surface of the dissolving compact (**Figure 1**) during dissolution [10]. The compact was produced from SD powder compressed directly by a Perspex cylinder, a component of the apparatus, and retained in a holder that was later screwed into the base of the dissolution cylinder to begin the test. There was a protruding metal stud fixed on the base plate to produce an indentation in the center of the compact in which the probe could rest. A motor on one side of the axis of the stirrer shaft was used to drive the shaft by means of a cog system. A metal tube inserted into the central core of the shaft was located centrally at the top of the dissolution cell over the dissolving compact for a micro-pH probe. The micro-pH probe comprising a miniature glass/reference electrode had a hemispherical pH-sensitive tip that contacted the maximum area of the solid/liquid interface. The holder retaining the compact was screwed into the base of the dissolution cylinder. Surface pH data were recorded every 5 min. The probe contacted the interface for a 30 s period only and was removed between measurements. The authors claimed that the recorded pH value reflected an average pH over this hemisphere. This measurement method required a specific dissolution apparatus and formulation preparation for measuring the surface pH. For this reason, the method was not applied widely. However, this method yielded successful surface pH measurements in which the surface pH data were correlated with dissolution release data of the systems studied.

Another method published around the same time was the pH measurement of a slurry [32], in which it was established that the surface pH of a pharmaceutical solid corresponded to the pH of its saturated solution (or slurry). This method has since been used in many studies to investigate the pH_M, such that the pH of the concentrated suspension of the formulation in water was determined using a pH meter [42-45]. The name of the slurry pH method itself evokes a preparation in which the sample has significantly high water concentration. Moreover, the slurry pH is dependent on the concentration of the slurry if the compound is not highly pure. In this method, a known amount of solid, ~ 20 – 40% (w/w) in excess of its solubility, is added to a polypropylene centrifuge tube containing distilled water and mixed for 15 min [45]. The pH of suspension is then measured by potentiometry. The pH of the saturated aqueous phase of the suspension should be almost identical to the pH of the suspension, indicating that an equilibrium pH has been achieved. The pH of the concentrated slurry is considered to reflect the pH of the solid surface only, and this is a simple and reliable measurement that may closely represent solid surface pH.

A recent study by Pudipeddi *et al.* [45] compared the slurry method with the indicator dye-sorption method in the measurement of solid surface pH. Actually, this method was first reported over 50 years ago by Walling [46]. The solid surface pH is determined by comparing base/acid peak ratios of the UV-visible diffuse reflectance spectra (DRS) of adsorbed dyes on the solid with the calibration plots of dye solutions in aqueous standard buffers of known pH. In this technique, the spectrophotometer is equipped with an integration sphere for diffuse reflectance measurements. The color of the adsorbed dye is also compared with that in a solution of known pH [45,47]. The assumption of this technique is that the ionization constant (pK_a) of the indicator in the adsorbed state and the solution state remains unchanged or

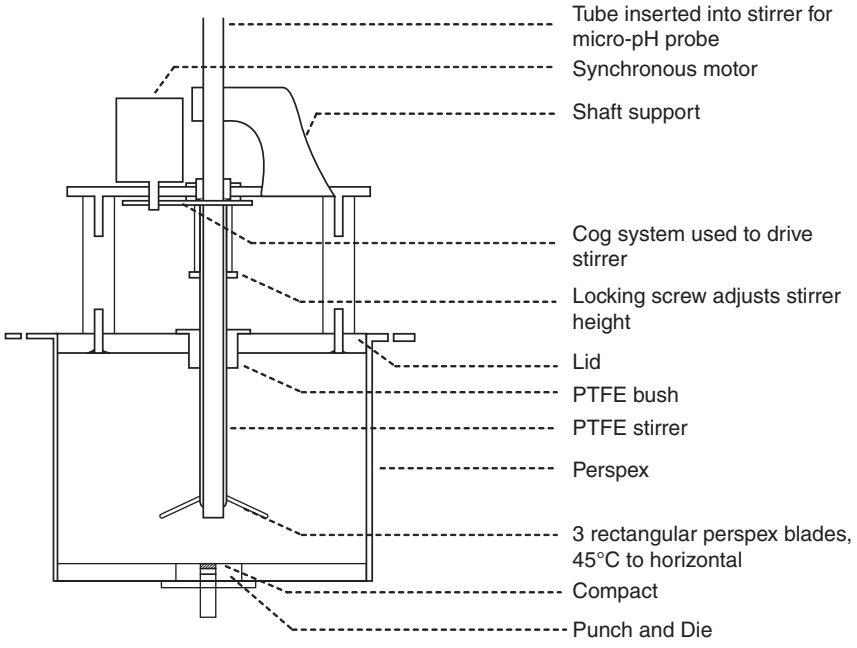

Figure 1. Cross-sectional diagram of modified dissolution apparatus to measure pH of a dissolving surface using a micro-pH probe.

changes in the same manner. Calibrations are generated with selected indicators to cover a wide working range of pH from acid to base. Some suggestions for the calibration were: i) the optimal indicator concentration had to be minimal, but the base/acid peak ratio was independent of indicator concentration and both acid and base peak heights were between 0.1 and 1.1 absorbance units; and ii) stock solutions (dissolved indicators in methanol/water mixture) should be diluted by buffers of sufficient buffer capacity in the pH range of each indicator [45]. The solid surface pH can then be estimated when the indicator stock solution at the same concentration as the concentration used in the calibration is added drop-wise to the solid (1 ml of indicator per gram of solid) and mixed. The solid is then air dried and placed in a cuvette to record DRS. The blank in this measurement is the solid treated in the same manner without indicator. One advantage of this method is that it can be carried out on a dry or nearly dry solid, whereas most other methods require a certain level of water for the mobility of the probe. However, the shortcoming of this method is that the solution state calibration plots may not always be applicable for calculating the solid surface pH, particularly when there is some extent of pK_a change, perhaps owing to the nature of the compound or the indicator used, as observed by the difference in color of the indicator in the adsorbed and dissolved states.

