Effect of vinylpyrrolidone polymers on the solubility and supersaturation of drugs; a study using the Cheqsol method

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Abstract

The development of methods to increase the bioavailability of drugs is of great interest, especially for those which are poorly soluble or permeable. One of the strategies to enhance the solubility (which in turn has the potential of increase bioavailability) of drugs is the use of additives in the formulation process, so that the drug can stay supersaturated in biological fluids for a period of time long enough to allow absorption. The use of polymers as pharmaceutical excipients in order to stabilize the supersaturation of drugs is common practice. In this work, the ability of different polymers of vinylpyrrolidone (K-12, K-17, K-25, K-29/32, K-90) and a copolymer of vinylpyrrolidone and vinylacetate (S-630) have been tested for their impact on the supersaturation of drugs. Sixteen drugs of different chemical nature have been selected, and analyzed using the Cheqsol method. The results of the drug alone, and of physical mixtures with the different polymers at several polymer:drug ratios have been compared in terms of supersaturation extent and duration. It has been observed that acidic compounds displayed enhanced solubility in different ways: sometimes the supersaturated state of the drug is maintained for a long time, due to the precipitation of an amorphous solid, as determined by X-ray diffraction studies; on other occasions supersaturation increases but only for a short time, compared to the drug alone, and then the drug precipitates to a crystalline form. Only a few basic drugs displayed enhanced solubility in the presence of PVP polymers, in contrast to acidic compounds.

1. Introduction

Pharmaceutical compounds obtained with new synthesis procedures have tended towards higher molecular weights and lipophilicity, which allows drugs to cross membranes more easily. However, molecular properties that promote permeation often decrease solubility, and then bioavailability is diminished. In addition, some poorly water-soluble molecules are also not very lipophilic (Box and Comer, 2008). To understand the relationship between solubility and permeability, and visualize its potential impact on drug absorption, the Biopharmaceutics Classification Scheme (BCS) is used (FDA Guidance, 2015). This scheme classifies all molecules in 4 different classes on the basis of solubility and permeability. Molecules in class I are considered to be highly soluble and highly permeable, very suitable for pharmaceutical purposes. Molecules in class II have limited solubility but are permeable, while molecules in Class III are soluble but poorly permeable. Finally, molecules in Class IV have low solubility and low permeability (Box and Comer, 2008; Tsume *et al.*, 2014).

In order to achieve desirable drug absorption, active molecules should be soluble to a given extent in aqueous media to ensure they are dissolved in biological fluids once inside the human body (Takács-Novák *et al.*, 2013). Therefore, aqueous solubility is, amongst others, an essential property to assess during early stages of drug development (Shoghi *et al.*, 2013). Several methods can be used to increase drug solubility, especially for class II compounds which often exhibit solubility-limited absorption. Some of them are focused on solubilizing formulations (i.e. enhancing the solubilizing capacity in the gastrointestinal environment), and other methods are focused on maintaining the drug in a supersaturated state, so it can be available at higher concentrations than its equilibrium solubility for a certain period of time (Williams *et al.*, 2013; Brouwers *et al.* 2009). However, it must be considered that solubility increase in biological fluids may only need to be fleeting, so the maintenance of a temporary state of supersaturation would be enough to make the drug available for permeation (Warren *et al.*, 2010). In other words, keeping the concentration of the drug

higher than its equilibrium intrinsic solubility only during the digestion time may be sufficient to promote absorption.

For pure drugs, kinetic solubility S_k (or concentration when first precipitation occurs) is generally higher than the intrinsic solubility S_0, indicating that the drug solution is frequently supersaturated just before precipitate is first observed (Box and Comer, 2008; Shoghi *et al.*, 2009). However, a supersaturated drug solution is thermodynamically unstable and has the tendency to return to the equilibrium state by precipitation to the crystalline most stable form of the drug. This process can be slowed down or inhibited using some solubility enhancement strategies ((Williams *et al.*, 2013; Brouwers *et al.* 2009; Xu and Dai, 2013; Ilevbare *et al.*, 2013). Among other approaches, the use of different pharmaceutical excipients like polymers, surfactants or cyclodextrins as stabilizers of supersaturation is common practice. In these cases, the stabilizer effect does depend not only on the type of stabilizer, but also on the excipient:drug ratio, and the initial degree of supersaturation of the drug (Brouwers *et al.* 2009; Ilevbare *et al.*, 2013; Khougaz and Clas, 2000; Chauhan *et al.*, 2013).

