

# Alkalisating agents in urinary tract infections: theoretical contraindications, interactions and synergy

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*Ther Adv Drug Saf*

2022, Vol. 13: 1–14

DOI: 10.1177/  
20420986221080794

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## Abstract

**Introduction:** Alkalisating agents have the potential to enhance the efficacy of many antimicrobial agents used in the treatment of Urinary Tract Infections; they also have the potential to cause significant patient harm if used incorrectly. This work seeks to illustrate and quantify these risks and synergies by modelling drug solubility and supersaturation against pharmacokinetic data for commonly used antibiotic agents.

**Methods:** Solubility-pH relationships are employed to quantify the crystalluria risk for compounds which may be reasonably expected to be co-prescribed—or co-administered—with urinary alkalisers (amoxicillin, nitrofurantoin, trimethoprim, sulfamethoxazole and ciprofloxacin). These results are correlated against reports of crystalluria in the literature and in the EU Adverse Drug Reaction database.

**Results and Discussion:** We find a correlation between the maximum theoretical supersaturation attainable and crystalluria reports for sulfamethoxazole, amoxicillin and ciprofloxacin. Shifts in urine pH which can be induced by alkalisating agents may produce supersaturated states (and thus induce crystalluria) and may also affect antimicrobial efficacy. The importance of employing biorelevant media to improve predictive capacity of this analysis is also discussed.

**Conclusion:** Despite their widespread use, alkalisating agents have significant effects on the pharmacokinetics of the most common drugs used to treat UTIs. With self-care set to increase, all OTC products should be critically re-evaluated to ensure patient safety, particularly within contexts where healthcare professionals are not involved in treatment selection. This analysis suggests a need for consistency across patient and healthcare professional documents to improve clarity.

## Plain Language Summary

### OTC Alkalisating agents need additional warning information

Alkalisating agents (e.g., sodium and potassium citrate) can be purchased in many locations without the supervision of a healthcare professional.

Although they are thought as innocuous agents, alkalisers can greatly influence the way some antibiotics behave in the body and this can potentially cause patient harm.

This work illustrates these risks and synergies by modelling drug solubility and supersaturation against pharmacokinetic data for commonly used antibiotic agents.

Manufacturers and patients should be aware that the use of alkalisating agents with these drugs (and potentially many others) may cause unintended consequences.

**Keywords:** antimicrobial, excretion, pH efficacy, supersaturation, urinary alkalisating, urinary pH, urinary tract infection, clinical pharmaceuticals.

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Received: 31 August 2021; revised manuscript accepted: 26 January 2022.

## Introduction

Urinary alkalisating agents are classified as General Sale List products in the United Kingdom and Ireland and as such, they are widely available in supermarkets where they can be sold without the supervision of a healthcare professional. The market for Over-The-counter (OTC) medicines is worth \$34 billion in the United States and \$3.54 billion in the United Kingdom<sup>1</sup> and advocates for the increased use of OTC products predict dramatic healthcare savings in these continents.<sup>2,3</sup> This analysis suggests that OTC products will play a new role in future healthcare, and as such, they need to be critically evaluated within this new context to ensure patient safety.

Dysuria is one of the most common conditions encountered in primary care and can be treated by urinary alkalisers alone, or as adjuvants to antibiotics (e.g. trimethoprim, nitrofurantoin or ciprofloxacin). Some advocate for alkalization of the urine to improve antibiotic efficacy,<sup>4</sup> however, there are number of factors to consider, discussed herein. Although alkalisation of the urine has been shown to decrease pain and urinary frequency associated with urinary tract infections (UTIs),<sup>5</sup> systematic analysis indicates that evidence of their effectiveness is lacking.<sup>6</sup> In a wider context, clinicians have utilised urinary alkalisation to reduce the systemic toxicity of acidic drugs,<sup>7</sup> prevent crystalluria,<sup>8,9</sup> and treat acid-base imbalances. The effect of alkalisating agents on urinary pH is determined by the patient biochemistry at the point of administration, which is known to change dramatically throughout the day. This can result in minimal (or no effect) in some patients and dramatic shifts in others.

Urine alkalisation can be achieved with citrate or bicarbonate salts, which act through their own distinct mechanism.<sup>10</sup> If bicarbonate ions reach the renal tubules intact, they will cause increases in urinary pH. Urine alkalisation by citrate has been suggested to arise from its metabolism via the citric acid cycle to release CO<sub>2</sub> which is then catalysed to bicarbonate by carbonic anhydrase. However, the precise mechanism is likely to be more complex and renal handling of citrate has been discussed extensively by Simpson<sup>11</sup> and later by Hamm.<sup>12</sup> Oral alkalisers can cause a pH shift of >1 unit in less than 1 hour (mean 12 h).<sup>7</sup> Alkalisation can also occur as an unintended side-effect of other drugs such as antacids, which can

also raise urinary pH. One study illustrated that this effect is more pronounced when urine pH is approximately 5, where pH can increase up to 1 pH unit.<sup>13</sup> A follow-up study by the same authors determined that it takes approximately 24 h for these changes to occur and they remain until approximately 24 h after cessation of treatment.<sup>14</sup>

Solution pH has a strong effect on the solubility of endogenous and exogenous species and rapid changes, therefore, may result in supersaturation and ultimately their precipitation. In the context of pharmaceutical care, this is referred to as drug induced crystalluria.<sup>9</sup> Figure 1 illustrates that pH has a dramatic effect on the solubility of ionisable species. This becomes more important as pH approaches the pK<sub>a</sub> of the drug.