A spectroscopic technique reported by Siepe *et al.* [48], electron paramagnetic resonance imaging (EPRI), was originally used to evaluate pH_M inside pH-controlled matrix tablets containing pH-sensitive spin labels (nitroxyl radical MEP). EPRI also uses calibration plots in different buffer solutions over a pH range from acid to base to estimate the pH of the solid dosage form. Calibration samples had the same formulation and received the same treatment as sample tablets but without drug and pH modifiers. The EPR signal was recorded as a change in the spin density of the nitroxide group resulting from protonation of the spin label. This study monitored the pH_M of HPMC-based matrix tablets containing a weakly basic drug and an acidifier as a function of distance across the tablet. The spin label, MEP, was not suitable for determining pH values >pH 5.5. Moreover, pH_M could not be determined by this technique on some regions of the tablets without water penetration because of the limited mobility of the spin label molecule. Depending on the conditions of the experiment, such as sample size or formulation design, the sensitivity of spectrometers can be selected by choosing the X-band or L-band. For example, the L-band (1.5 GHz) had decreased sensitivity but increased penetration depth of microwaves into a sample imbibing water; thus, the L-band was used instead of the ordinary X-band (9 – 10 GHz) in this study because samples were <1 mm and the HPMC structure was not hydrated sufficiently in the early stages of the test. Therefore, this technique is limited to samples in the dry solid-state.

For pH_M investigations by optical observation, ~ 0.1% (w/w) of a pH-sensitive indicator, methyl red, was added to the matrix tablet [14,41,49]. Methyl red is yellow >pH 5.8 but maintains its red color in acidic conditions and is thus used to monitor the pH_M within the tablet during drug release. Tablets containing a weakly basic drug with an acidifier testing at pH 6.8 were obviously yellow at the edge but the

inner core was red, and vice versa with tablets containing weakly acidic drug and alkalizers. Such results proved that the pH modifier within the core of the solid dosage form can maintain an optimal pH_M for drug release behaviors during the dissolution. Another study by Pygall *et al.* [50] used Universal pH indicator to observe the gel layer colors of citrate-buffered HPMC matrices. Without buffer, the formulation had very little intrinsic buffering capacity (the red color indicated acidic pH). With 50% sodium citrate, the yellow color indicated that the pH had reached 6 throughout the gel layer of the matrix within 15 min, whereas the red color in some areas or in the entire dosage form indicated lowering of pH in the outer regions of the gel after 1 h or complete conversion to low pH after 2 h, respectively. Notwithstanding, this assessment was only a qualitative analysis. Another approach that not only provided high-resolution optical images but also allowed quantification of spatial distribution pH_M is confocal laser scanning microscopy (CLSM). Before Cope *et al.* [51] released their ratiometric CLSM method on hydrated immediate release pellets, other authors had used CLSM to assess pH distribution within microspheres; however, these earlier results were not fully quantitative for pH_M because there were no means of differentiating low fluorescein concentration from low pH, or they were only semi-quantitative because the fluorophores fluoresced only in the green range [52,53]. Cope *et al.* also indicated that application of pH-responsive fluorophores in CLSM was not limited to biodegradable microspheres. A pH microprobe was also placed on the pellet surface for pH validation and to investigate a correlation with the fluorescence method. Generally, the developed ratiometric CLSM method requires a fluorescent molecule possessing a suitable pK_a value in the pH range of interest, pH-dependent fluorescence at one wavelength for sensitive pH response, and pH-independent fluorescence at a second wavelength for use as an internal standard and determination of fluorophore concentration. The concentration range of the fluorescent probe is usually prepared over a range of pH to determine the fluorescent response with respect to pH and concentration. Predictive pH values can be calculated from the measured fluorescence intensities at dual wavelength as follows:

$$\mathrm{pH} = \left[\frac{-(F_1 - a_0)\alpha}{b_1 \ln\left(1 - \frac{F_2}{F_S}\right)} - \frac{b_0}{F_S} \right] \quad (3)$$

where F_1 and F_2 are the measured emission intensities (pixel intensity values) at pH-dependent and pH-independent fluorescence wavelength, respectively; F_s is the saturated fluorescence level obtained at high fluorophore concentrations; α (g/l) is a parameter obtained from the data; a_0 is a constant value obtained from the linear form showing the relationship between F_1 and the fluorophore concentration; b_1 and b_0 are the slope and the constant values obtained from a linearity of a gradient value (the slope of the above linear form) against pH, respectively. The CLSM still has limited application in dry solids and is not widely used for determination of tablet pH_M. This technique can be used to map spatially pH changes in various solid dosage forms and to observe directly the influence of both acidifiers and alkalizers on pH_M.