Poly(vinylpyrrolidone) (PVP) polymers have been extensively studied regarding their ability to modify drugs' solubility. Some works are centered on the impact of PVP on the inhibition of crystallization of drugs (Khougaz and Clas, 2000; Chauhan *et al.*, 2013; Ozaki *et al.*, 2013); other works are focused on the knowledge of the specific interactions between drugs and PVP (Khougaz and Clas, 2000; Karavas *et al.*, 2006; Karavas *et al.*, 2007; Tajber *et al.*, 2005; Nair *et al.*, 2001; Molyneux and Frank, 1961a; Molyneux and Frank, 1961b) which, according to FTIR experiments, seems to be related to the ability of PVP units to form hydrogen bonds either through the nitrogen or the carbonyl group on the pyrrole ring. Most of these studies employ only one particular type of PVP (i.e. with a particular degree of polymerization, which ranges from 12 to 90 in the above mentioned studies) and a few different drugs. In the present work, a systematic study taking into account the degree of polymerization of the PVP and the

PVP:drug ratio is addressed. In particular, the effect of these two parameters on the degree and extent of supersaturation of different BCS class II drugs is evaluated.

2. Materials and methods

2.1. Instruments

All solubility assays were carried out by the CheqSol method (Stuart and Box, 2005) using a PCA200 titrator from Sirius Analytical Instruments Ltd. (Forest Row, UK), equipped with a Sirius D-PAS spectrometer, a bifurcated fibre-optic dip probe from Hellma Analytics (Müllheim, Germany) with path length of 1 cm, and a two channels solvent degasser from SMI-LabHut Ltd. (Churcham, UK). The apparatus was controlled from a computer running the RefinementPro2 and Cheqsol software. Acidity constant determinations were performed using either the PCA220 or a GLpK_a titrator also from Sirius Analytical Instruments Ltd.

The X-Ray diffraction (XRD) characterization was performed using a *PANalytical X'Pert PRO MPD* θ/θ powder diffractometer of 240 mm of radius equipped with a PIXcel detector from PANalytical B.V. (Almelo, The Netherlands). The apparatus was set in a configuration of convergent beam with a focalizing mirror and a transmission geometry, with flat samples sandwiched between low absorbing films. The detector active length was 3.347º. Work power was 45 kV – 40 mA with a defined beam height of 0.4 mm. Five repeated scans were performed from 2 to 60 2θ º with a step size of 0.026 2θº and a measuring time of 40 seconds per step.

2.2. Reagents

Dimethyl sulfoxide >99.9% (DMSO), 0.5 M potassium hydroxide tritisol and 0.5 M hydrochloric acid tritisol were purchased from Merck (Darmstadt, Germany). Potassium

chloride >99% was from Sigma (St. Louis, MO, USA), and potassium hydrogen phthalate >99% was from Probus (Strassen, Luxembourg). PVP K-12, K-17, K-25, K-29/32, K-90 and S-630 were from International Specialty Products (Wayne, NJ, USA), and provided by Ashland (Covington, KY, USA). K-type PVP are homopolymers of polyvinylpyrrolidone that differ in molecular weight (MW) and glass transition temperature (T_g); K represents degree of polymerization, thus the higher K the higher MW and T_g. PVP S-630 is a 60:40 random copolymer of vinylpyrrolidone and vinylacetate; it has a lower T_g and is less hygroscopic than K-type PVP (Ashland Inc., 2013). Water was purified by a Milli-Q plus system from Millipore (Bedford, MA, USA) with resistivity of 18.2MΩcm.

A total of 16 test compounds were used. Papaverine hydrochloride (>98%), dibucaine hydrochloride (>99%), cyproheptadine hydrochloride (99%), bendroflumethiazide (Ref. Std.), bupivacaine hydrochloride (Ref. Std.), isoxicam (An. Std.), propranolol hydrochloride (>98.5%), warfarin (>98%), ketoprofen (>98%), and diclofenac sodium salt (>98.5%) were from Sigma-Aldrich (St. Louis, MO, USA). Benzthiazide (Ref. Std.), haloperidol (>98%), maprotiline hydrochloride (>99%), olanzapine (>98%), pindolol (>98%), and tetracaine (>98%) were from Sigma (St. Louis, MO, USA).

2.3. Procedures

2.3.1. pK_a determination

All measurements were performed at least in triplicate, under argon atmosphere, at 25 ± 0.1 ºC, using standardized 0.5 M HCl and 0.5 M KOH solutions as titrants. The pH electrode (Ag/AgCl, Sirius Analytical Instruments Ltd.) was calibrated titrimetrically in the pH range 1.8-12.2. Temperature was monitored through a temperature probe during the course of the measurement.

