Original Article

Correlation of *in vitro* dissolution rate and apparent solubility in buffered media using a miniaturized rotating disk equipment: Part II. Comparing different buffer media

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ABSTRACT: A correlation of the logarithmic values of the *in vitro* dissolution rate, *G*, and apparent solubility, *S*, was made for seven different drug substances from all of the classes in the Biopharmaceutics Classification System (BCS), in four different phosphate buffers. The effect of inorganic salts added as sodium chloride, sodium nitrate, sodium phosphate and sodium sulfate in the buffer media was investigated for the correlation. Triethanolammonium acetate buffer was also included in the study of the correlation of log*G vs.* log*S*. The pH was 7.0 ± 0.1 in all of the buffers to mimic a pH condition in intestinal fluids.

The dissolution rate was determined with a newly constructed miniaturized rotating disk equipment, which enables fast determinations and consumes only minute quantities of substance (about 5 mg). The solubility was determined by conventional shake-flask methodology, using 1.5 mL solution volumes. All quantifications were performed with reversed phase high-performance liquid chromatography (RP-HPLC) and diode array detection (DAD).

The different inorganic anions seemed to affect the solubility more than the dissolution rate. The phosphate and nitrate ions decreased the solubility for amines compared to the chloride ion. The best correlations of log*G* and log*S* were however obtained with a triethanolammonium acetate buffer. The good correlation (R^2 = 0.991) may be sufficient in initial screening of drug solubility, based on dissolution rates in aqueous buffer media.

Keywords: Dissolution rate, solubility, *in vitro* models, correlation, HPLC (high-performance liquid chromatography)

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1. Introduction

The dissolution rate for a drug substance that goes into solution in the gastrointestinal (GI) tract is one of the important factors for systemic absorption of the drug using oral administration (*1*). This dissolution is a complex process and the factors affecting it can generally be divided into three sections (*2,3*). Physicochemical properties of the drug represent the first part *i.e.* pK_a, solubility, stability, diffusivity and lipophilicity. Physiological factors characterize the second part and include GI pH, gastric emptying, intestinal transit, GI blood flow, gut wall metabolism, active transport including drug efflux and other absorption mechanisms. Moreover surface tension, solubilisation, osmolality, viscosity, buffer capacity and the volume of the luminal content play a vital role for the dissolution (*4,5*). The third part comprises the formulation factors *e.g.* surface area and drug particle size, crystal form, salt formulation and type of dosage form. Kinetic factors concerning the drug dissolution as described by the Noyes-Whitney model (*6-10*) are dependent on the three parts stated above. The physiological factors will in addition vary with the position in the gastrointestinal tract, as well as by the ingestion of food (*11*).

It has been found that the ionic strength can affect drug solubility and dissolution (*12-14*). The so called common ion effect can also have an impact on dissolution and solubility for *e.g.* hydrochloride formulated weak bases in chloride containing solutions (*15-17*). The effect on solubility and dissolution rate of different added ions in the media have been investigated (*16-19*), however only few studies (*13,20-22*) were found to use anions as additives to a buffer as in this study.

The experimental medium composition is a key for obtaining a good *in vitro-in vivo* correlation (IVIVC), where drug solubility and permeability are principal parameters according to the Biopharmaceutics Classification System (BCS) (*23*). *In vitro* dissolution testing is used at several stages during the drug

development. Valuable information can thereby be achieved for the drug substance itself (by the rotating disk method) or for a certain formulation (by USP apparatuses), and for the selection of appropriate excipients in a formulation (*24*). The effect of buffer media composition on the *in vitro* solubility and dissolution have been studied extensively (*25-28*) and the type of buffer can have a pronounced effect on dissolution and solubility of a substance (*13,29*). The composition of biorelevant media are now based on maleate buffers (*30*), but phosphate buffer has traditionally been used in the fasted state simulated intestinal fluid (FaSSIF) and acetate buffer in the simulated fed state intestinal fluid (FeSSIF) (*27*).

In this study, based on the Noyes-Whitney equation, the correlation of the logarithmic values of the *in vitro* dissolution rate, *G*, and the apparent solubility, *S*, was evaluated. Seven different test substances and five different buffer media were used in the correlation studies. To be physiological relevant, a pH of 7 was chosen since this mimics a pH in intestinal fluids as well as gastric pH under some conditions (*11*). The triethanolammonium acetate buffer was chosen to obtain a high buffer capacity at pH 7.0 compared to ammonium acetate buffer, which has a very low buffer capacity at this pH (*31*). Different anions were added to a phosphate buffer in this study to investigate if this generates an effect on dissolution rate and/or solubility, at a constant ionic strength. The aim of the study was to evaluate the possibility to predict the solubility in different aqueous buffer media from the dissolution rate, determined by a miniaturized rotating disk equipment.