Regarding direct pH assessment, the method presented by Doherty and York [10] is scarcely considered because of its complicated apparatus. Some scattered studies have proposed direct methods for pH_M measurement. For example, a glass pH microelectrode tip was allowed to penetrate directly a hydrate matrix tablet so as to measure the pH_M at the center of the matrix and was held until a stable reading was obtained [34]. The latest method for direct pH_M determination, created by Siepe *et al.* [17], was easily performed and applicable to a dry solid and subsequently applied in recent studies [9,18]. In this method, the solid dosage forms (tablets or capsules) are removed from the dissolution medium at specific time intervals and immediately frozen. The pH_M is determined potentiometrically using a surface pH electrode. This pH meter differs from a typical meter in that it can directly measure the pH of a solid. Therefore, the equipment presented the opportunity to measure pH not only at the surface but also in the interior of each section of the solid dosage form. The gradient from the surface to the interior, maybe even to the center of the dosage form, can thereby be determined. For this reason, the solid dosage form is sliced and the sections are designated as a fractional distance (d/d_o) depending on the fractional dimension of the length of the dosage form. The pH_M is plotted against d/d_o only or as a function of time at different d/d_o. d_o is the distance from the edge to the center. For example, d/d_o can be symbolized as d/d_o = 0, 1/3, 2/3 or 1, where d/d_o = 1 represents the center, d/d_o = 0 indicates the edge (surface) and the others describe the inner regions of the tablet. **Figure 2** illustrates this pH_M determination on a tablet through different fractional sections.

4. Instrumental characterization and dissolution rate

The interaction among drug dissolution and release of pH modifier, structural behaviors and pH_M modulation is an intimate relationship. Two highly regarded methods for characterizing drug crystallinity are powder X-ray diffraction (PXRD) and differential scanning calorimeter (DSC) analyses. The disappearance of a melting peak in the DSC or a distinctive peak for the drug in the diffractogram in the SD systems indicates that the drug is present in amorphous form or that a high concentration of the drug is dissolved in the solid-state [54-57]. Generally, when the structure of the drug is more amorphous, greater increases in the drug dissolution rate from SD can be obtained. A simple method

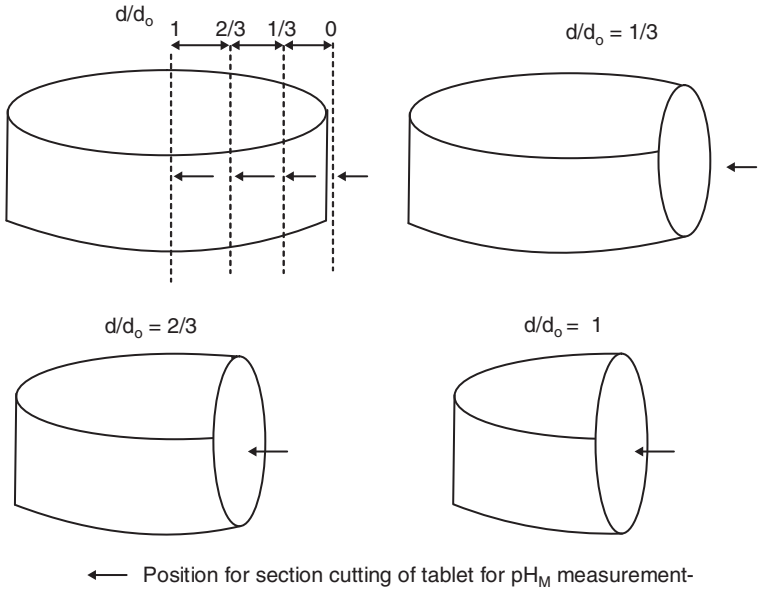

Figure 2. pH$_M$ determination on a tablet through different fractional sections.

to govern the drug crystallinity of SD is to increase the ratio of carrier to drug [58,59]. However, the addition of carrier cannot enhance drug release constantly until it reaches a particular level. In other words, the addition of carrier should be halted as the crystal structure of drug changes into totally amorphous, because more carrier will not increase the effect or may even inhibit drug release owing to harder diffusion or the growth of semicrystalline areas [4]. The fact that incorporation of only hydrophilic polymer and drug into SD with an appropriate preparation method and a high ratio of carrier-to-drug provides the best dissolution rate of drug is not as straightforward as it may appear. Although SD has an apparent total amorphous structure based on PXRD and DSC, drug dissolution in some cases cannot reach 100% release or improves only trivially or cannot be improved at all [9,18]. Strategies have been suggested to solve this problem, including incorporation of a secondary agent such as a copolymer or surfactant or simply changing the preparation method. Nevertheless, these strategies are beyond the scope of this paper and have been presented elsewhere. However, as mentioned above, an effective tool to enhance the dissolution rate of weakly basic or acidic drugs is the introduction of pH modifiers into SDs. In terms of its effects on drug structural behaviors, a pH modifier can promote an amorphous structure of SD or prevent recrystallization. Previously, the incorporation of an internal buffer system into SD, as reported by Doherty and York [10], showed none of the apparent surface recrystallization observed for the unbuffered formulation. Recently, the use of some alkalizers in the ternary Gelucire (GUC)-based SD of aceclofenac (AFC) was shown to increase effectively the amorphous structure of the binary GUC-based SD without alkalizer [9]. **Figure 3** illustrates the changes of PXRD patterns in drug structure by pH modifiers. GUC assisted the natural crystalline AFC in the binary SD to decrease some of the distinct peaks exposed in the PXRD diffractogram, indicating that the structure of drug changed from crystalline to partially crystalline. Ternary SDs, including alkalizers, changed drug structures into partially amorphous (bentonite, MgO, Na_2HPO_4, K_2HPO_4, $CaCO_3$ and arginine) or almost totally amorphous (meglumine, $NaHCO_3$ and Na_2CO_3). These alkalizers, except for bentonite, enhanced the drug release rate in gastric fluid over that of SD without alkalizer, although the extent of this enhancement depended on the type of alkalizer. The best enhancement of drug release was obtained with Na_2CO_3, the alkalizer that promoted the strongest structural changes into amorphous form. Therefore, in addition to modulating pH$_M$, the role of pH modifiers in promoting the carrier to change drug structural behaviors is indispensable in obtaining the highest dissolution rate. Tran *et al.* [9] also described a phenomenon named spring-like precipitation, which occurs because a drug has low supersaturation solubility in gastric fluid. They investigated a solution that prevented the precipitation by the addition of a secondary polymer. Interestingly, the addition of Poloxamer 407 not only prevented spring-like precipitation but also improved the AFC dissolution rate by >100%. The mechanism was explained by the fact that, in DSC and PXRD, AFC appeared in the quaternary SD system containing secondary polymers in a totally amorphous structure.