Spectrophotometric titration was the method of choice to determine acidity constants of the test compounds. pK_a values were determined from pH–dependent multi-wavelength UV spectra collected by the D-PAS system. In each experiment, 50 μL of a drug stock solution (10 mM in DMSO) were introduced in 10 mL of a 0.15M KCl ionic strength adjusted (ISA) aqueous solution, and titrated between pH 2 and pH 12.

The pK_a of haloperidol and the second pK_a of dibucaine, whose ionisable groups showed not enough UV activity (Allen *et al.* 1998), were determined through a conventional potentiometric titration (Albert and Serjeant, 1984) in methanol-water mixtures. The aqueous pK_a values were obtained through Yasuda-Shedlovsky extrapolation (Avdeef et al, 1993; Takács-Novák et al., 1997; Yasuda, 1959; Shedlovsky, 1962).

2.3.2. Solubility determination

Solubility measurements were carried out using the CheqSol method, which is described in detail elsewhere (Stuart and Box, 2005). Briefly, 10 mL of ISA solution are added to an accurately weighted amount of drug. The pH is immediately adjusted to a value where the compound exists predominantly in its ionized form, titration starts (by addition of amounts of KOH or HCl, according to the nature of the compound), and solubility is reduced by increasing the concentration of the neutral species. When a certain extent of supersaturation is achieved, precipitation starts. At this point, small amounts of acidic and basic titrant are alternately added, creating subsequent positive and negative pH gradients, which in turn make the drug solution go alternately from subsaturated to supersaturated. The solubility of the neutral species (S_0) is determined from the point at which the pH gradient becomes zero, i.e. where no net dissolution or precipitation of the compound occurs, through mass and charge balances and the pK_a of the compound. All measurements were performed at least in triplicate.

The weight of sample needed to perform the assay depends on the compound's intrinsic solubility and may vary between 5.00-20.00 mg. The temperature was set to

25±0.5°C and an argon atmosphere was used to avoid the presence of carbon dioxide in solution and its influence on the titration data. When carrying out the solubility assays in the presence of PVP, a physical mixture of the drug and the PVP was used. The percentage of PVP in the assay was calculated as follows:

$$PVP\ \% = \frac{PVP\ weight}{(drug\ weight + PVP\ weight)} \cdot 100 \quad (1)$$

2.3.3. Supersaturation determination

Extent and time in which a solution stays supersaturated are the parameters used to evaluate supersaturation. Determinations performed through the CheqSol method provide this information since the drug concentration is monitored over time. Henceforth, dividing the maximum measured concentration of neutral species (C_{max}) by the intrinsic solubility (S_0), the supersaturation ratio (R_{ss}) can be calculated.

$$R_{SS} = \frac{C_{max}}{S_0} \quad (2)$$

Also the duration of the supersaturation state (t_{ss}) can be measured from the concentration vs. time data by calculating the time lapse Δt in which supersaturation occurs (Hsieh *et al.*, 2012).

2.3.4. X-Ray diffraction characterization

In order to characterize the precipitate obtained while the solution is supersaturated, the solubility assay was aborted at the desired time point. Then, the solid was filtered through a 0.45 µm filter paper, and the filters were then left in a vacuum dessicator for one day. The solid material was carefully collected and prepared for XRD characterization.

3. Results and discussion

3.1. Physicochemical properties of studied compounds

Structures of the tested compounds are shown in Table 1. They are of different chemical nature, and include 2 diprotic acids (bendroflumethiazide and benzthiazide) which belong to the same family, 4 monoprotic acids (diclofenac, isoxicam, ketoprofen, and warfarin), 3 diprotic bases (dibucaine, olanzapine and tetracaine), and 7 monoprotic bases (bupivacaine, cyproheptadine, haloperidol, maprotiline, papaverine, pindolol, and propranolol). pK_a and S_0 of the compounds have been determined and results are also shown in Table 1. Bupivacaine is the most soluble of the drugs with log S_0 = -2.93±0.05, whereas isoxicam is the least soluble with log S_0 = -5.61±0.14. It is normal behavior that compounds show a certain degree of supersaturation just before precipitation occurs (Hsieh *et al.*, 2012). For this reason, it is important to know the extent of the supersaturation of the compound itself, so that the effect of the addition of PVP can be correctly interpreted. The maximum concentration of neutral species (C_{max}), and supersaturation ratio (R_{ss}) and time (t_{ss}) of the drugs are also provided in Table 1. As an example, Figure 1 shows the concentration profile of bendroflumethiazide during a typical Cheqsol experiment. In this exemplary experiment C_{max} is around 1500 μM, whereas S_0 is 80 μM, which provides a R_{ss} around 18, *i.e.* the concentration of bendroflumethiazide is 18 times higher than its equilibrium solubility just before precipitation starts. In this example the duration of the supersaturation state, t_{ss}, is about 12 minutes. Values provided in Table 1 are the average of several replicate measurements. It can be observed that C_{max} and t_{sat} often have high standard deviations. This is not unusual because as supersaturation is a non-equilibrium process, it can be easily affected by many environmental factors, which lead to high dispersion in the obtained values even in replicate measurements. According to the obtained results, papaverine and isoxicam are the compounds that supersaturate most highly, compared to the intrinsic solubility, reaching concentrations almost sixty-fold

