ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 209–213

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Surface acidity of solid pharmaceutical excipients III. Excipients for solid dosage forms

Carl-Alexander Scheef[a], Dieter Oelkrug[b], Peter C. Schmidt[a,*]

[a]*Department of Pharmaceutical Technology, Eberhard Karl University, Tübingen, Germany*
[b]*Institute for Physical and Theoretical Chemistry, Eberhard Karl University, Tübingen, Germany*

Received 10 August 1997; accepted 14 January 1998

Abstract

The surface acidities of pharmaceutical excipients are detected by color changes of acid–base indicators on the substrate's surface. To quantify the indicator's transition interval on the surface of hydrophilic excipients, as an organic solvent methanol is introduced for the preparation of indicator–excipient mixtures. The influence of the particle size on the determination of the surface acidity is investigated and particle size did not influence the determination within the particle size range investigated. Surface acidities of common excipients used in preparation of solid dosage forms are presented. © 1998 Elsevier Science B.V. All rights reserved

Keywords: Surface acidity; pH-Stability; Pharmaceutical excipient; Filler; Binder; Disintegrant; Lubricant; Effervescent tablet

1. Introduction

The stability of hydrolytic sensitive drug substances in solid dosage forms is influenced by the pH of the surrounding medium [1]. In solution, drug substances show a characteristic pH–stability profile. In solid products the situation seems to be similar [2,3]. Hydrolyzable drugs show characteristic incompatibilities with certain excipients. Little is known about the acid or alkaline properties of solid excipients used in solid dosage forms. The acid–base properties of a solid are usually detected electrochemically by the pH of a 1% or 10% suspension [4]. Due to electrochemical interactions of the solid particles with the electrode, such a method of determination is not correct [5]. Glombitza et al. described a new method to determine the acid–base properties of pharmaceutical excipients [6]. According to these workers the surface acidity of a substance is described as the ability to convert an adsorbed indicator base into its conjugated acid. However, this method has been applicable only to excipients insoluble in water. As many pharmaceutical excipients are water-soluble or swellable, a new method has been developed to determine the surface acidities of hydrophilic substances.

The conversion of the indicator into its conjugated acid is detected by the UV-VIS diffuse reflectance spectrum of the indicator–excipient mixture. Although the spectra are recorded as the relative diffuse reflectance related to a sample without indicator, the influence of particle size on the diffuse reflectance spectra has to be examined. As the scattering coefficient is dependent on the wavelength and the particle size [7] and since pharmaceutical excipients show a wide range of particle sizes, the aim of the study is to show that the resulting pH-equivalent (pH_{eq}), expressing the surface acidity, is independent of the particle size of the sample.

2. Materials and methods

2.1. Materials

Indicators used were: bromocresol green, bromophenol

* Corresponding author. Department of Pharmaceutical Technology, Eberhard Karl University, Auf der Morgenstelle 8, 72076 Tübingen, Germany. Tel.: +49 7071 2972462; fax: +49 7071 295531.

0939-6411/98/$19.00
PII S0939-6411(98)00025-3

blue, bromoxylenol blue, chlorophenol red, cresol red, thymol blue and *p*-xylenol blue, all from Merck (Darmstadt, Germany).

Fillers and binders used were: Avicel® PH 101, 102, 105, 200 (FMC Corporation, Philadelphia, PA, USA); Vivacel® 101 and 102 (J. Rettenmaier and Söhne, Ellwangen, Germany); Lactose D30® and Granulac 200® (Meggle, Wasserburg, Germany); Lactose DCL 21®, DCL 11®, 100 M®, 200 M® (DMV, Veghel, The Netherlands); sorbitol (Deutsche Hydrierwerke, Rodleben, Germany); Karion Instant®, mannitol, xylitol and lactitol (Merck); Neosorb® (Roquette, Lestrem, France).

Disintegrants used were: Ac-Di-Sol® (FMC Corp.); Nymcel ZSX®, ZSB-16® and ZSB-10® (Metsä-Serla, Nijmegen, Netherlands); Kollidon CL® (BASF, Ludwigshafen, Germany); ECG 505® (Nichirin Chemical Ind., Tokyo, Japan); L-HPC® (Shin-Etsu Chemical Corp., Tokyo, Japan).

Natural and modified starches used were: potato starch, wheat starch and maize starch (Roquette); Explotab® (Eastman Kodak, Kingsport, USA); Starch 1500® (Colorcon, Orpington, UK).