The same results were obtained in a previous report [18] in which the dissolution of poorly soluble Telmisartan (TEL) was enhanced in intestinal fluid by the incorporation of alkalizers in Polyethylene glycol (PEG) 6000 to form ternary

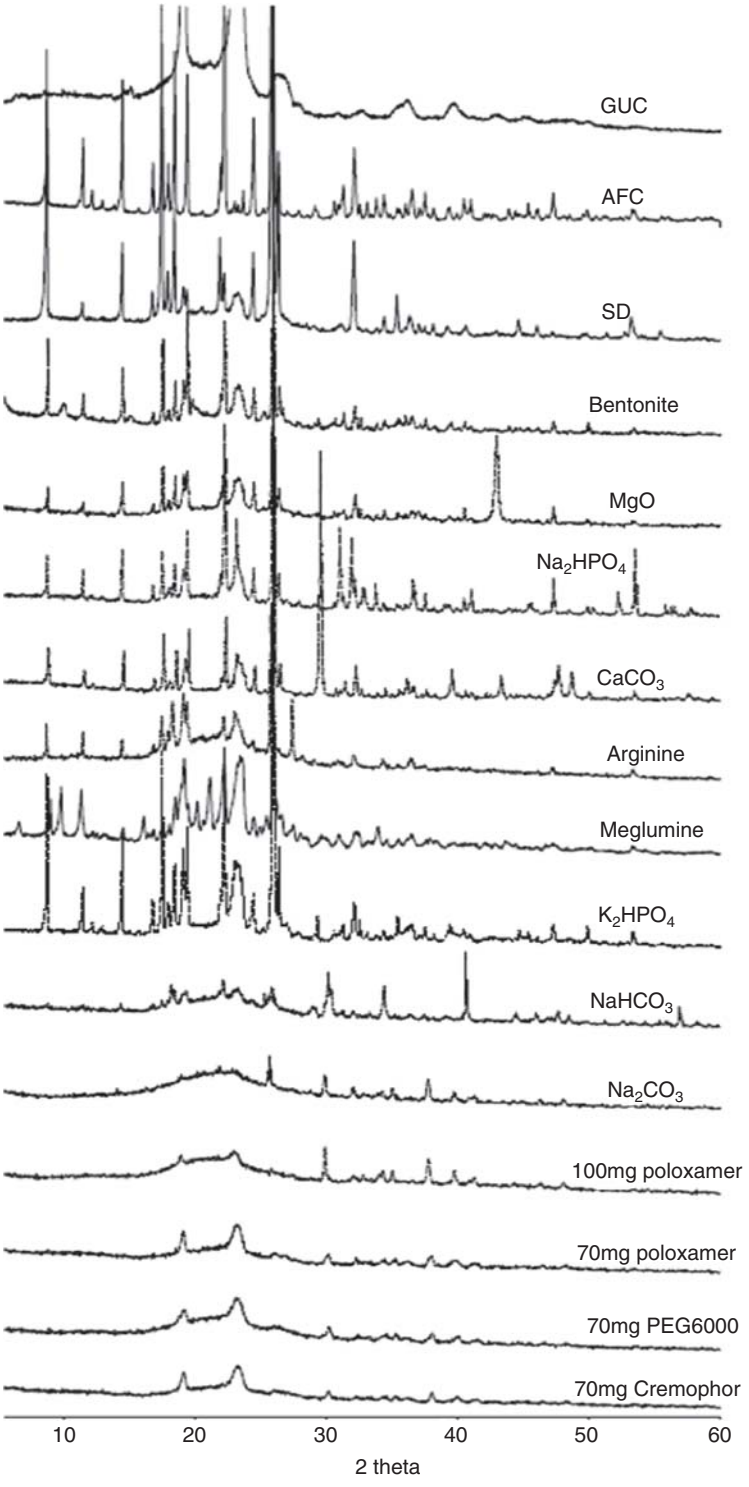

Figure 3. Powder X-ray diffraction patterns from the top: GUC, pure drug, binary SD (AFC and GUC), ternary SDs (AFC, GUC and one of the following alkalizers: bentonite, MgO, Na_2HPO_4, $CaCO_3$, arginine, meglumine, K_2HPO_4, $NaHCO_3$, Na_2CO_3), and quaternary SDs (AFC, GUC, Na_2CO_3 and one of the following secondary polymers: 100 mg Poloxamer, 70 mg Poloxamer, 70 mg PEG 6000, 70 mg Cremophor).