greater than S_0. On the contrary, bupivacaine and tetracaine hardly supersaturate, since the ratio C_{max}/S_0 is close to 1. With regards to supersaturation time, the longest supersaturation times following precipitation are around 15-20 minutes, whereas the shortest ones are in the range 4-5 minutes.

3.2. Effect of PVP on the solubility of the drugs

To check the effect of PVP on drugs solubility, Cheqsol experiments were repeated using physical mixtures of drug-PVP. The effect of all available PVP at different PVP:drug proportions was tested. Three different trends were observed for the selected compounds related to their supersaturation, and three model compounds have been selected to explain each one of the behaviors: bendroflumethiazide (case A), benzthiazide (case B), and tetracaine (case C).

3.2.1. Case A: long-time stabilization of the supersaturated state

This is the case of bendroflumethiazide, diclofenac, ketoprofen, and warfarin. Figure 2A shows how the concentration of bendroflumethiazide changes with time when different proportions of PVP K-12 are present in the mixture. In the absence of PVP, after reaching C_{max}, concentration decreases until the S_0 value is reached. However, when PVP are present, solutions stay supersaturated at nearly the C_{max} concentration of the drug for the whole duration of the experiment. So, in this case PVP do not increase the maximum concentration of drug in solution, but keep this concentration stable for a long time, improving the potential bioavailability. As regards the effect of the PVP:drug ratio, there is a slight decrease of supersaturation concentration when the percentage of PVP increases. Nevertheless, all solutions keep supersaturated at all ratios PVP:drug, with degrees ranging from 7.6 (70%) to 15 (10%) for more than 2 hours. It is worth noting that the reproducibility between replicate measurements is more variable

263 at low PVP:drug ratios (Figure 2B). Best reproducibility is obtained in the range 40-70%
264 PVP.

265 The effect of the PVP polymerization degree has also been tested. Figure 3 shows the
266 results of solubility measurements for bendroflumethiazide when different PVP (all of
267 them in a 50% PVP:drug ratio) are used. Apparently there is no effect of the degree of
268 polymerization on the supersaturation of the drug, since all K-type PVP provide the
269 same results. Previous studies based on FTIR measurements had already pointed out
270 existing interactions between bendroflumethiazide and K-type PVP (Tajber *et al.*, 2005,
271 Frontini and Mielck, 1997), mainly through hydrogen bonding interactions of the
272 sulfonamide groups of bendroflumethiazide and the vinylpyrrolidone units. However,
273 PVP S-630, which contains vinylacetate moieties randomly distributed in addition to the
274 vinylpyrrolidone ones, hardly modifies solubility behavior of bendroflumethiazide. This
275 latter polymer was tested at different PVP:drug ratios obtaining similar results (Table
276 S1 of the supporting material) at all S-630 levels.

277 Diclofenac, ketoprofen and warfarin behave as bendroflumethiazide in the presence of
278 PVP. Results for these three other compounds are shown in Figure 4. Diclofenac (Fig.
279 4A) and ketoprofen (Fig. 4B) interact only with K-type PVP, and solubility of the
280 compounds is stabilized at 17-fold and 2-fold its intrinsic solubility value, respectively.
281 Warfarin (Fig. 4C) shows positive interaction not only with K-type PVP, but also with
282 PVP S-630. All types of PVP make the solubility of warfarin increase approximately 20
283 times.