2. Materials and Methods

2.1. *Chemicals*

Naproxen met USP specifications, enalapril maleate, nortriptyline hydrochloride, chlorprotixene hydrochloride, clomipramine hydrochloride, prednisone, bendroflumethiazide and terfenadine were minimum 98%, carbamazepine 99%, sodium chloride (NaCl) minimum 99.5%, sodium nitrate ($NaNO_3$) minimum 99.0% di-sodium sulfate (Na_2SO_4) ACS Reagent Grade, all from Sigma-Aldrich (Chemie GmbH, Steinheim, Germany). Sodium di-hydrogen phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$) *p.a.*, Acros Organics (Springfield, NJ, USA), di-sodium hydrogen phosphate dihydrate ($Na_2HPO_4 \cdot 2H_2O$) *p.a.* and trifluoroacetic acid ≥ 99.0%, both from Fluka Chemika (Chemie GmbH, Buchs, Switzerland). Ammonium acetate (NH_4Ac) *p.a.*, Riedel-de Haën, Sigma-Aldrich (Laborchemikalien GmbH, Seelze, Germany). Triethanolamine ($(CH_2CH_2OH)_3N$) *p.a.* and acetic acid (CH_3COOH) 99.8%, Riedel-de Haën, RdH Laborchemikalien GmbH & Co., Seelze, Germany. Acetonitrile, HPLC grade, was bought from Fisher Scientific (UK Limited, Leicestershire, UK). The water in this study was purified in a Milli-Q® Academic system (18.2 MΩ·cm/0.22 μm), Millipore, (Burlington, MA, USA).

2.2. *Experimental*

2.2.1. *Dissolution media and drug substances*

Sodium phosphate buffer pH 7.0 ± 0.1 (65.5 mM), PB, and ammonium acetate buffer pH 6.8 ± 0.3 (10 mM), AmAc, were prepared as described previsously (*32*). The buffer capacity, β, (*33*) in PB was 32.8 mM (*32*). Triethanolammonium acetate buffer 7.0 ± 0.1, TeAmAc, was prepared by mixing 173.8 mM triethanolamine and 150.5 mM acetic acid in Milli-Q® water as diluent. TeAmAc had an ionic strength of 150 mM while AmAc had an ionic strength of 10 mM. In TeAmAc, β was 50.8 mM compared to 0.21 mM in AmAc. The phosphate buffer, PB, was diluted ten times, Dil_PB, (6.55 mM) and the ionic strength was calculated to 13 mM. The ionic strength will not be one tenth of the ionic strength in the PB due to changes in the stoichiometric acidity constants of phosphate buffer system (*34,35*). The pH remained constant during dilution. In Table 1, Dil_PB buffer was considered to be an initial buffer, and to this buffer different anions were added to investigate the eventual effect of different ions in the phosphate buffer system. The addition were $NaNO_3$ (Dil_PB+NO_3), NaCl (Dil_PB+Cl) or Na_2SO_4 (Dil_PB+SO_4) to obtain an ionic strength of 150 mM, See Table 1. The pH was still constant at 7.0 ± 0.1. In Dil_PB the buffer capacity was calculated to 3.8 mM. This is also valid for the phosphate buffers with the presence of chloride, nitrate or sulfate. In Dil_PB the concentration of sodium ions is 11 mM and with addition of sodium chloride or nitrate the concentration is raised to 147 mM.

The stochiometric pK_a-values used for the phosphate buffer preparation for I = 0.15 M were 1.89, 6.67 and 11.68 and for I = 0.013 M 2.19, 6.99 and 12.10 (*36*). For the preparation of the triethanolammonium acetate buffer the pK_a-value for acetic acid was 4.53 (I = 0.15 M) (*37*) and 7.77 for triethanolamine (*38*). The pK_a-value

Table 1. The phosphate media compositions and ionic strengths. The pH was 7.0 ± 0.1. For clarification of the abbreviations, see the text section above the table.

Medium	Additive (anionic)	Concentration of additive (mM)	Ionic strength (mM)
Dil_PB	-	-	13
PB	$H_2PO_4^-$	18.8	150
	HPO_4^{2-}	40.2	
Dil_PB+Cl	Cl^-	136	150
Dil_PB+NO_3	NO_3^-	136	150
Dil_PB+SO_4	SO_4^{2-}	45.6	150

of ammonium used in the ammonium acetate buffer preparation was 9.20 (I = 0.15 M) (*37*). The structures of the drug substances used in this study was given in (*31*) and pK_a-values were as followed; naproxen (4.18), carbamazepine (N/A), nortriptyline HCl (10.21), bendroflumethiazide (8.77), prednisone (N/A), terfenadine (9.25), enalapril maleate (2.99 and 5.39), clomipramine HCl (8.83) and chlorprotixene HCl (8.80). N/A = not applicable, aprotic.