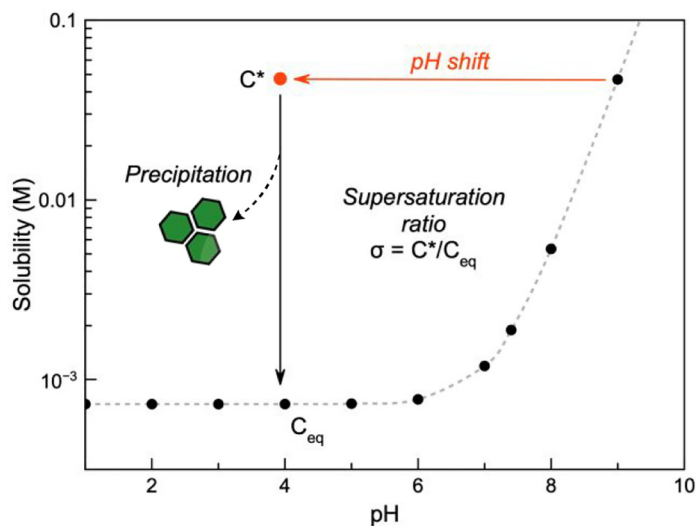
This pH effect on solubility also manifests itself *in vivo* in any anatomical site which can dramatically change the solution pH. Unsurprisingly, drug crystals have been observed in the gastrointestinal tract,<sup>15</sup> macrophages (specifically their lysosomal compartment),<sup>16</sup> and the renal system.<sup>8</sup> The function of the kidneys is such that there are marked changes in filtrate composition (and pH) along the renal tubules as substances are excreted, metabolised and reabsorbed. Urine pH fluctuates over 24 h, usually within 5 to 8.5 but this range can extend in pathological situations (4.5–9).

Large shifts in urinary pH from alkalisers may cause renal damage resulting from the induction of crystalluria or alter the pharmacokinetic and pharmacodynamic activity of various drugs, including those used to treat UTIs. Although thought of as innocuous agent, like any drug product, its use has its associated risks. The aim of this work is to provide an analysis of these risks to minimise patient harm.

## Methodology

### *Analysis of products available in United Kingdom, United States, and Irish markets*

The Food and Drug Administration (FDA) Drugs.com (USA), the electronic medicines compendium (UK) and the Health Products Regulatory Authority (HPRA) databases were searched for 'alkaliser', 'urinary alkaliser', 'alkalizer', 'urinary alkalizer', 'bicarbonate' and 'citrate'. These searches were manually screened,



**Figure 1.** When the pH of a saturated solution of a weak acid ( $pK_a = 7.2$ ) at pH 9 is rapidly decreased to pH 4, the drug will eventually precipitate out of solution to reach the new solubility equilibrium; precipitation is not always instant and the rate is proportional to the supersaturation ratio (i.e., the difference between the momentary solubility,  $C^*$  and the equilibrium solubility,  $C_{eq}$ ).

and alkalisng agents were added to the list compiled in Table 3.

be definitively proven that the drug is the cause of the observed event.

#### Literature survey of drug induced crystalluria

The Scopus database (Search performed on December 2020) was searched for ‘ciprofloxacin’, ‘trimethoprim’, ‘sulfamethoxazole OR co-trimoxazole’, ‘amoxicillin’, ‘nitrofurantoin’ AND ‘crystalluria’. Article abstracts and titles were then manually screened and articles that discussed new cases which identified drug induced crystalluria were used in the analysis (Figure S1).

#### Analysis of EU database for Suspected Adverse Reactions (EUADR)

Employing methodology published previously,<sup>17</sup> The EUADR database was searched for products containing ciprofloxacin, trimethoprim, sulfamethoxazole (co-trimoxazole), amoxicillin, and nitrofurantoin. Results were screened to those reported by healthcare professionals only and refined by renal. The author recognises the limitations of this database, namely: the number of reports may be related to the publicity of the drug and or its adverse reactions, no information regarding how often the drug is prescribed accompanies the reports and, in many cases, it cannot

#### pH solubility curves

Equilibrium solubility studies were selected which allowed the drug to equilibrate for 24 h in 37 °C, in aqueous solvents with ionic strength > 0.1 M across the range of pH found in the urine where possible. Studies that employed biorelevant media were rare but used when available. Data were extracted using WebPlotDigitiser (v. 4.4) and modelled using the Henderson-Hasselbalch model which has been derived previously<sup>18</sup> (Table 1). The  $pK_a$  for each molecule was determined using the  $pK_a$  calculator implemented in Marvin which makes a prediction based on calculations of partial charges of atoms in the molecules.