284 *3.2.2. Case B: increase of the supersaturation concentration for a limited time*

285 In this other case, the effect of PVP on drug's solubility is completely different. Now, the
286 addition of PVP makes C_{max} of the drugs increase, but for a limited period of time.
287 Thus, the drug could be potentially more bioavailable, but because of the higher
288 concentration in the supersaturated solution. This is the case of benzthiazide, isoxicam,
289 olanzapine, and pindolol. Focusing on benzthiazide as a model compound, the addition

of K-type PVP makes C_{max} increase from around 100 μM to about 1000 μM, depending on the added PVP and its percentage (Table S2 of the supporting material). In the same way, supersaturation time increases from 4 minutes (benzthiazide alone) to a range between 15 and 45 minutes, depending on the PVP and percentage added. There is not a clear trend that relates R_{ss} with the polymerization degree or the percentage of PVP. However, it seems that higher percentages of PVP enlarge the supersaturation time of the drug. The addition of PVP S-630 provokes a greater effect than K-type PVP on benzthiazide solubility (Figure 5A). R_{ss} is increased from 8 to 44 when the percentage of S-630 is 10%, to 109 when it is 50%, and to 720 at 75% of PVP. In the same way, supersaturation time increases from 4 minutes to around 25, 30, and 40 minutes at 10%, 50%, and 75% S-630 respectively.

Although the general effect on solubility is the same for all mentioned compounds (an increase in the supersaturation concentration for a given period of time), the results obtained for each individual compound may change according the type of PVP and its percentage. For example, pindolol has a similar increase in supersaturation ratio (from 15 to 50-60) and time (from 6 to 20-30 minutes) independently of the percentage and type of PVP used (Figure 5B). However olanzapine shows a moderate increase in supersaturation degree depending on the used PVP, and also an important modification in the supersaturation time; it changes from nearly 6 minutes to 25 minutes with a 65% S-630 addition (Figure 5C). Similar behavior is observed for isoxicam (Figure 5D), which shows a R_{ss} around two times the level of the compound alone, and a t_{ss} 3 or 4-fold higher. The results obtained as regards C_{max}, R_{ss} and t_{ss} for the aforementioned compounds are summarized in Table S2 of the supplementary information.

3.2.3. Case C: no effect on the solubility of the drugs

In the third case there is no interaction at all between the drug and the different PVP, so that solubility is not affected by the addition of the polymers. This happens to

bupivacaine, cyproheptadine, dibucaine, haloperidol, maprotiline, papaverine, propranolol, and tetracaine. Figure 6 shows the supersaturation profile of tetracaine in absence and presence of 50% of K-type and S-630 PVP. In all instances the profile is identical, and practically the same results are obtained at other percentages (Table S3 of the supplementary information). Although small increases in t_s are observed in some instances, they can be attributed to the kinetic factors which can delay or accelerate the precipitation of a compound.

3.3. Effect of PVP on the morphology of the precipitates

X-Ray diffraction (XRD) assays were performed for the two model compounds that presented a clear modification of solubility behavior in presence of PVP, *i.e.* bendroflumethiazide and benzthiazide. This analysis was performed with the PVP that caused stronger modifications to the solubility of the mentioned compounds, so K-12 was chosen for bendroflumethiazide and S-630 for benzthiazide. The aim was to assess if observed changes in drugs solubility behaviors were due to modifications in solid forms when precipitation occurred, induced by the presence of PVP. XRD spectra were performed on the commercial drug samples, pure K-12 and S-630 PVP, the solid obtained after drug precipitation during Cheqsol determinations in the absence of PVP, and the solid obtained during Cheqsol determinations in the presence of PVP. Results can be observed in Figure 7. Pure drugs spectra (a) show high intensity peaks reporting periodic arrangement of atoms, thus, crystalline solids. After Cheqsol experiments in absence of PVP (b) all drugs precipitate also in a crystalline form, but different from the initial one, so both compounds show some kind of polymorphism. Thus, intrinsic solubility reported for the drugs correspond to the obtained polymorph, and not to the original crystalline form. The spectra obtained for both pure PVP (K-12 and S-630) are very similar (c), and characterized by the absence of sharp peaks. Instead, wide bands are observed, which are indicative of amorphous solids. Finally,

Cheqsol determinations were repeated in the presence of 50% of K-12 (for bendroflumethiazide) and 50% S-630 (for benzthiazide). Spectra show different results in this case. Bendroflumethiazide spectra belongs to an amorphous solid (Fig 7A,d). Only two sharp peaks are present, which belong to the KCl present in the titration measurements. In this case PVP induces the precipitation of a metastable amorphous form, with higher solubility than the crystalline one (Hsieh *et al.*, 2012). Instead, the spectra obtained for benzthiazide (Fig 7B,d) belongs to a crystalline solid, and can be considered equivalent to the one obtained in absence of PVP. In this case the presence of PVP may inhibit precipitation, and higher concentrations of drug can be reached in solution. However, after a relative short time the polymorph of benzthiazide starts to precipitate in the same form obtained in absence of PVP, so concentration in solution falls to the S_0 value.