2.2.2. *Apparent solubility determination by shake-flask methodology*

For the apparent solubility determinations microtubes MCT-200-C homo-polymer (2.0 mL) from Axygen scientific (Union City, CA, USA), a horizontal shaker from KABI AB (Stockholm, Sweden) and Spectrafuge 16 M microcentrifuge from Labnet International Inc. (Woodbridge, NJ, USA) were used. The pH monitoring was carried out using a pH Meter 744, Metrohm (Herisau, Switzerland) with electrode CMAW711 (ø 4.5 mm) from Thermo Russell (Auchtermuchty Fife, Scotland).

Each drug substance was added in an excess to 1.5 mL of dissolution media. The amount added to achieve this excess was between 2 mg and 50 mg in the phosphate systems. In the triethanolammonium acetate buffer 100 mg of nortriptyline HCl was required. Enalapril maleate was too soluble in the triethanolammonium acetate buffer to be studied, more than 200 mg per 1.5 mL of medium was necessary. Noticeable was that nortriptyline HCl in Dil_PB+NO_3 seemed to re-crystallize and was found attached along the walls of the microtubes.

The drug-buffer suspensions were shaken at room temperature (21.0 ± 1.5°C) for 24 h. Centrifugation was used in separating the excess of substance from the dissolution medium. The pH was always measured in the buffers before addition of drug substance and after the centrifugation, but was not adjusted after the completed experiments. Solid phase of terfenadine and bendroflumethiazide were partly located at the medium surface (supernatant) after centrifugation, which generated experimental difficulties when diluting aliquots in mobile phase. In order to avoid precipitation and due to high absorbance, the supernatant was diluted 600 times in mobile phase before HPLC analysis. Four samples were analyzed in duplicates for each substance and buffer. The solubility, S, was reported as the average value together with the relative standard deviation (RSD), $n = 8$.

2.2.3. *In vitro dissolution rate studies*

The miniaturized equipment has been described previously (*31*,*32*). A magnetic stirrer with graded rotating speeds was obtained from Heidolph MR 3001K (Lenzkirch, Germany). The external HPLC-pump was a Jasco PU-1585, Jasco Inc. (Tokyo, Japan). For the dissolution rate studies the chromatography was performed on an Agilent 1100 Series HPLC system with a binary pump, degasser, autosampler and diode-array detector (DAD), Agilent Technologies Inc. (Palo Alto, CA, USA). A six-position switching valve with a 20 µL stainless steel loop attached to it. The analytical column, Zorbax SB-C8 (2.1 × 50mm, 5 µM), was also purchased from Agilent Technologies Inc. The temperature of the column compartment was ambient (25-28°C) and constant within approximately 2°C in one experiment. Data were collected by ChemStation Rev.A.10.02 from Hewlett Packard, Agilent Technologies Inc.

The dissolution media were used at room temperature (21.0 ± 1.5°C) and were deaireated. The making of the miniaturized disks were according to the method in (*31*,*32*). The Plexiglas cell was the same as used in the previously study (*31*). The flow into the chamber of Plexiglas was always 1.0 mL/min and the rotation speed was 300 rpm (*31*). Triplicates of the disks were analyzed for all substances in the different media. The average values were calculated together with the relative standard deviations (RSD), $n = 3$. The analysis by HPLC has been described earlier in the references by Persson *et al.* (*31*,*32*).

3. Results and discussion

The newly constructed miniaturized equipment for dissolution rate determinations is suited for screening studies. The dissolution rates are to be used for prediction of apparent solubilities in drug development. In order to evaluate the usefulness of this approach, some general factors (*e.g.* common ion effect, type of counter ions and buffer capacity) affecting the solubility and/or the determination of dissolution rate were investigated.

3.1. *Apparent solubility (S) determination*

The results from the solubility study are shown in Figure 1 and 2. Figure 1 shows the logarithmic apparent solubility values and Figure 2 the ΔpH, which is the change in pH before addition of drug substance in the medium to the stop at 24 h in the shake-flask study. The data from PB and AmAc originates from reference (*31*). The triethanolammonium acetate buffer was used for comparison to AmAc since the latter, despite the low buffer capacity, was found to give a good correlation when plotting log*G* versus log*S* cf. (*31*). Good precision was obtained in general, RSD ≤ 10%, in the solubility determinations. Highest RSD-values were obtained for drug substances which were partially located at the medium surface after centrifugation (see Experimental).

The two acids, naproxen and bendroflumethiazide,

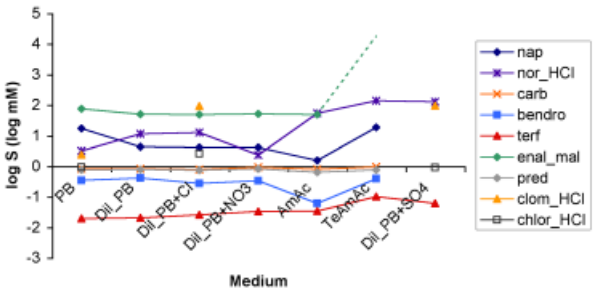

Figure 1. The average logarithmic apparent solubilities, logS, in aqueous dissolution media (24 h in room temperature). See Experimental for the media abbreviations. nap = naproxen, nor_HCl = nortriptyline hydrochloride, carb = carbamazepine, bendro = bendroflumethiazide, terf = terfenadine, enal_mal = enalapril maleate, pred = prednisone, clom_HCl = clomipramine hydrochloride and chlor_HCl = chlorprotixene hydrochloride. The raw data can be found in the Supplementary data section.