Solubility data from Yu *et al.* was combined with that of Dahlan, McDonald, and Sunderland as they measured equilibrium solubility of trimethoprim closer to physiological temperatures of 37°C, whereas the latter tested solubility at 32°C. Performing supersaturation analysis using data obtained from Dahlan, McDonald, and Sunderland predicted a supersaturation was greater than 1. The absence of literature reports regarding trimethoprim induced crystalluria

**Table 1.** Summary of data used in calculations.

Drug	pK <sub>a</sub> <sup>a</sup>	Solubility (mM) <sup>b</sup>	Maximum urinary concentrations (mg/L) [mM]	Maximum Supersaturation ratio <sup>c</sup>
Amoxicillin <sup>d</sup>	7.16	41-2,877 <sup>19</sup>	~12,500,000 [29,832] <sup>23</sup>	70 (727)
Ciprofloxacin	6.18; 8.73	0.23-91 <sup>24-27</sup>	1981 [5.98] <sup>28</sup>	395 (26)
Nitrofurantoin	7.2	1.68-47 <sup>22,29</sup>	320 [1.34] <sup>30</sup>	28 (<1)
Sulfamethoxazole	6.16	1.1-817 <sup>31</sup>	1016 [3.2] <sup>32</sup>	743 (2.9)
Trimethoprim	7.2	3.2-40 <sup>33,34</sup>	720 [2.48] <sup>35</sup>	12 (<1)

<sup>a</sup>The pK<sub>a</sub> calculator implemented in Marvin predicts pK<sub>a</sub> data based on calculations of partial charges of atoms in the molecules.

<sup>b</sup>Minimum-maximum solubility in biorelevant media when available.

<sup>c</sup>Supersaturation attainable from maximum reported urinary concentrations in parenthesis.

<sup>d</sup>Amoxicillin trihydrate.

prompted reanalysis with data closer to physiological temperatures.

One study evaluated the solubility of amoxicillin in the urine,<sup>19</sup> although it was used in this analysis there are no details of the specificity of the quantification method for other penicillin derivatives or breakdown products and no details of the phase remaining (or its purity) after 24 h equilibrium studies. This is an important consideration as amoxicillin is known to degrade >70% in aqueous solutions buffered to pH 7 within 24 h.<sup>20</sup>

Another study suggested that complexation with urea and creatinine (found in the urine at approximately 250 mM and 1.5 mM respectively) will contribute to increased nitrofurantoin solubility and suggested that the shape of a solubility curve using urine may deviate from that obtained using pH buffers.<sup>21,22</sup> As such, the concentration of nitrofurantoin in these solutions was taken as the intrinsic solubility to increase the accuracy of the supersaturation model.

#### Pharmacokinetic data

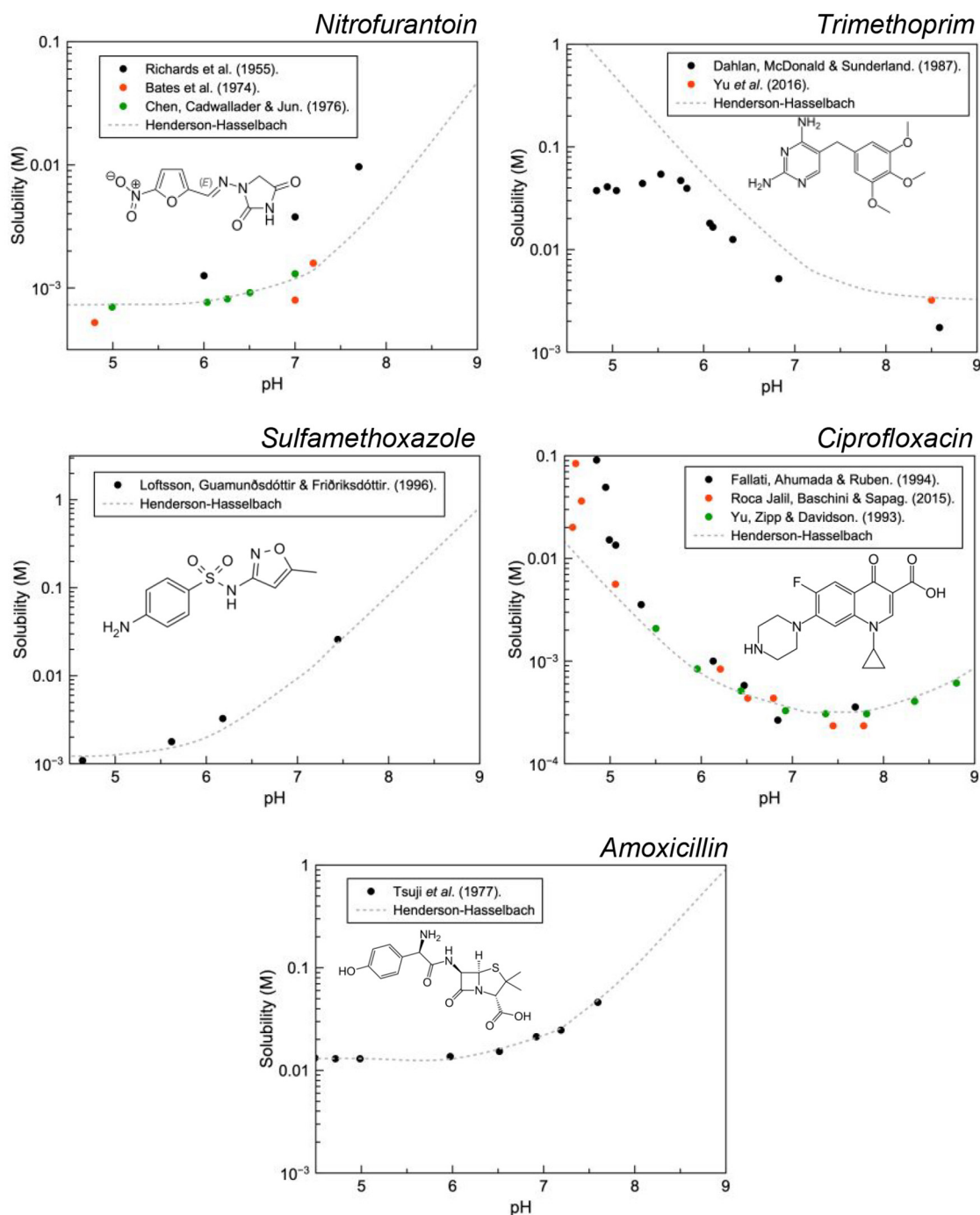
Pharmacokinetic data for amoxicillin,<sup>23,36,37</sup> nitrofurantoin,<sup>38-40</sup> ciprofloxacin,<sup>28,41,42</sup> co-trimoxazole<sup>32,43</sup> (trimethoprim C<sub>max</sub>)<sup>35</sup> was extracted from the literature as before with WebPlotDigitiser (v. 4.4). The highest observed datapoint is highlighted in the figure, was used to calculate the supersaturation that could have been generated in that patient. When available, the data was inserted