Lubricants investigated were: magnesium stearate (Bärlocher, Munich, Germany); stearic acid and calcium arachinate (Caelo, Hilden, Germany); talc (Norwegian Talc, Bad Soden, Germany); glycerol tristearate (Dynamit-Nobel, Troisdorf, Germany); polyethylene glycol (Hoechst, Frankfurt, Germany). Solvents used were freshly distilled water and methanol LiChroSolv® from Merck.

2.2. Instrumentation

The UV-VIS spectra were recorded using a Lambda 16® (Perkin Elmer, Überlingen, Germany) spectrometer equipped with an integration sphere, as previously described by Glombitza et al. [6].

2.3. Preparation of samples using methanolic indicator solutions

Samples were prepared using methanolic indicator solutions. The indicator was dissolved in methyl alcohol and 5.0 ml of the indicator solution were mixed with 15 g of the excipient using pestle and mortar. The wetted mass was dried for 12 h at 50°C in a tray-dryer. The dried mixtures were broken down in a mortar using a pestle and stored for 2 weeks at room temperature over a saturated sodium bromide solution (59% r.h.). A reference sample was prepared in the same manner using methyl alcohol without indicator for the background correction of the UV-VIS spectra.

2.4. Preparation of samples using aqueous indicator solutions

Samples of microcrystalline cellulose, Avicel PH 101®, were prepared using aqueous indicator solutions as described by Glombitza et al. [6]. 35.3 mg bromophenol blue were suspended in 5 ml ethanol and 30 ml of water were added. The pH of the suspension was adjusted to pH 7 using 0.1 N sodium hydroxide solution. The suspension was treated for 5 min in an ultrasonic bath and filled up to 100.0 ml with distilled water. 15 g Avicel PH 101® were wetted with 5 ml of the aqueous indicator solution, mixed and treated as described above which resulted in an indicator load of 0.144 mg g^{-1}.

2.5. Preparation of the samples of different particle size

Microcrystalline cellulose samples of different particle sizes were prepared using commercially available Avicel®-types. All samples were prepared as described above using the methanolic bromophenol blue indicator solutions resulting in an indicator load of 0.114 mg g^{-1}. Sorbitol was fractionated via sieving into fractions larger than 350 μm, from 350 to 180 μm and from 180 to 90 μm using a Retsch sieve tower. A sample of 100 g was sieved for 5 min. The particle size distributions were analyzed using a laser diffraction particle analyzer (Sympatec, Clausthal-Zellerfeld, Germany). Samples of the various sorbitol fractions were prepared using the methanol procedures described above.

2.6. Spectra and analysis

The spectra were recorded as described by Glombitza et al. [6]. First the solvent treated excipients were transferred into the two 5-mm pathlength quartz cells and a background correction from 850 to 250 nm was performed. Then the indicator–excipient mixture was transferred into one of the quartz cells and the spectra were recorded against the solvent treated excipient as reference. In order to account the influence of scattered light, a Kubelka–Munk-transformation of the spectra was performed. The peak ratio was calculated from the indicator's long wavelength peak maximum divided by the indicator's short wavelength peak maximum. This peak ratio was correlated with peak ratios obtained from the aqueous indicator solutions at different pH-levels. The steps of the method are shown in Fig. 1.

3. Results and discussion

3.1. Determination of the surface acidity of water soluble excipients

The determination of the surface acidity presented by Glombitza et al. [6] is not applicable to hydrophilic excipients. The indicator-loaded samples were prepared using aqueous indicator solutions so that the excipient could be dissolved or swelling could take place. It is preferable, however, if the surface acidity shall express the properties of the

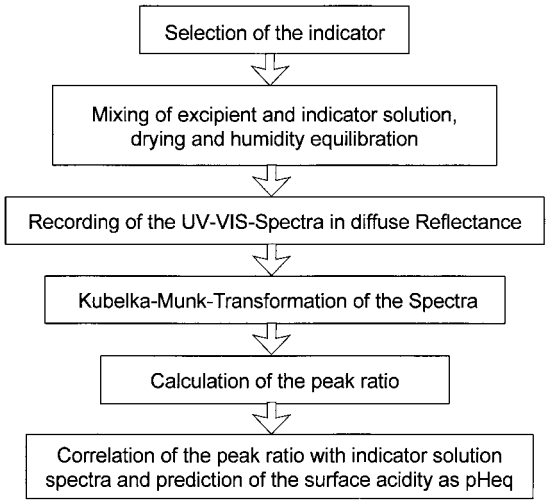

Fig. 1. Unit operations for the determination of the surface acidity.