According to the observed results it is difficult to predict a clear effect of PVP on a given drug. However, it must be pointed out that all the acidic compounds of the present work modify its solubility behavior in presence of PVP; on the other hand, solubility of basic compounds is hardly affected by PVP, although some bases like olanzapine and pindolol improved temporarily their supersaturation degree and duration by the addition of PVP. Molyneux et al. (Molyneux and Frank, 1961a; Molyneux and Frank, 1961b) already indicated that anionic aromatic compounds interact with PVP polymers. They demonstrated that the binding constants anion-PVP increased as the volume of the anionic compound increased (possibly due to coulombic repulsions between the anions bound to the polymer coil). In the same studies, they reported that basic compounds did not interact with PVP. However, other studies have shown interactions between some basic compounds and PVP, especially with compounds containing heterocyclic nitrogen atoms in highly conjugated rings (Karavas *et al.*, 2007) or sulphonamide groups (Tajber *et al.*, 2005). In these cases a hydrogen bond can form between the -N-H moiety of the drug and the oxygen of the

371 pyrrole group of PVP. That might be the case of olanzapine and pindolol, which contain
372 heterocyclic nitrogen atoms in highly conjugated structures.

373 **4. Conclusions**

374 The used methodology provides an excellent way to study the supersaturation state of
375 drug formulations, since the constant measurement of drug concentration in solution
376 allows the determination of supersaturation extent and duration. The results from the
377 present study demonstrate that the use of PVP polymers in the formulation of certain
378 drugs can potentially improve their bioavailability by increasing the concentration of the
379 drug in solution for a given period of time. In general, solubility of acidic compounds is
380 clearly affected by PVP, although two different behaviors have been observed with
381 such kind of compounds: in the first case PVP maintain a supersaturated system for a
382 long period of time by the stabilization of the amorphous form of the compounds, as
383 evidenced by the solid state characterization; in the second case PVP maintain the
384 solution supersaturated in a higher degree compared to the compound alone, but only
385 for a limited period of time. Then a crystalline form of the drug precipitates, and
386 solubility drops to the equilibrium solubility value of the drug.

387 The type of PVP and the PVP:drug ratio play a role in the supersaturation of the drugs,
388 but there is not a clear relation between the obtained effect and the type and ratio of
389 PVP, since different effects have been observed in different drugs.

390 From the ten basic compounds studied in the present work, only two showed modified
391 solubility behavior by the addition of PVP. This fact points out that the effect of PVP on
392 solubility of basic drugs is not so evident, being the modification of solubility behavior
393 by PVP highly drug-structure dependent.

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487

Figure captions

Figure 1: Supersaturation profile and parameters for bendroflumethiazide.

Figure 2: (A) Supersaturation profile of bendroflumethiazide alone (○) and in presence of different ratios of PVP K-12: 10% (◇), 20% (◆), 30% (▲), 40% (□), 50% (●), 60% (✳), 70% (△). (B) Variation of bendroflumethiazide solubility with the percentage of PVP K-12 present in the physical mixtures.

Figure 3: Supersaturation profile of bendroflumethiazide alone (○) and in presence of 50% of PVP K-12 (■), K-17 (■), K-25 (■), K-29/32 (■), K-90 (■), and S-630 (◆).

Figure 4: Supersaturation profile of (A) diclofenac alone (○) and in presence of 50% PVP K-25 (■), and 50% of PVP K-29/32 (■); (B) ketoprofen alone (○),and in presence of 50% PVP K-12 (■), K-17 (■), K-25 (■), K-29/32 (■), and K-90 (■); (C) warfarin alone (○), and in presence of 5% PVP K-29/32 (■), 10% PVP K-29/32 (■), 15% PVP K-29/32 (■), and 5% PVP S-630 (◆).

Figure 5: Supersaturation profile of (A) benzthiazide alone (○), and in presence of 10% (◆), 50% (◆), and 75% (◆) of PVP S-630; (B) pindolol alone (○), and in presence of 50% PVP K-90 (■), 50% PVP S-630 (◆), and 70% PVP S-630 (◆); (C) olanzapine alone (○), and in presence of 50% PVP K-25 (■), 50% PVP K-90 (■), and 50% PVP S-630 (◆); (D) isoxicam alone (○), and in presence of 50% of PVP K-12 (■), K-17 (■), K-25 (■), K-29/32 (■), and K-90 (■).

Figure 6: Supersaturation profile of tetracaine alone (○) and in presence of 50% of PVP K-12 (■), K-17 (■), K-25 (■), K-29/32 (■), K-90 (■), and S-630 (◆).