into an excel sheet to obtain the standard deviation and mean, as this data was not available for sulfamethoxazole, the range was used as a surrogate for standard deviation.

#### Results and discussion

With relevance to the clinical context of dysuria, equilibrium solubility data has been obtained from the literature for ciprofloxacin, trimethoprim, nitrofurantoin, amoxicillin and sulfamethoxazole and modelled using Henderson-Hasselbalch to aid illustration (Figure 2). Importantly all of these drugs have a pK<sub>a</sub> within the range of physiological urinary pH, therefore, rapid changes to the pH brought about by urinary alkalisers can present a risk for precipitation. Conversely, the opposite can be applied if crystalluria is determined to be caused by these drugs, patients could be treated with the acid or base to increase drug solubility and potentially redissolve the crystals.

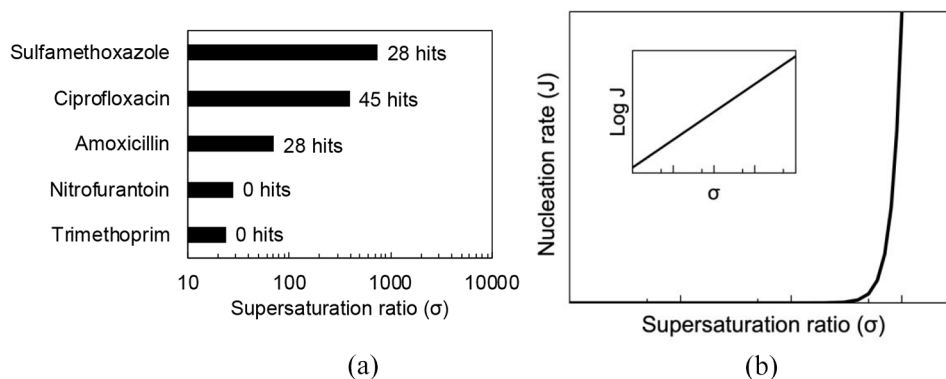
Theoretically, precipitation is possible for all of these compounds as they all exhibit pH dependent solubility in the range of urinary pH. Critically, sulfamethoxazole, ciprofloxacin and amoxicillin have been identified in clinical isolates using FTIR,<sup>44</sup> MS<sup>45</sup> and XPS.<sup>46</sup> In an attempt to quantify the risk of precipitation (i.e., crystalluria) solubility data must be placed in the context of supersaturation. Supersaturation describes the driving force for crystallisation where increased supersaturation reduces the critical cluster size and the nucleation rate. Equation 1 is a practical



**Figure 2.** Equilibrium solubility data as a function of solution pH obtained from the literature for nitrofurantoin, trimethoprim, ciprofloxacin, sulfathiazole and amoxicillin.

expression of the relationship between supersaturation,  $\sigma$  and nucleation rate,  $dN/dt$  where  $k$  and  $m$  denote the nucleation rate constant and nucleation order respectively.<sup>47,48</sup>

$$\frac{dN}{dt} = k\sigma^m \quad (1)$$



**Figure 3.** (a) Maximum supersaturation ratio of UTI anti-infectives (nitrofurantoin,  $\sigma \approx 3$ ; ciprofloxacin,  $\sigma \approx 303$ ; trimethoprim,  $\sigma \approx 24$ ; amoxicillin,  $\sigma \approx 70$  and sulfamethoxazole,  $\sigma \approx 1345$ ) labelled with number of hits from literature analysis. (b) Supersaturation on crystal nucleation rate.