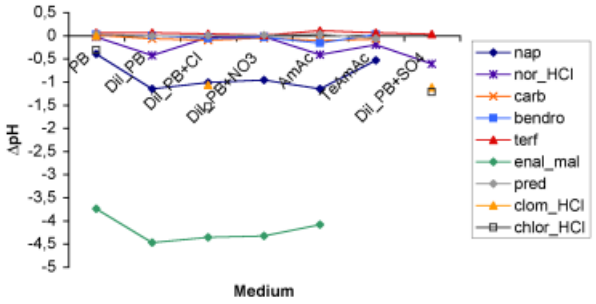

Figure 2. ΔpH, which is the change in pH before addition of drug substance in the medium to the stop at 24 h in the shake-flask study in aqueous dissolution media (24 h in room temperature). See Experimental for the media abbreviations and Figure 1 for the substance abbreviations. The raw data can be found in the Supplementary data section.

shows similar solubility properties in all media as can be seen in Figure 1. The decreased solubility of bendroflumethiazide in AmAc can partly be explained by the decrease in pH (Figure 2), compared to the other buffer media. The solubility of naproxen is higher in PB compared to the Dil_PB media. As expected, the better buffer capacity in the buffer media, the higher solubility of acidic drug compounds. The concentration of sodium ion in the different buffers had no effect on the solubility of the acids in this study, which is in agreement with reference (*25*). However, the finding contradicts some previously published results cf. (*39,40*).

There are small differences in the solubility of the aprotic substances (carbamazepin and prednisone) in the different buffers, Figure 1. Apparently, the ionic composition in the media is of less importance for their solubility in these buffer systems.

A significant decrease in pH was found in all media when dissolving enalapril added as the salt maleate, Figure 2. Enalapril maleate was too soluble in TeAmAc to be studied practically (indicated as a dotted line in Figure 1). At a concentration of 271 mM the solution was still not saturated. As was observed for the acids the solubility of enalapril was dependent on the buffer capacity, cf. PB and Dil_PB in Figure 2. When changing anions in the diluted phosphate buffers, no effect on the solubility of the ampholytic enalapril was obtained as observed for another ampholytic drug substance (doxycycline) in water with added anions, cf. (*41*). This divergence might be due to the very high solubility of enalapril maleate in this study.

The solubility of nortriptyline seems to be dependent on the type of anion added to the diluted phosphate buffer, see Figure 1. Phosphate and nitrate ions in the media decreased the solubility of nortriptyline, whereas additional chloride ions in the buffer gave the same solubility as observed in Dil_PB (despite the change in ionic strength). This indicates that it is not mainly the common ion effect that decreases the solubility of nortriptyline hydrochloride in this study. However, it has been established that the common ion effect at low pH-values do effect the solubility of an amine salt (*16,19,42,43*). Furthermore, the effect on solubility by different counter ions, as observed in this study and by previously published results (*e.g.* (*16,17,19*)) will depend on the physico-chemical properties of the drug substance. These properties are often described by the solubility product, K_{sp}, and this value for a given protolyte is dependent on the counter ion used. This complicates the choice of a general dissolution medium in the screening of solubility for a drug candidate.

In order to further investigate the effect of the common ion and/or counter ion on the solubility, three different amines formulated as hydrochloride salts and one free base were studied The selected screening media for this purpose were phosphate buffers with chloride and sulfate additives respectively, Figure 1 and 2. It can be seen that all hydrochloride salts have higher solubilities in Dil_PB+Cl compared to PB. This verifies that the phosphate ion ($H_2PO_4^-$ and/or HPO_4^{2-}) decreases the solubility more than the chloride ion for the hydrochloride bases, at an initial pH of 7 in the media. The results indicate that the Ksp for the phosphate ion is lower than for the chloride ion. This was also seen for haloperidol in reference (*44*). In Dil_PB+SO_4 the solubility is equal for clomipramine HCl compared to in Dil_PB+Cl, while nortriptyline HCl and terfenadine shows increased solubility. However, the solubility of chlorprotixen HCl is decreased in Dil_PB+SO_4 compared to in the chloride containing media. The conclusion was drawn that the types of counter ions added in the medium have different impact on the solubilities of the amines at a certain pH in the media.