Figure 7: XRD spectra of (A) bendroflumethiazide: (a) commercial drug, (b) drug obtained after cheqsol experiments, (c) PVP K-12, (d) solid obtained after Cheqsol experiments of a mixture bendroflumethiazide:K-12 PVP at 50% ratio; (B) benzthiazide:

512 (a) commercial drug, (b) drug obtained after cheqsol experiments, (c) PVP S-630, (d)
513 solid obtained after cheqsol experiments of a mixture bendroflumethiazide:S-630 PVP
514 at 50% ratio.

Figure(s)

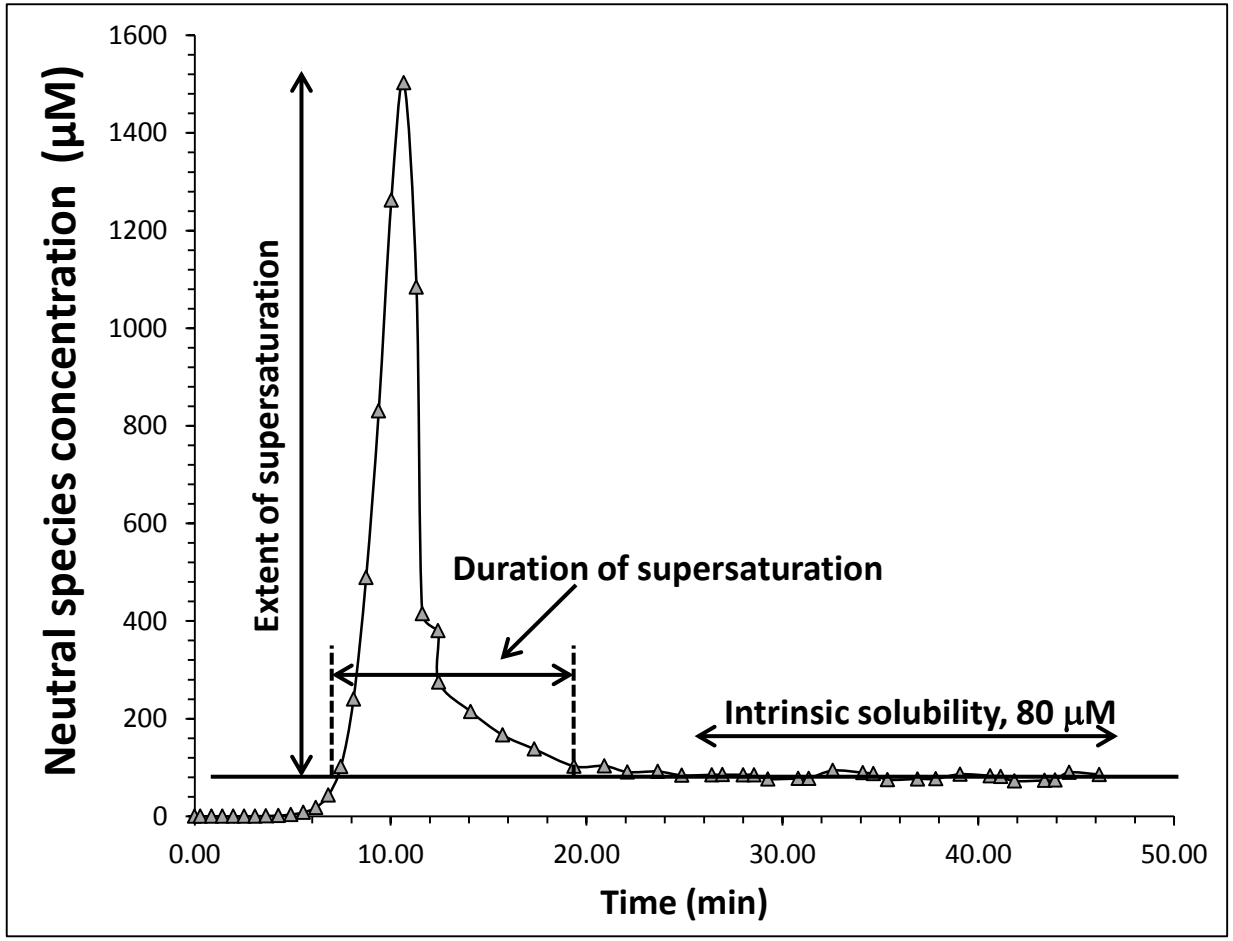
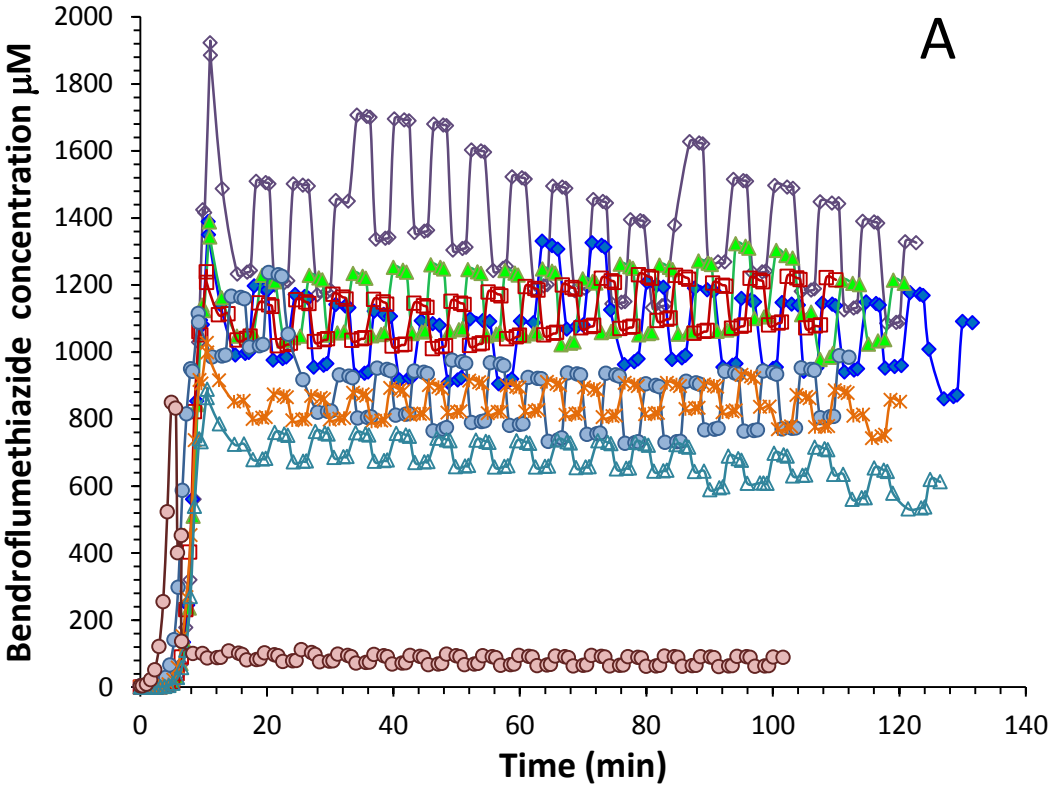