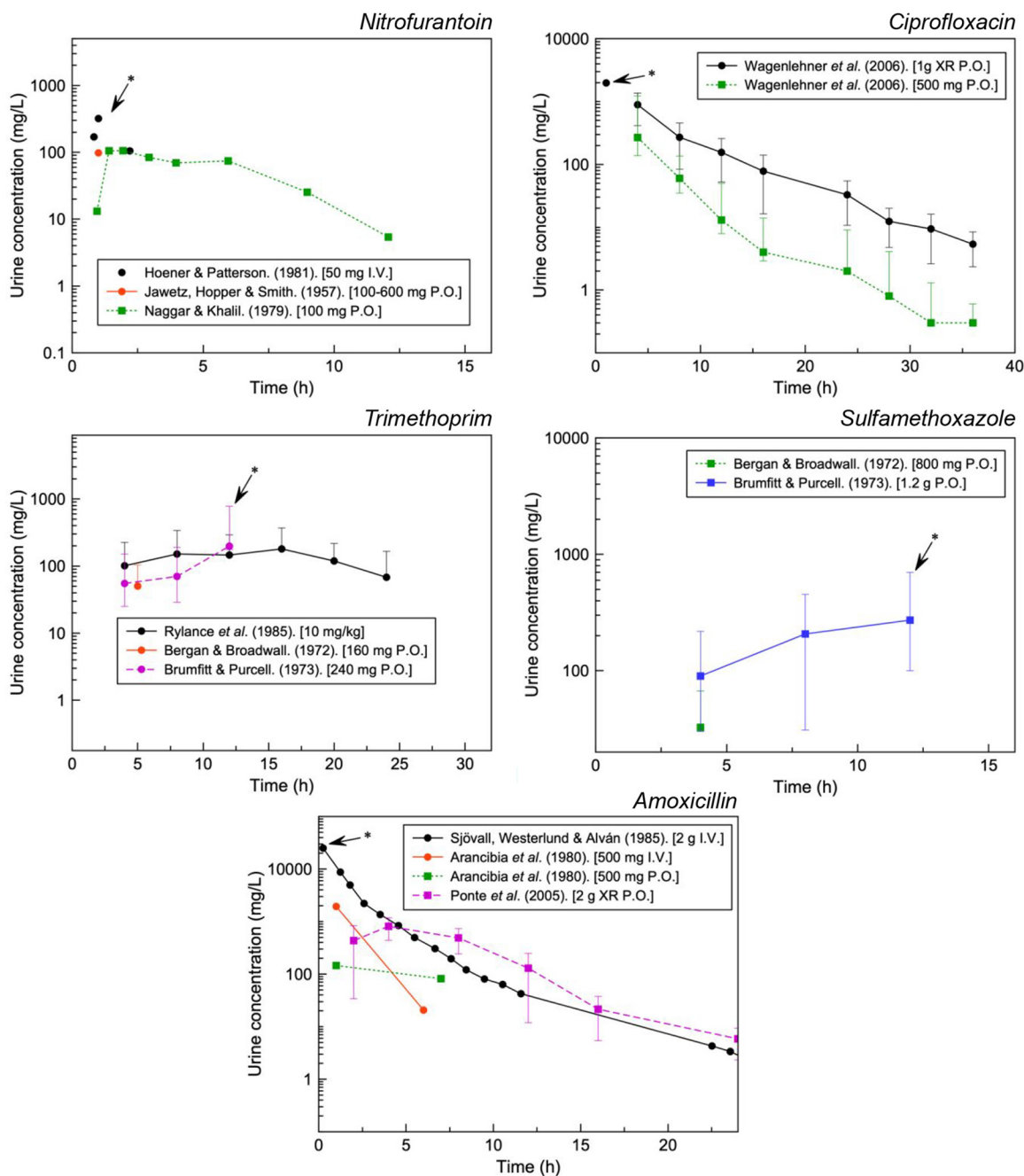
Figure 3 reveals the maximum supersaturation attainable (calculated from the maximum and minimum solubility values across the pH range) for each agent alongside the number of hits from a literature analysis. Interestingly it highlights the significant risk of crystalluria with compounds that can attain large supersaturation indexes  $\geq 70$ .

Crystalluria has been observed in trimethoprim products, but only as trimethoprim/sulfamethoxazole.<sup>49</sup> This is unsurprising, as crystalluria is a common feature of sulfonamide antibiotics and is associated with urine pH  $< 7$ .<sup>9,50–52</sup> Amoxicillin induced crystalluria is also well characterised and has been widely reported,<sup>8,23,45</sup> it is associated with acidic urine around pH 5.<sup>23</sup>

Ciprofloxacin crystalluria may be induced by increasing urine pH from 4.5 to 7.<sup>53</sup> Although it has been postulated (manufacture information) that this is because ciprofloxacin solubility is decreased in alkaline environments, this is not strictly correct.<sup>46</sup> From the pH solubility diagram in Figure 2 it is apparent that ciprofloxacin solubility increases above pH 7.5. This is due to the formation of a low solubility complex which precipitates from solution,<sup>54–56</sup> these results could be extrapolated to other quinolones which are known to precipitate in alkaline solutions in the presence of certain metal cations.<sup>27</sup> Alarmingly, crystalluria was observed in half ( $n=3/6$ ) of the participants administered 500 mg ciprofloxacin alongside sodium bicarbonate (42 mEq, three times daily for four doses) with additional fluid intake (not quantified).<sup>46</sup>