samples as used in the formulation of solid dosage forms. Thus for the preparation of the excipient–indicator mixtures of water-soluble substances an organic solvent, no change in surface properties is required. Methanol is a suitable solvent for the indicator; however, it is not only a poor solvent for most of the excipients but it is highly volatile and UV-inactive. To evaluate the influence of the methanol on the diffuse reflectance spectra, both methods were compared. The diffuse reflectance spectra of Avicel PH 101®-bromophenol blue mixtures prepared with an aqueous indicator solution and a methanolic indicator solution are shown in Fig. 2. The peak intensity of the indicator's spectra is slightly different than the aqueous spectra. The variation may be attributed to a difference in distribution pattern of the indicator on the surface of the microcrystalline cellulose. However, the peak ratio and the resulting surface acidity are the same. The influence of the methanol and its amounts were also investigated with lactose, but significant influence on the spectra was not observed. It can be concluded that methanol is an appropriate solvent for the preparation of water-soluble or water-swellable samples.

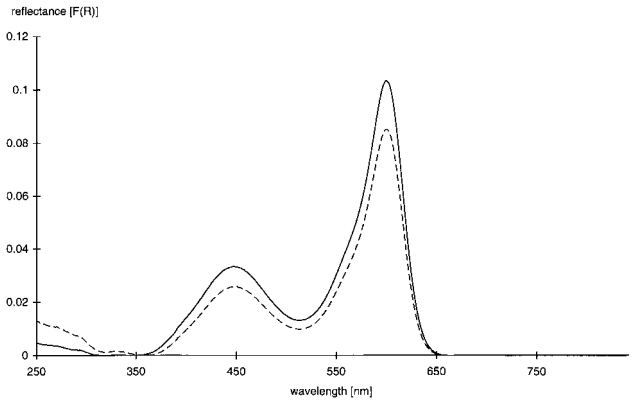

Fig. 2. Diffuse reflectance spectra of Avicel PH 101® bromophenol blue mixtures prepared with aqueous indicator solution (———) and methanolic indicator solution (- - -).

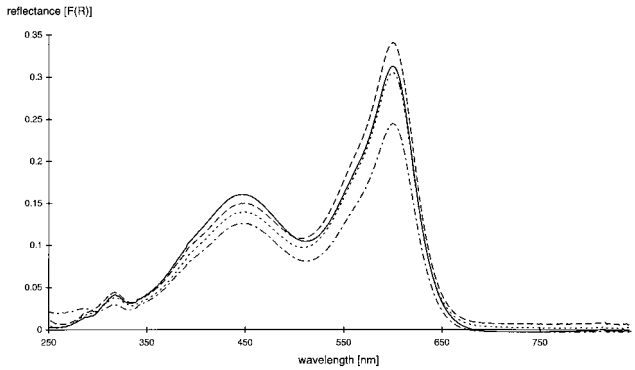

Fig. 3. Diffuse reflectance spectra of Avicel PH 101® (———), Avicel PH 102® (- - -), Avicel PH 105® (– – –) and Avicel PH 200® (– – –) with bromophenol blue (0.144 mg g^{-1}).

3.2. Influence of particle size

The diffuse reflectance spectra of microcrystalline cellulose and sorbitol indicator mixtures of different particle sizes were compared. Dye absorption measured from diffuse reflectance is not only a function of dye concentrations in acid or basic form but also of the scattering and absorption properties of the supporting excipient. The reflectivity and the scattering coefficient of the excipient decreases with particle size and the absorptivity in the UV increases. As a consequence the absolute intensities of the diffuse reflectance spectra depend on particle size, as shown in Fig. 3. It should be noted, however, the peak ratios are almost constant for all samples.

The most important factor to be considered in the determination of diffuse reflectance spectra is the particle size, i.e. the particle size of the reference as well as the sample. Reference samples of different particle sizes that are used for the background correction can lead to a distortion of the spectra, resulting in a wrong peak ratio. Unequal particle sizes lead to a deviation of the reflectance, particularly at long wavelength, where the indicator shows no absorption. The reflectance between 750 and 850 nm therefore has to be within a limit from 95% to 105% in the scanning mode, so that a distortion of the diffuse reflectance spectra of the excipient–indicator mixtures is excluded. The results of the surface acidities of the Avicel®-types and the sorbitol

Table 1

Surface acidities of microcrystalline cellulose and sorbitol of different particle size