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AFC: Aceclofenac; GUC: Gelucire 44/14; SD: Solid dispersion.

Table 1. Physicochemical properties of some typical pH modifiers.

Acid type	pK_a at 25°C	Acidity (pH) at 25°C (aqueous solution)	Aqueous solubility (g/ml) at 20°C	Basic type	Alkalinity (pH) at 25°C (aqueous solution)	Aqueous solubility (g/ml) at 20°C
Fumaric acid	3.03;4.54	2.15 (0.5% w/v)	0.005	Sodium bicarbonate	8.3 (0.1 M)	0.091
Citric acid	3.13;4.76; 6.39	2.2 (1% w/v)	1.000	Sodium hydroxide	12 (0.05% w/v)	1.111
Succinic acid	4.21;5.57	2.7 (1.2% w/v)	0.077	Sodium citrate dihydrate	7 – 9 (5% w/v)	0.667
Tartaric acid	2.93;4.23	2.2 (1.5% w/v)	1.333	Potassium bicarbonate	8.2 (0.1 M)	0.357
Malic acid	3.4;5.05	2.35 (1% w/v)	0.500 – 0.666	Potassium hydroxide	13.5 (0.1 M)	1.111
Ascorbic acid	4.17;11.57	2.1 – 2.6 (5% w/v)	0.286	Magnesium oxide	10.3 (saturated)	Very slightly soluble

Data obtained from Handbook of Pharmaceutical Excipients.

SDs. The ternary PEG-based SD including alkalizers exposed the amorphous form, whereas the binary SD without alkalizers still showed crystalline peaks of drug. Structural changes of drug crystallinity into the amorphous structure by the alkalizers were considered a contributing factor for the enhanced dissolution of TEL in SDs. In addition, the latest research about the incorporation of acidifiers into SDs containing weakly basic drug elucidated that fumaric acid was the best among acidifiers for maintaining the structural amorphousness of PVP-based SD, and hence produced the best dissolution rate of drug [37].

The limitations of these instrumental analyses should be noted. First, crystallinity <2% generally cannot be detected with DSC, which may explain why the DSC thermograms of drug in the partially amorphous form cannot be detected [4]. For this reason, PXRD should also be carried out in order to explain more clearly the structural differences of alkalizers in SDs for enhanced drug dissolution. However, crystallinities of <5 – 10% cannot generally be detected with X-ray diffraction either [4].

Therefore, drugs in SDs containing pH modifiers should be investigated further with Fourier transform infrared spectroscopy (FTIR) at the molecular level because structural changes and the lack of a crystal structure can lead to changes in hydrogen bonding and van der Waals force between functional groups [4,9,18]. It is possible to differentiate between peaks that are sensitive to changes in crystallinity and those that are not through the IR spectrum [4,60]. However, there have been very few reports investigating the possible molecular interactions of functional groups contributing to pH_M. As indicated in the work of Tran *et al.* in 2009 [9], the FTIR spectra revealed a molecular interaction between AFC and pH modifiers resulting in changes in pH_M, drug crystallinity and dissolution. Specifically, the carboxylic acid O–H peak disappeared, implying deprotonation by means of a Bronsted acid–base interaction. Distinct absorption bands were absent with alkalizers that remarkably enhanced drug dissolution release and changed the drug into an almost totally amorphous form. Similarly, the report [18] about PEG-based SDs of TEL also showed that the drug frequency of the C=O band decreased and the O–H broad band in FTIR spectra disappeared when some alkalizers were added. These formulations also contained alkalizers that enhanced drug dissolution and promoted amorphous drug structure. The best enhanced dissolution was ascribed to the alkalizer magnesium oxide, which showed a strong molecular interaction that correlated with the highest pH_M. Interestingly, together with the measured pH_M value, the FTIR spectra elucidated why the formulation including the alkalizer, $NaHCO_3$, produced no amorphous drug structure change but did enhance dissolution. Therefore, possible interactions should be considered one of the mechanisms that enhance drug release from SDs containing pH modifiers.

5. Selection and applications of pH modifiers to enhance drug dissolution rate

Most of the pH modifier applications have introduced acidifiers into sustained release dosage forms of weakly basic drugs to obtain pH-independent drug release. The sustained release dosage forms were usually matrix tablets or pellets. The acidifiers used in those studies included citric, fumaric, tartaric, adipic, glutaric and succinic acids. The acidifier that possesses lower ionization constant (pK_a) and therefore higher acid strength, together with low aqueous solubility, has a high potential to produce lower pH_M values and thus to increase the release rates of weakly basic drugs. **Table 1** shows pK_a and aqueous solubility of some popular acidifiers and alkalizers. The most effective and frequently reported acidifier is fumaric acid, which enhances the release of ZK 811 752 from a single unit of the extended-release matrix forms of the poorly swellable mixture of polyvinylacetate/polyvinylpyrrolidone (PVA/PVP), the water-insoluble and almost unswellable ethylcellulose (EC), and the water-soluble and highly swellable hydroxypropyl methylcellulose (HPMC) [41], and from a multiparticulate extended-release mini-matrix tablet formed by PVA/PVP [49]; of dipyridamole from HPMC matrix tablets and matrix minitablets [17,35,48]; of verapamil hydrochloride from EC or HPMC matrix tablets [14] or from extended-release formulations based on the naturally