While nitrofurantoin associated crystalluria is not widely described in the literature, one report was identified<sup>57</sup> and due to the acidity of the patients urine reported, and the solubility data above, nitrofurantoin crystalluria is plausible. However, it is possible that the authors have misidentified the, ‘small purple crystals’ observed. Purple crystals in urine catheter bags are commonly due to the precipitation of indirubin and indigo crystals, known as ‘Purple bag syndrome’.<sup>58</sup> This has been documented since 1857<sup>59</sup> and was described by their contemporaries as a well-known event in geriatric patients.<sup>60</sup> Although they report disappearance of the crystals after cessation of nitrofurantoin, presumably the authors changed the catheter, the nidus of the infection which may have contained the bacteria that catalysed the conversion of indole sulphate to indirubin and indigo.

The EU database of Suspected Adverse Drug Reactions reveals that—although rare—crystalluria has been suspected in all of the drugs used in UTIs, in descending order: co-trimoxazole ( $n=87/2,330,256$ ), ciprofloxacin ( $n=52/25,853$ ), amoxicillin ( $n=25/30,683$ ), nitrofurantoin ( $n=7/6,325$ ), trimethoprim ( $n=2/2,891$ ) and sulfamethoxazole ( $n=0/611$ ). The implication of ciprofloxacin, amoxicillin and co-trimoxazole in drug-induced crystalluria can be rationalised from the analysis above, and the absence of sulfamethoxazole reports is probably because it is almost exclusively prescribed as co-trimoxazole. A deeper analysis of nitrofurantoin hits revealed other drugs which may be responsible; separate

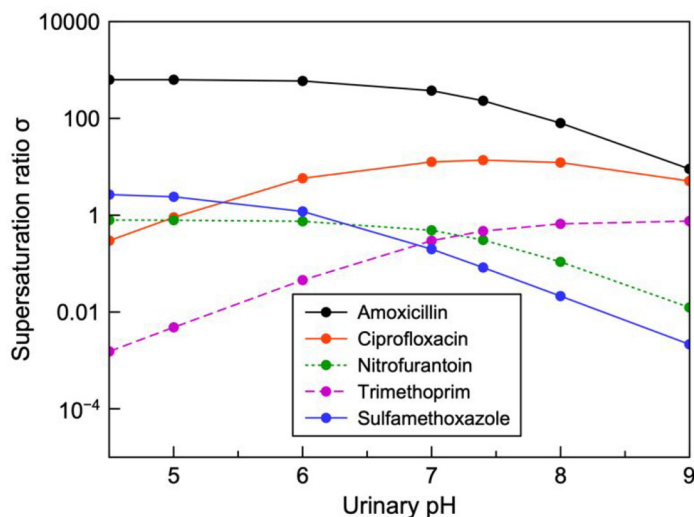


**Figure 4.** Urinary concentrations for various formulations of UTI antibiotics. Maximum urinary concentrations used for further analysis indicated with an arrow.

reports contained methotrexate, amoxicillin, ciprofloxacin and piperacillin-tazobactam. One report may have been mischaracterised as it is associated with a publication that does not mention nitrofurantoin crystalluria (in fact the paper describes nitrofurantoin induced pneumonitis)<sup>61</sup> which leaves two remaining reports. The two

reports involving trimethoprim do not appear to have been mischaracterised.

Further context can be provided with the concentrations of drug that have been observed in the urine (Figure 4). With the exception of sulfamethoxazole, urinary concentrations can reach



**Figure 5.** Supersaturation ratio plotted as a function of urinary pH for observed maximum urinary concentrations of various antibiotics used in the treatment of UTIs. When supersaturation exceeds 1 the drug is prone to precipitation.

approximately  $10^2$  to  $10^3$  the respective plasma concentrations for the drugs analysed ( $C_{\max}$  as per manufacturer information: trimethoprim, 1–2 mg/L; amoxicillin, ~6 mg/L; ciprofloxacin, 0.56–3.7 mg/L; nitrofurantoin, ~1 mg/L and sulfamethoxazole, 57.4 mg/L).

Figure 5 aims to highlight the risk supersaturation with clinically relevant concentrations. This may account for the quantity of reports for ciprofloxacin, amoxicillin and sulfamethoxazole with nitrofurantoin and trimethoprim illustrating undersaturation even at the highest concentrations available in the literature.