Sample		Mean particle size (μm)	Peak ratio	Surface acidity (pH_{eq})	95% confidence
Avicel®	PH 200	38	2.2757	3.95	0.0029
	PH 101	30	1.9603	3.88	0.0022
	PH 102	29	2.1975	3.94	0.0030
	PH 105	16	1.9130	3.88	0.0140
Sorbitol	>350 μm	362	3.3782	4.14	0.0110
	180–350 μm	234	3.8568	4.21	0.0063
	90–180 μm	125	3.9590	4.23	0.0068

Table 2

Surface acidities of fillers and binders

Excipient	Indicator	Ind. load	pH_{eq}	95% confidence
Avicel PH 101®	bpb	0.114	3.88	0.0038
Vivacel 101®	bpb	0.114	3.83	0.0321
Vivacel 102®	bpb	0.114	3.81	0.0060
Lactose D30®	bpb	0.114	3.17	0.0465
Granulac 200®	bpb	0.114	3.42	0.0525
Lactose DCL 21®	bpb	0.114	3.31	0.0371
Lactose DCL 11®	bpb	0.114	3.48	0.0291
Lactose 100 M®	bpb	0.114	3.60	0.0189
Lactose 200 M®	bpb	0.114	3.42	0.0075
Sorbitol DHW®	bpb	0.114	4.21	0.0110
Karion instant®	bpb	0.114	3.27	0.0355
Neosorb®	bpb	0.114	3.55	0.0424
Mannit	bpb	0.114	3.23	0.1195
Xylit	bpb	0.114	3.36	0.1933
Lactit	bpb	0.114	3.10	0.1336

fractions are shown in Table 1. Differences of 0.07 for the Avicel® types and 0.09 pH_{eq} for Sorbitol were found to be significant according to an analysis-of-variance test, but with no relevant influence. Thus when the sample and the reference are of equal particle size, the influence of the particle size on the determination of the surface acidity can be ignored.

3.3. Surface acidities of excipients for solid dosage forms

The surface acidities of commonly used fillers and binders are shown in Table 2. The data were obtained from three independent samples and the mean of three replications. Surface acidities between 3.0 and 4.2 pH_{eq} are shown. Among the excipients listed, the spray-dried Karion Instant® shows the most acidic surface, followed by Neosorb®, which is crystallized from a melt. Sorbitol DHW® is a highly crystalline product, dried conventionally and showing a neutral pH_{eq}. As noted above, the different Avicel® types show negligible differences and even a microcrystalline cellulose from another supplier, Vivacel®, shows the same surface acidity. Surprisingly, the lactose samples show little variation in surface acidity, irrespective of their modifications and different suppliers.

Table 3

Surface acidities of disintegrants

Excipient	Indicator	Ind. load (mg/g)	pH_{eq}	95% confidence
Ac-Di-Sol®	cpr	0.083	4.79	0.0271
Nymcel ZSX®	bcg	0.2	4.11	0.0050
Nymcel ZSB-16®	bcg	0.2	4.88	0.0229
Nymcel ZSB-10®	bcg	0.2	4.89	0.0260
Kollidon CL®	bpb	0.114	4.25	0.0113
ECG 505®	bpb	0.114	3.69	0.0057
L-HPC®	cpr	0.083	4.6	0.0127
Potato starch	bcg	0.2	4.49	0.0265
Wheat starch	bcg	0.2	4.77	0.0078
Maize starch	bcg	0.2	4.9	0.0048
Explotab®	bcg	0.2	4.6	0.0060
Starch 1500®	bcg	0.2	4.2	0.0048

Most compressed solid dosage forms contain a disintegrant beside the drug substance itself and a filler or binder. Therefore, the surface acidities of commonly used disintegrants and natural starches were analyzed. The results are shown in Table 3. Because of the variation in their chemical nature, the disintegrants show larger differences in the surface acidities. Ac-Di-Sol® and the Nymcel®-types are both sodium carboxymethylcelluloses (CMC). Nymcel ZSX® is a cross-linked CMC-type showing a lower surface acidity than the linear types Nymcel ZSB-16® and ZSB 10®. The difference in the degree of substitution of Nymcel ZSB 10® and 16® seems to have no influence on the surface acidity. The calcium salt, CMC ECG 505®, shows significant lower surface acidities as compared to the sodium salts. L-HPC®, a hydroxypropyl cellulose of low molecular weight, having a surface acidity of 4.6, is in the same range as those of the CMC-types. Kollidon CL®, a cross-linked povidone, has a surface acidity of 4.25. The natural starches show all surface acidities between 4.5 and 4.9. Surprisingly, Explotab®, a sodium starch glycolate, shows no deviation, with a surface acidity of 4.6. Starch 1500®, a pregelatinized starch, has a more acidic surface, showing a pH_{eq} of 4.2.