A complementary investigation (Experimental not shown) of the solubility for nortriptyline, formulated as the hydrochloride salt, was also made. The media was based on Milli-Q® water of different pH containing dissolved salt of chloride, nitrate or sulfate to an ionic strength of 0.15 M. Regulation of pH was made by adding hydrochloric or nitric acid to the water medium. As reference, a solution of pure Milli-Q® water was used. The concentration of nortriptyline was determined

after 24 h and two weeks respectively. The chloride ion concentration was also determined after two weeks by use of a chloride selective electrode. In the reference solution, the nortriptyline concentration was 12 mM and the chloride concentration was 13 mM. In the pH region (2.4-6.5) where the positively charged form of nortriptyline dominates, the concentration was 31 mM while the chloride concentration was 26 mM. The solubility of the amine in the 0.15 M chloride containing medium was lower (8.9 mM), which is in agreement with the theory based on the common ion effect. In the 0.15 M nitrate medium however, the concentration of nortriptyline was even lower (1.7 mM). The chloride ion concentration was here found to be 22 mM, even though the chloride only originates from the nortriptyline hydrochloride itself. The K_{sp} for the nitrate salt is obviously lower than for the chloride salt. In the reference solution and the two media mentioned above, the nortriptyline concentration was found to be constant after 24 h and two weeks. In the sulfate containing medium on the contrary the nortriptyline concentration was very high after 24 h, 100 mM, but after two weeks it had decreased to 21 mM. The chloride concentration after two weeks in this medium was 110 mM, which approximately corresponds to the nortriptyline concentration determined after 24 h. The results in the sulfate medium indicate that the solubility equilibrium is slow, and also that nortriptyline might form a sulfate salt. This is important to account for when comparing the solubility results of the four amines in Dil_PB+SO_4 with the results in the other the media stated above.

The solubility in the different buffer systems (phosphate and acetate) was mainly dependent on the protolytic properties of the drug compound, Figure 1 and 2. In TeAmAc, the solubilities of nortriptyline HCl and terfenadine are higher than in PB, whereas acids have about the same solubility in these media. All of the drug substances, but the aprotic ones, seems to have increased solubility in TeAmAc compared to in AmAc. The triethanolammonium ion itself might generate an amplified effect of the solubility due to its organic character. This divergence might indicate that there are differences in the solubility product of the phosphate and acetate salts for the amines. The K_{sp} for the acetate salt may have a higher value compared to the phosphate salts. The buffer capacity of the medium is of course important for the solubility determinations of the protolytic drug substances.

3.2. *In vitro dissolution rate (G) determination using the miniaturized apparatus*

The logarithmic *in vitro* dissolution rates in the different media at 300 rpm for the drug substances are shown in Figure 3. RSD was at maximum 16% during the dissolution rate studies.

As also observed in the solubility study (Figure 1), there is no significant difference in the dissolution rates of the aprotic substances in the different buffers. Furthermore, the effect of the altered media on the dissolution rate of acids was similar as to the solubility results, see Figure 1. This may indicate that the pH in the saturated medium of a drug substance is approximately the pH in the diffusion layer for that substance, cf. (*42*,*44-47*). As stated before, a better buffer capacity in the diffusion layer will generate a more stable pH-value and as a consequence higher dissolution rates and solubilities will be achieved for the acids. No major influence on the dissolution rate by an increased sodium ion concentration was observed.

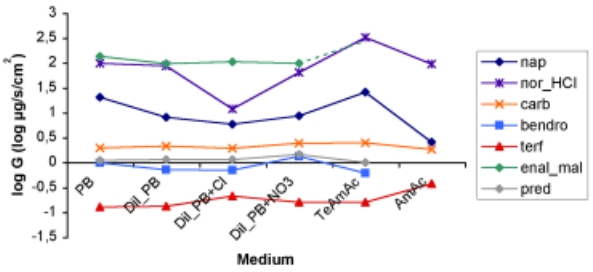

Figure 3. The logarithmic *in vitro* dissolution rate, log*G*, in aqueous dissolution media (300 rpm with 1.0 mL/min in room temperature). See Experimental for the media abbreviations and Figure 1 for the substance abbreviations. The raw data can be found in the Supplementary data section.

The two drug substances formulated as salts, nortriptyline HCl and enalapril maleate, have the highest dissolution rates of all compounds in all of the buffer media. The dissolution rate of enalapril maleate was very high in TeAmAc, why it was difficult to experimentally measure an accurate value (shown as a dotted line in Figure 3). This difficulty has previously been observed using the miniaturized rotating disk apparatus with the small substance disk in combination with high dissolution rate of a drug substance, cf. (*32*). In contrary to the observations of the solubility of nortriptyline HCl in Dil_PB+Cl, the dissolution rate is significant lower than for the rates in the other buffer media possibly due to the common ion effect cf. (*48-50*). The nature of buffer media was of less importance for the dissolution rate of terfenadine, see Figure 3.