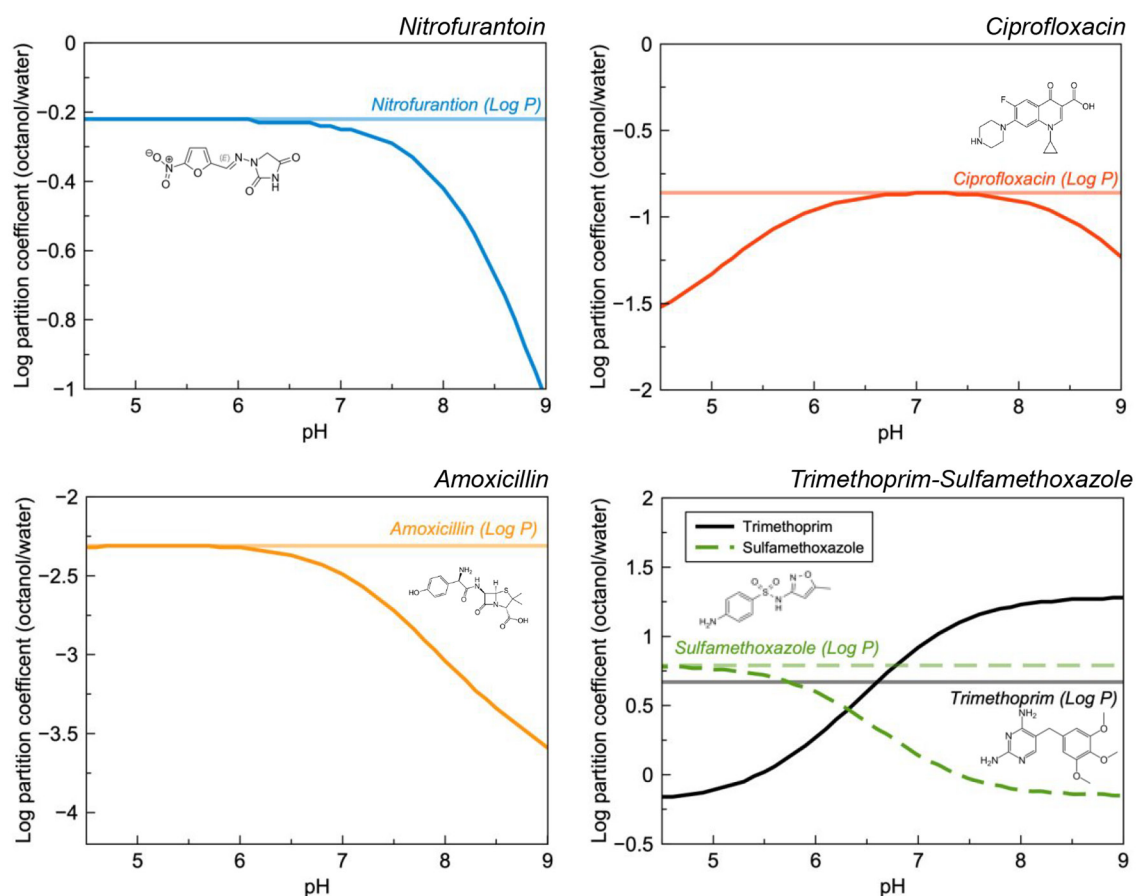
Changing solution pH (i.e. renal filtrate pH) can also alter the excretion of some drugs which is explained—in part—by their increased solubility in the medium. This may be rationalised by the influences of the drugs  $pK_a$  and its dramatic effect on the pH solubility curve and log D (Figure 6). This is generally illustrated using the classic examples of aspirin,<sup>62</sup> methamphetamine<sup>63</sup> and methotrexate.<sup>64</sup> In the context of dysuria, key pharmaceuticals which are likely to be co-prescribed include nitrofurantoin, trimethoprim and ciprofloxacin and amoxicillin. Although this author could find no evidence to suggest that amoxicillin exhibits pH dependant excretion and clinical studies suggest that pH does not affect excretion of ciprofloxacin,<sup>65</sup> it is possible that increased excretion could be seen

at the extremes of urinary pH for each of these drugs. Alkaline urine is known to increase the excretion rate of nitrofurantoin<sup>29</sup> and the pH effect on trimethoprim and sulfamethoxazole is well characterised.<sup>66</sup>

Notwithstanding active excretion/reabsorption, the propensity for the drug to penetrate into tissues can be estimated using log P and log D. Log D has a higher predictive capacity as it describes the partition coefficient—between octanol and water—of a drug molecule across the pH scale; this becomes particularly important for ionisable drugs as the unionised form has higher solubility in the organic phase (i.e. unionised molecules are expected to penetrate across biological membranes to a greater degree than their ionised counterparts). It could be hypothesised therefore, that increased ionisation could result in increased solubility in the urine, reduced reabsorption in the kidney, and subsequently increased clearance.

Evidence suggests that many antibiotics used in the treatment of UTIs demonstrate pH dependant synergy,<sup>67</sup> which could be exploited to reduce the treatment failure rate (Table 2). Although this is not the first time hypothesis has appeared in the literature, this author could find no randomised controlled trials to demonstrate that *in vitro* pH synergy is clinically translatable. With co-trimoxazole, alkalinisation demonstrated





**Figure 6.** Calculated log P and D as a function of pH for nitrofurantoin, ciprofloxacin, trimethoprim-sulfamethoxazole and amoxicillin. A decreasing log D value is correlated with increased solubility in water.

increased efficacy against a variety of clinically relevant strains,<sup>67,68</sup> in *E. coli* (a common UTI pathogen), these effects become pronounced particularly at pH 7.<sup>69</sup> One study suggested that urinary pH > 6.5 is likely to decrease nitrofurantoin activity,<sup>70</sup> while acidic conditions increased activity.<sup>67</sup> Ciprofloxacin activity is also positively influenced by alkaline pH<sup>67</sup> whereas amoxicillin activity does not change.<sup>4</sup> In the context of Log D, it could be postulated that this pH efficacy is related to the propensity of membrane penetration into the bacterial cytoplasm.