occurring polymer sodium alginate [61]. The second acidifier that has some marked effects on pH_M modulation is citric acid. The addition of citric acid to HPMC matrix tablets of pelanserin hydrochloride produced greater dissolution rates according to citric acid content [38]. However, this study suggested that the enhanced dissolution effect was mainly due to the formation of a porous matrix structure by citric acid. This explanation contrasted with that of Siepe *et al.* [17], who claimed that pH_M modulation is the main contributor to enhanced drug release. Spheronized citric acid crystals have also been used as starter cores in coated pellets containing propiverine and several layers of functional coatings [36]. The resultant extended-release pellets were able to maintain a low pH within the pellet core and hence sufficiently increased drug solubility. This preparation method prolonged the release of pH modifier that had a high aqueous solubility, but the fact that drug release could also be slowed in some cases should be considered. Furthermore, there are some studies in which alkalizers were incorporated with weakly acidic drugs in controlled-release dosage forms, although this type of incorporation was rarely reported. Rao *et al.* produced controlled-release matrix tablets for the weakly acidic drug divalproex sodium by compression of drug, HPMC and Eudragit E 100 or dibasic calcium phosphate [62]. Owing to the relative inability to elevate the pH and the shorter residence time of dibasic calcium phosphate in the matrix relative to Eudragit E 100, which is soluble at low pH and insoluble at higher pH, formulations containing the former were less effective than those containing the latter in terms of pH-independent drug release. However, this is not a typical case in which the best effect is expected to be an alkalizer because Eudragit E 100 is commonly used as a protective and taste-masking film-coating agent. Addition of magnesium hydroxide and magnesium oxide was subsequently found to maintain high pH_M within PVA/PVP mini-matrix tablets during release of 8-Prenylnaringenin at pH 1 over 10 h, resulting in pH-independent drug release [16]. Recently, a study reported the effects of the alkalizing buffer sodium citrate in HPMC matrices on accelerating the release of the weak acid felbinac in the immediate release phase, although the extended-release phase was dependent on the type of HPMC used [50].

Still, none of the systems mentioned introduced a SD-bearing dosage form. Actually, pH_M control of the dissolution behaviors of water-insoluble drugs in SD systems was applied widely a few decades ago. An internal buffer system comprising various disodium hydrogen orthophosphate and citric acid ratios incorporated into frusemide-polyvinylpyrrolidone SD was used to control the pH_M and, consequently, successfully increased the dissolution rate of weakly acidic frusemide in acidic media and retarded the rate in alkaline media [10]. The pH_M measured by a micro-pH probe during the dissolution of constant surface area disks showed a correlation with the drug dissolution rate independent of the dissolution medium pH. However, a higher phosphate/citric acid ratio and hence a higher pH_M could increase drug dissolution in acidic dissolution medium compared with that from the SD without the internal buffer system. On the other hand, a low phosphate/citric acid ratio led to a lower pH_M and reduced the dissolution rate, even in the high pH dissolution medium. Actually, the incorporation of both pH modifiers is quite unusual because an acidifier is normally introduced into a SD containing a weakly basic drug and vice versa. Preventing crystallization of the drug from the SD and pH modulation were factors governing drug dissolution in this study. Still, it is not clear how the inclusion of the buffer system in the SD is related to drug crystallinity. Although the author mentioned that the four components comprising the SDs can interact with each other and with the reactive dissolution medium, they did not prove any molecular interactions through any analysis such as FTIR.

Recently, there have been only three reports about SD systems including pH modifiers [9,18,37]. One is the incorporation of alkalizers in non-emulsifying PEG 6000-based SD, which readily modified drug crystallinity and pH_M of TEL, hence leading to enhanced drug release at pH 6.8 [18]. The special solubility properties of TEL over a range of pH have been investigated; the solubility of TEL at 37°C was ~ 521.55 μg/ml at pH 1.2 and 0.28 μg/ml at pH 6.8, but 491.56 μg/ml at pH 10. Thus, either alkalizer or acidifier could increase drug release. In a preliminary solubility study, they determined that, despite the slightly increased solubility with some acidifiers, alkalizers greatly increased TEL solubility. For this reason, nine alkalizers were investigated in pH_M modulation: MgO, NaOH, KOH, Na_2CO_3, $NaHCO_3$, bentonite, Na_2HPO_4, K_2HPO_4 and arginine. The weight ratio of alkalizers, drug and PEG 6000 used to prepare the ternary SDs was 1:8:24. Among the alkalizers, MgO, NaOH, KOH and Na_2CO_3 significantly increased the drug dissolution rate at pH 6.8. Modulation of pH_M was clearly observed as a function of time at different fractional dimensions of the tablet. Incorporation of alkalizers could adjust the pH_M inside the tablet to a highly basic value, especially MgO, which caused the highest pH_M of SD and hence best enhanced the drug release. Moreover, another major factor in the enhanced dissolution of TEL in SDs containing alkalizers was structural changes of drug crystallinity into an amorphous form by means of molecular interactions revealed through DSC, PXRD and FTIR analyses. This is also a special case where the incorporation of alkalizers did not enhance drug dissolution at pH 1.2, but did at pH 6.8 owing to the special drug solubility properties.