3.3.*Correlation of dissolution rate and apparent solubility*

The modified Noyes-Whitney equation has previously been used to correlate solubility and dissolution rate (*31*, *51-54*). In this study, the applicability of the equation to correlate apparent solubility and *in vitro* dissolution rate using a miniaturized rotating disk apparatus was tested. The usefulness of the equation would be to predict solubility from dissolution rate data. The logarithmic form of the modified Noyes-Whitney equation will give a straight line when plotting log*G* versus log*S* according to Eq. 1 (cf. (*31*)).

$$\log G = \log S + \log k \qquad \text{Eq. 1}$$

The logarithmic values of *G* and *S* were correlated in Figure 4 A-E for the different buffer media and substances. Triplicates of log*G* are shown in the figures, while average values are used for log*S*. The correlation was made at the pH in the solubility solutions after 24 h. This will according to references (*42*,*44-47*) be the pH of the diffusion layer, rather than to the pH of the bulk solution in the rotating disk experiments.

Since the dissolution rate of the substances in the different media do not always follow the same pattern as the solubility, the different media will obviously give different correlations of dissolution rate versus solubility. Previously it was seen that nortriptyline HCl was deviating from the more linear correlation pattern in PB (*31*), which also was found in this study (Figure 4A). A deviation in the correlation of dissolution rate and solubility was also observed for nortriptyline HCl in other buffer media. Interestingly the best correlation, as described by the coefficient of determination (R^2) was however found in TeAmAc (R^2 = 0,991, n = 6). In TeAmAc only six substances were used for correlation since enalapril maleate was excluded due to the high solubility. Dil_PB+Cl, which might be comparable to the buffers used in biorelevant media, gave a good correlation as well including nortriptyline HCl (R^2 = 0.952, n = 7). So far, TeAmAc and Dil_PB+Cl seem to be best suitable for predicting the solubility from the experimental *in vitro* dissolution rate at pH 7.

Presented in Figure 5 is the correlation of the dissolution rate and the solubility for seven drug compounds and buffer media tested thus far. It is seen that nortriptyline HCl, nor_HCl, deviates from the correlation line in three of the buffers as discussed above. If these three values of nortriptyline HCl are discarded the R^2 value will be 0.967 (shown as dashed line and italic equation). This correlation