An analysis of products available on the British, American and Irish markets (Table 3) reveals that while sodium bicarbonate has similar effectiveness,<sup>72</sup> citrate salts are used almost exclusively in OTC products. All products surveyed have a statement which reminds patients to speak to their doctor or pharmacist if they are on other

medicines, this advice might be unclear for many patients; when specific drug related advice does appear, it is inconsistent. Some products have a statement which draws attention to interactions with other drugs, but these generally focus on the role of potassium and sodium as they are the predominant counter-ions to citrate (e.g., they recommend care with potassium sparing diuretics). Oracit®, Cytra-2®, Bicitra® expand this list to include salicylates and other agents such as antacids and Cymaclear, effercitra and Potassium citrate (Thornton & Ross), note the potential increased clearance of drugs and specifically mention nitrofurantoin. The British National Formulary monograph on citric acid and potassium citrate does not identify these risks highlighted by the manufacturers.

With self-care set to increase, all OTC products should be critically re-evaluated to ensure patient

**Table 2.** Effect of alkalisation on UTI antibiotics.

Drug	Maximum $\Delta$ Solubility [M] <sup>a</sup>	Maximum $\Delta$ log P <sup>b</sup>	Pharmacokinetics	Pharmacodynamic effects
Sulfamethoxazole	0.816	-0.93	Increased excretion	<i>in vitro</i> synergy
Trimethoprim	-1.613	1.46	Decreased excretion	<i>in vitro</i> synergy
Nitrofurantoin	0.046	-1.56	Increased excretion	<i>in vitro</i> interaction
Ciprofloxacin	0.084	-0.94	No effect	<i>in vitro</i> synergy
Amoxicillin	0.899	-1.28	-	-

UTI: urinary tract infection.  
<sup>a</sup>Solubility shift as calculated from the Henderson-Hasselbach except in the case of trimethoprim which reaches  $pH_{max}$  when solution  $pH = 6$ .  
<sup>b</sup>The log D calculator implemented in Marvin predicts Log D of a molecule based on the atomic log P increment of its constituent atoms as per Viswanadhan *et al.*<sup>71</sup>

**Table 3.** Selection of products available in United States, United Kingdom, and Irish markets.

Drug name	Manufacturer(s)	Active ingredient(s)	Region
Poly-Citra K	Janssen Pharmaceuticals	Citric acid and potassium citrate	USA
Potassium citrate	Generic (Rising, Zydus Pharma, Strides Pharma, Teva Pharms, Ani Pharms, Biopharma inc., Ascent pharms, Eywa).	Potassium citrate	USA, IRL and UK
UROKIT-K	Mission Pharma	Potassium citrate	USA
Cytra-K	Cypress Pharma	Citric acid and potassium citrate	USA
Virtrate-3	Virtus Pharmaceuticals, LLC	Citric acid, sodium and potassium citrates	USA
Oracit	CMP Pharma	Citric acid and sodium citrate	USA
Bicitra	Janssen Pharmaceuticals	Citric acid and sodium citrate	USA
Cystopurin	Pharmapac Ltd.	Potassium citrate	UK and IRL
Potassium citrate	Available generically	Potassium citrate	UK
Effercitate	Cambridge Healthcare Supplies Ltd	Potassium citrate and citric acid	UK
Cymaclear	Teva Pharma	Potassium citrate	UK
Cymalon	Actavis Group	Sodium citrate	UK
Cystitis relief	The Boots Company	Sodium citrate	UK and IRL

Product information obtained from Drugs@FDA, Drugs.com (USA), the electronic medicines compendium (UK) and the Health Products Regulatory Authority (Ireland).

safety, particularly within contexts where healthcare professionals are not involved in treatment selection. This analysis suggests a need for consistency across patient and healthcare professional documents to improve clarity.

### Conclusion

This work has illustrated how solubility-pH relationships can enable an analysis of crystalluria risk for compounds which may be reasonably expected to be co-prescribed—or

co-administered—with urinary alkalisers, namely: ciprofloxacin, amoxicillin and sulfamethoxazole. These empirical relationships have been validated with systematic literature analysis and further explored with the EUADR database. The importance of employing biorelevant media to improve predictive capacity is also discussed particularly for nitrofurantoin and amoxicillin.

Future studies may expand on the *in vitro* results in the literature which suggest increased antimicrobial efficacy for trimethoprim (the most widely prescribed UTI antibiotic in the United Kingdom),<sup>73,74</sup> sulfamethoxazole and ciprofloxacin, at increased pH, which could be achieved with alkalisers and *vice versa* for nitrofurantoin. Greater depth is needed to quantify the relationship between plasma and urinary concentrations and to relate urine pH to its the pharmacokinetic effects and to explore if there are other common drugs taken by patients that may be associated with crystalluria or changes in pharmacokinetics, this is a particular concern for drugs with a  $pK_a$  in the range of urinary pH.

### Ethics

Our study did not require an ethical board approval because it does not contain identifiable patient information. All information is also available on the public domain.

### Author contributions

**Oisín N. Kavanagh:** Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Visualisation; Writing—original draft; Writing—review & editing.


### Conflict of interest statement

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author received no financial support for the research, authorship, and/or publication of this article.

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### Supplemental material

Supplemental material for this article is available online.

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