The second is the investigation of alkalizers and polymers in nanoemulsifying GUC 44/14-based SD containing weakly acidic AFC [9]. Ternary GUC-based SD containing alkalizers, mainly Na_2CO_3 and $NaHCO_3$, enhanced the initial release rate of AFC at pH 1.2; the release rate then gradually decreased owing to precipitation, a phenomenon that the author described as 'spring-like' precipitation. In addition to the structural change into totally amorphous form, the best modulation of dissolution rates by Poloxamer 407 was also

because of its high hydrophilic-lipophilic balance (HLB) value and surface-active properties, which decreased interfacial tension and droplet size as the surfactant concentration increased. Poloxamer 407 and Na_2CO_3 facilitated nanoemulsion formation (80 – 140 nm) at pH 1.2, as visualized by TEM, and hence prevented the precipitation. The quaternary SD system consisting of drug, GUC, Na_2CO_3 and Poloxamer 407 at a weight ratio of 70:70:28:70 successfully yielded complete dissolution of poorly water-soluble AFC. Furthermore, the authors claimed that modulation of pH_M and reduction of drug crystallinity into an amorphous form by alkalizers by means of molecular interactions were the main factors contributing to the enhanced dissolution rate. The presence of an alkalizer consistently increased pH_M. Na_2CO_3 produced the highest pH_M on the surface and inside SD-loaded capsules, which corresponded to the highest dissolution profile. Meanwhile, the pH_M produced by the rest of the alkalizers did not create a sufficiently basic environment; their effects on drug dissolution rates were therefore almost negligible. Interestingly, the incorporation of a secondary polymer such as Poloxamer 407 in SD-loaded capsules containing Na_2CO_3 gave almost identical pH_M. The pH_M decreased slightly as a function of time but changes were almost negligible. In contrast to the two SD systems above, alkalizers enhancing the release of the weak acid AFC at pH 1.2 obeyed the general rule of pH modifiers incorporated with ionizable poorly water-soluble drug. This research also recommended a drug solution with spring-like precipitation to provide a favorable nanoemulsion-forming environment in solution.

Another system conforming to the general rule that an acidifier can enhance dissolution of weakly basic drug is the latest report [37]. This research investigated the role of acidifiers in modulating drug structure profiles related to molecular interactions and pH_M in an 'amorphous' polyvinyl pyrrolidone (PVP)-based SD in the control of drug dissolution rates and compared with physical mixtures as well. Only fumaric acid maintained structural amorphousness of PVP-based SD as characterized by DSC and PXRD. Moreover, FTIR of this ternary SD also demonstrated, by the lack of NH and C=O peaks of IDP, that only fumaric acid produced intermolecular hydrogen bonding between drug and PVP, similar to that in the binary PVP-based SD. Thus, based on FTIR, DSC and PXRD studies, fumaric acid did not affect the amorphous formation of IDP and PVP. Hence, fumaric acid produced the best dissolution among the acidifiers, although all of them could create an acidic microenvironment. However, a simple physical mixture of acidifier with PVP was not efficient for improving dissolution rate of drug.

6. Conclusions

The influences of pH modifying agents on the drug release mechanism from SDs include the synergistic effects of pH_M modulation and the alteration of drug crystallinity to an amorphous form by means of possible molecular interactions, mainly hydrogen bonding and van der Waals forces. All of the factors are attributed to the enhanced dissolution release rate of weakly acidic drugs or weakly basic drugs from SDs bearing pH modifiers. Analyses such as DSC, PXRD and FTIR are common and simple analyses for physical characterization and investigation of molecular interactions, whereas pH_M determination and quantification of pH modifier release must be considered two very important tools for understanding the dissolution-modulating mechanisms in such pH modifier studies. The prerequisite condition of such successful systems is the selection of a suitable pH modifier based on the pH-solubility profile of the drug and the pH modifier's p*K*a and aqueous solubility. An optimal pH modifier is one that not only greatly modulates the pH_M of the solid dosage form at the best pH condition for high drug solubility, but also maintains this condition for a sufficiently long time. In general, a pH modifier-bearing SD consists of drug, pH modifier and polymer. However, depending on the intentional design of solid dosage form or an accidental phenomenon such as precipitation, the composition of the system can be adjusted. Under favorable conditions, pH modifiers not only enhance poorly water-soluble drug release but also stabilize the system by preventing recrystallization in some cases. **Figure 4** sketches out the typical pharmaceutical process for studying a SD system incorporating a pH modifier with a weakly basic drug or weakly acidic drug.

7. Expert opinion

Few studies of SDs bearing pH modifiers have been published so far. The dissolution-modulating mechanism of pH modifiers inside SD systems is different from that in other SD systems in which pH modifiers are introduced separately by means of other preparation methods. Incorporation of a pH modifier as a component of the SD has a remarkable effect on the structure and pH_M. The pros and cons of each technique should thus be considered. Indeed, instead of either ternary SDs bearing pH modifiers or extended-release dosage forms containing pH modifiers without an SD system, why not design a system that combines both approaches, such as a sustained-release dosage form containing a SD bearing pH modifiers? The diffusion of the pH modifier in this design can be slowed for sufficient pH_M generation to facilitate enhanced drug release during the long dissolution process. Such a solid dosage form design could be a highly effective treatment and easily produced. Regarding techniques for explaining the dissolution-modulating mechanism of pH modifier-bearing SDs, because of the shortcomings of DSC, PXRD and FTIR, other more specific instrumental analyses such as nuclear magnetic resonance (NMR), Raman spectroscopy and X-ray photoelectron spectroscopy (XPS) should be used to investigate thoroughly the physicochemical properties influenced by pH modifiers. Moreover, a direct method for pH_M determination on the surface and the interior