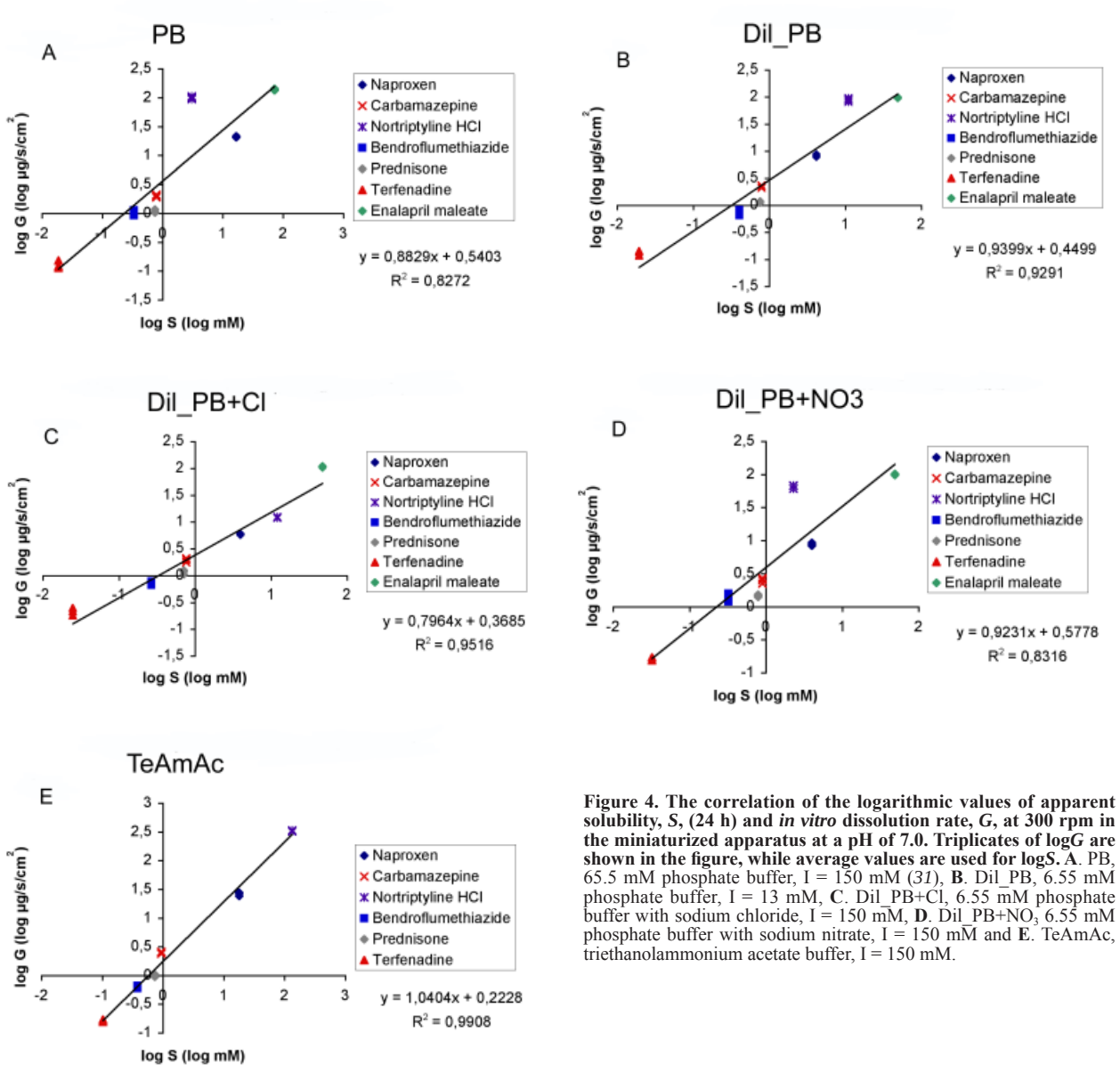

Figure 4. The correlation of the logarithmic values of apparent solubility, *S*, (24 h) and *in vitro* dissolution rate, *G*, at 300 rpm in the miniaturized apparatus at a pH of 7.0. Triplicates of log*G* are shown in the figure, while average values are used for log*S*. A. PB, 65.5 mM phosphate buffer, I = 150 mM (*31*), **B**. Dil_PB, 6.55 mM phosphate buffer, I = 13 mM, **C**. Dil_PB+Cl, 6.55 mM phosphate buffer with sodium chloride, I = 150 mM, **D**. Dil_PB+NO_3, 6.55 mM phosphate buffer with sodium nitrate, I = 150 mM and **E**. TeAmAc, triethanolammonium acetate buffer, I = 150 mM.

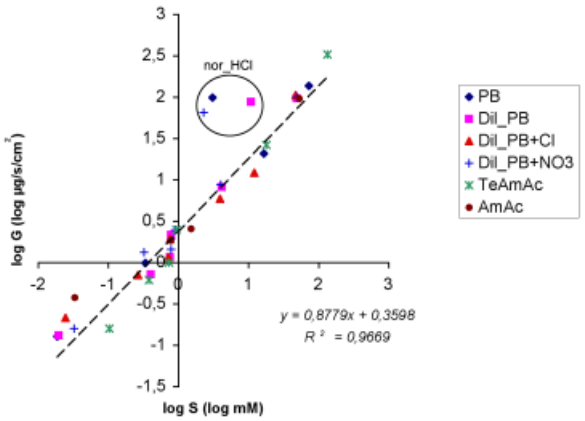

Figure 5. The correlation of the logarithmic values of apparent solubility, *S*, (24 h) and *in vitro* dissolution rate, *G*, at 300 rpm in the miniaturized apparatus at a pH of 7.0. The six different media were; PB, I = 150 mM (*31*), Dil_PB, I = 13 mM, Dil_PB+Cl, I = 150 mM, Dil_PB+NO_3, I = 150 mM, TeAmAc, I = 150 mM and AmAc = ammonium acetate buffer pH 6.8, I = 10 mM (*31,32*).

would probably be acceptable in a screening study of solubility from dissolution rate data during early phases in drug discovery. However, to obtain a general buffer where log*G* versus log*S* shows a good correlation for all types of drug substances, more types of buffers and drug substances both in free form and as salts have to be investigated.

4. Conclusions

A correlation study, based on the modified Noyes-Whitney equation, of solubility and dissolution rate was made. The apparent solubilities of seven different compounds were measured by a conventional shake-flask methodology. The dissolution rates were determined using a newly introduced miniaturized rotating disk apparatus. The rotating disk equipment decreased the time for determining the *in vitro* dissolution rate, whilst only consuming minute quantities of substance amount in the disks.

The influence of buffer system and buffer capacity as well as the common ion effect on the correlation was investigated using at maximum six different buffer media. The best correlations of log*G* versus log*S* were obtained with a triethanolammonium acetate buffer (R^2 = 0.991, n = 6). However, to compare the correlation with buffer used in biorelevant media, a phosphate buffer with the addition of chloride gave a good correlation for the drug substances in this study (R^2 = 0.952, n = 7). These results are encouraging, but more studies are needed in order to be able to select an optimal buffer for predicting the solubility based on dissolution rate data. Future studies, preferably by including multivariate data analysis, should include more buffer types and diverse substances. It should also be of interest to investigate the correlation of log*G* and log*S* in simulated intestinal fluids, *i.e.* FeSSIF and FaSSIF.

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Supplementary data 1

Raw data for the solubility study in six dissolution media, 24 h in room temperature. The apparent solubility, *S*, is the average of eight values (four samples with double injections). RSD = relative standard deviation (n = 8). pH is the value after the defined shake-time, 24 h, and ΔpH is the change in pH before addition of drug substance in the medium to the stop at 24 h.