Table 4

Surface acidities of lubricants

Excipient	Indicator	Ind. load (mg/g)	pH_{eq}	95% confidence
Magnesium stearate	cpr	0.083	5.12	0.0749
Stearic acid	p-xb	0.13	2.04	0.0219
Talc	bxb	0.21	6.08	0.0527
Calcium arachinate	bcg	0.2	4.81	0.1138
Glycerol tristearate	p-xb	0.13	2.19	0.0033
Polyethyleneglycol 6000	cpr	0.083	5.02	0.287

Another group of excipients used for tableting are lubricants. The pH_{eq} results are shown in Table 4. Although they are usually used in low concentrations, their acid properties could have a certain influence. The results are of particular interest, due to their poor wettability. Surprisingly, the alkaline earth metal salts of fatty acids, magnesium stearate and calcium arachinate, show less alkaline properties than expected. The stearic acid itself as well as its ester, glycerol tristearate, show very low surface acidity, probably due to free fatty acids. Polyethylene glycol 6000 as a lubricant shows a more or less neutral surface acidity. Talc, a lubricant known for its basic properties, shows a surface acidity of 6.08, being the most basic of the lubricants investigated.

For the formulation of effervescent tablets, an acid source and a carbon dioxide source are required. The surface acidity of these substances is presented in Table 5. Alkali carbonates are usually used as carbon dioxide-producing

Table 5

Surface acidities of effervescent components

Excipient	Indicator	Ind. load (mg/g)	pH_{eq}	95% confidence
Sodium carbonate	tb		8.58	0.0044
Sodium bicarbonate	tb		8.27	0.0240
Potassium bicarbonate	cr		8.05	0.0060
Trisodium citrate	bpb	0.114	3.84	0.0435
Disodium citrate	bpb	0.114	3.76	0.0314
Monosodium citrate	p-xb	0.13	2.1	0.0106
Citric acid	p-xb	0.13	1.45	0.0036

components. Here the potassium carbonates are less alkalinic compared to the sodium salts. The carbonates show more alkaline properties compared to the bicarbonates. The acid components are usually citric acid or salts thereof. The surface acidities of citric acid and its sodium salts are significantly influenced by the dissociation behavior of the salts, trisodium citrate showing a surface acidity of nearly 4 pH_{eq} and citric acid being very acidic with 1.45 pH_{eq}.

4. Conclusions

The stability of solid dosage forms containing hydrolytic sensitive drug substances is influenced by the choice of excipients. The surface acidity of the excipients will be one criterion for the selection of excipients in preformulation studies so as to achieve stable formulations. The presented list of surface acidities for common excipients may help to choose the ideal excipient for a given drug substance with a known pH–stability profile.

Acknowledgements

Thanks are due to the Deutsche Forschungsgemeinschaft which sponsored this project by grant No. Schm 1007/2–1. We also acknowledge the support by Perkin Elmer Bodenseewerk (Überlingen, Germany). Effervescent components were analyzed in cooperation with N. Yürtseven, Bayer AG, Leverkusen.

References

[1] J.T. Carstensen, Drug Stability Principles and Practices, Marcel Dekker, New York, 1990, pp. 155.
[2] B.W. Glombitza, P.C. Schmidt, Surface acidity of solid pharmaceutical excipients. II. Effect of the surface acidity on the decomposition rate of acetylsalicylic acid, Eur. J. Pharm. Biopharm. 41 (1995) 114–119.
[3] W. Grimm, Reaktionskinetische Untersuchungen mit festen Darreichungsformen, Teil 2: Praktische Beispiele, Pharm. Ind. 41 (1979) 385–390.
[4] M. Bertoni, F. Ferrari, M.C. Bonferoni, S. Rossi, C. Caramella, Functionality tests for tablet disintegrants: the case of sodium carboxymethylcelluloses, Pharmaceutical Technology Europe, November, 1995, pp. 17–24.
[5] G. Lee, D. Dick, E.M. Vasquez, K. Werner, pH measurements of suspensions, in: M.H. Rubinstein (Ed.), Pharmaceutical Technology Drug Stability, Wiley, New York, 1989, pp. 113–117.
[6] B.W. Glombitza, D. Oelkrug, P.C. Schmidt, Surface acidity of solid pharmaceutical excipients I. Determination of the surface acidity, Eur. J. Pharm. Biopharm. 40 (1994) 289–293.
[7] G. Kortüm, Reflexionsspektroskopie, Springer, Berlin, 1969.