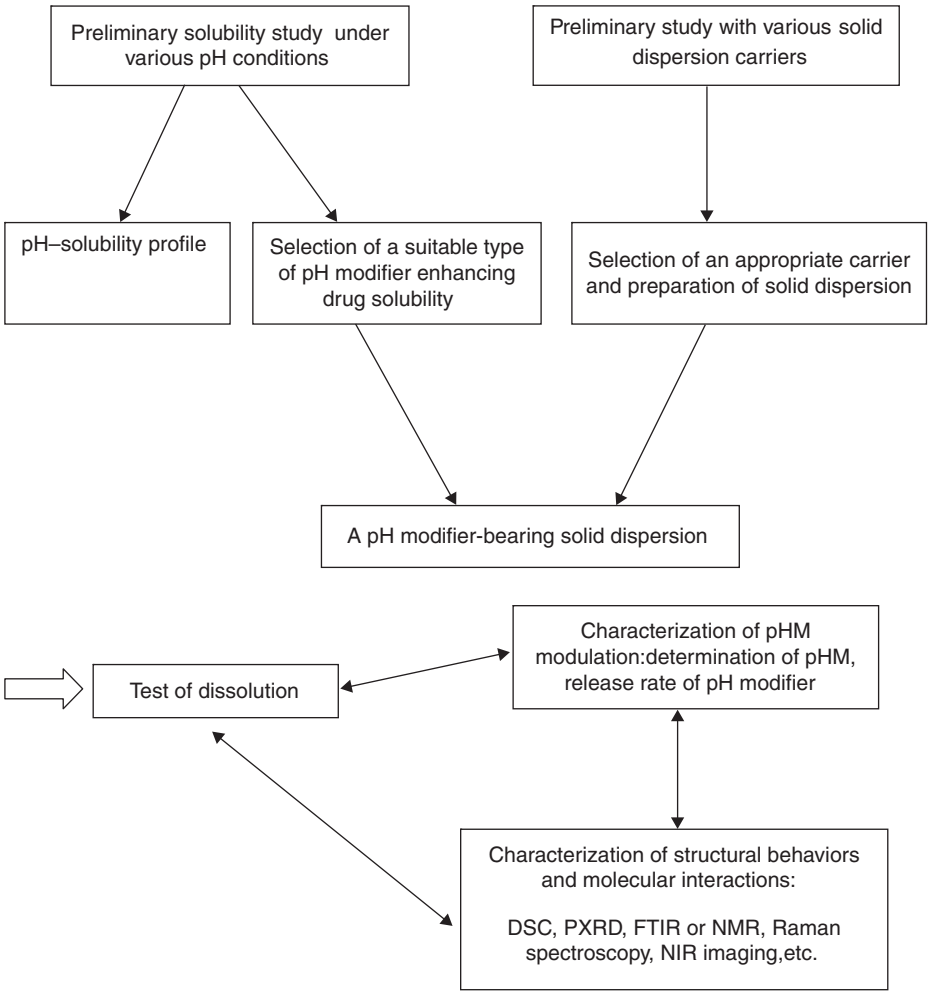

Figure 4. Typical pharmaceutical process for studying a solid dispersion system incorporating a pH modifier with a weakly basic drug or weakly acidic drug.

of the solid dosage form for both imaging and quantification purposes should be considered. For example, the technique for directly measuring pH at different fractional dimensions of a tablet might be coordinated with CLSM or some other high-resolution technique such as near-infrared (NIR) imaging or Raman imaging to identify the distribution of the components.

A matter that has not been mentioned in research of pH modifiers is the possibility that pH modifiers could cause gastrointestinal irritation. For this reason, an *in situ* test to observe potential gastrointestinal damage in laboratory animals should be included in future studies of such pH modifier-bearing SD systems. Once the mechanism is fully understood and a system for effective and safe treatment has been designed, this pH modifier-bearing SD can be widely applied to overcome some the obstacles of a conventional SD. Above all, an 'active' or functional SD will be a key in future perspectives for controlled release of not only one poorly soluble drug but also two or more active substances, including other poorly soluble drugs, in the same formulation, single unit or even multiparticulate, for scheduled and targeted treatment through clever pH modulation sequences.

Finally, the bottom line of an effective pH-modified SD is the way that may come from an approach that does not obey any regular rule. The drug properties are diversified and create an interesting area for formulation investigation, especially the pH-dependent poorly water-soluble drugs. The introduction of acidifiers into SDs of weakly basic drugs may be not always right, and vice versa. In other words, the approaches could be interchanged in some specific cases. Moreover, the success of a pH-modified SD system could be obtained only in a compatible moiety of the pH modifier and the carrier because the fact that pH modifiers could induce the crystallinity or inhibit the carrier structure to an amorphous state is considered an obvious phenomenon. Regarding this

point, the amorphous or crystalline state of drug probably is not always the main factor attributed to the enhanced drug release from these pH-modified systems, in which the pH plays a major role. Last but not least, an evaluation of *in vivo* research should be performed as an invaluable tool to affirm the effect of these pH-modified SD systems.

Declaration of interest

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