Medium and experimental values		Naproxen	Carbamazepine	Nortriptyline HCl	Bendroflu -methiazide	Prednisone	Terfenadine	Enalapril maleate
PB	S (mM)	17	0.74	2.8	0.34	0.76	0.019	74
	RSD (%)	0.30	3.6	11	5.2	16	16	1.5
	pH (24 h)	6.73	7.14	7.10	7.15	7.10	7.13	3.35
	ΔpH	-0.41	±0.00	-0.04	+0.01	+0.02	+0.05	-3.75
Dil_PB	S (mM)	4.2	0.80	11	0.41	0.77	0.020	50
	RSD (%)	2.1	2.9	3.8	13	8.7	5.8	2.2
	pH (24 h)	5.96	7.06	6.70	7.09	7.00	7.13	2.66
	ΔpH	-1.16	-0.08	-0.44	-0.01	-0.02	+0.05	-4.48
Dil_PB+Cl	S (mM)	4.0	0.78	12	0.27	0.73	0.025	48
	RSD (%)	4.5	5.7	0.85	16	7.9	11	2.2
	pH (24 h)	6.00	6.98	7.06	6.99	6.95	7.02	2.59
	ΔpH	-1.02	-0.11	-0.05	-0.07	-0.01	+0.03	-4.37
Dil_PB+NO_3	S (mM)	4.1	0.92	2.3	0.33	0.81	0.033	50
	RSD (%)	2.6	6.1	1.6	21	3.8	19	1.7
	pH (24 h)	6.01	6.97	6.99	6.94	6.93	6.98	2.62
	ΔpH	-0.97	-0.06	-0.03	-0.05	±0.00	±0.00	-4.34
AmAc	S (mM)	1.6	0.79	54	0.057	0.63	0.034	48
	RSD (%)	7.5	3.2	7.5	20	0.60	18	1.0
	pH (24 h)	5.30	6.40	6.13	6.57	6.85	6.56	2.78
	ΔpH	-1.16	-0.12	-0.42	-0.17	+0.02	+0.10	-4.09
TeAmAc	S (mM)	18	0.95	137	0.39	0.74	0.10	>271
	RSD (%)	1.7	3.4	0.89	20	4.1	30	
	pH (24 h)	6.58	7.06	6.77	7.10	7.08	7.08	
	ΔpH	-0.54	-0.09	-0.21	+0.01	-0.07	+0.05	

Supplementary data 2

Solubility raw data for the basic drug substances in three different phosphate buffer media (n = 8). clom HCl = clomipramine HCl, chlor HCl = chlorprotixene HCl, nor HCl = nortriptyline HCl and terf = terfenadine.

Drug Substance	PB				Dil_PB+Cl				Dil_PB+SO_4			
	S (mM)	RSD (%)	pH (24 h)	ΔpH	S (mM)	RSD (%)	pH (24 h)	ΔpH	S (mM)	RSD (%)	pH (24 h)	ΔpH
clom HCl	2.4	2.2	7.10	-0.02	93	1.9	5.99	-1.08	92	0.60	5.95	-1.13
chlor HCl	0.92	32	6.80	-0.32	2.6	1.5	5.52	-1.55	0.89	2.9	5.85	-1.23
nor HCl	2.8	11	7.10	-0.04	12	0.85	7.06	-0.05	127	1.1	6.46	-0.62
terf	0.019	16	7.13	+0.05	0.025	11	7.02	+0.03	0.055	14	7.03	+0.02

Supplementary data 3

The raw data for the *in vitro* dissolution rate values, *G*, in five dissolution media (300 rpm at a flow of medium at 1.0 mL/min). The values are presented as average values of three disks. RSD = relative standard deviation (n = 3). N/A = not applicable.

Medium and experimental values		Naproxen	Carbamazepine	Nortriptyline HCl	Bendroflu -methiazide	Prednisone	Terfenadine	Enalapril maleate
PB	G (µg/s/cm^2)	20	1.9	97	0.98	1.1	0.13	135
	RSD (%)	2.8	4.9	5.1	11	6.5	16	3.3
Dil_PB	G (µg/s/cm^2)	8.0	2.1	86	0.71	1.1	0.13	95
	RSD (%)	6.3	5.9	8.0	13	3.2	9.9	1.5
Dil_PB+Cl	G (µg/s/cm^2)	5.8	1.9	12	0.69	1.1	0.21	104
	RSD (%)	2.0	9.1	2.7	8.7	8.6	16	3.4
Dil_PB+NO_3	G (µg/s/cm^2)	8.6	2.4	64	1.3	1.4	0.16	98
	RSD (%)	5.0	9.1	6.2	15	3.7	5.8	1.9
TeAmAc	G (µg/s/cm^2)	26	2.4	323	0.60	0.98	0.16	N/A
	RSD (%)	6.8	3.9	2.6	5.3	5.5	5.8	