Figure 1

Figure(s)



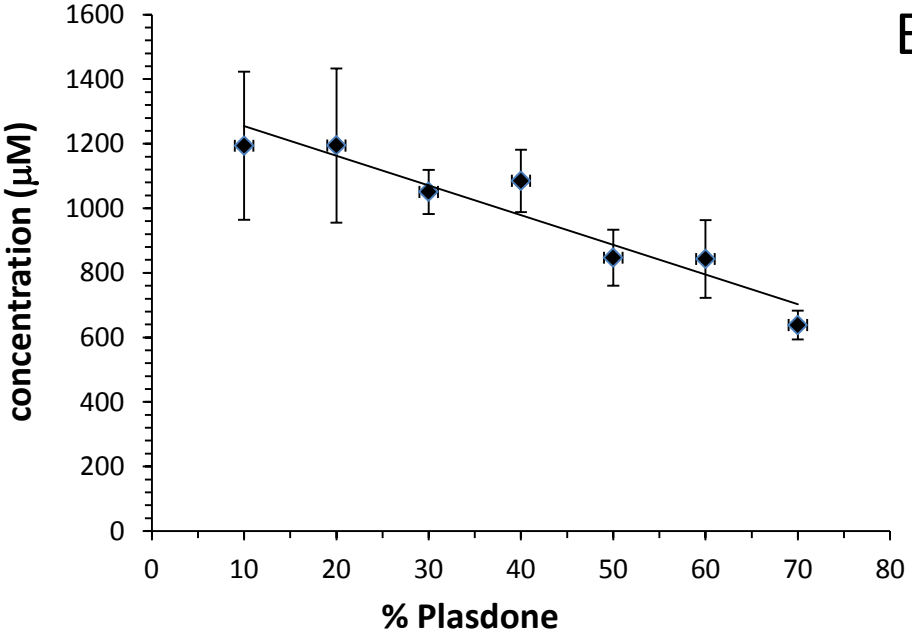


Figure 2

Figure(s)

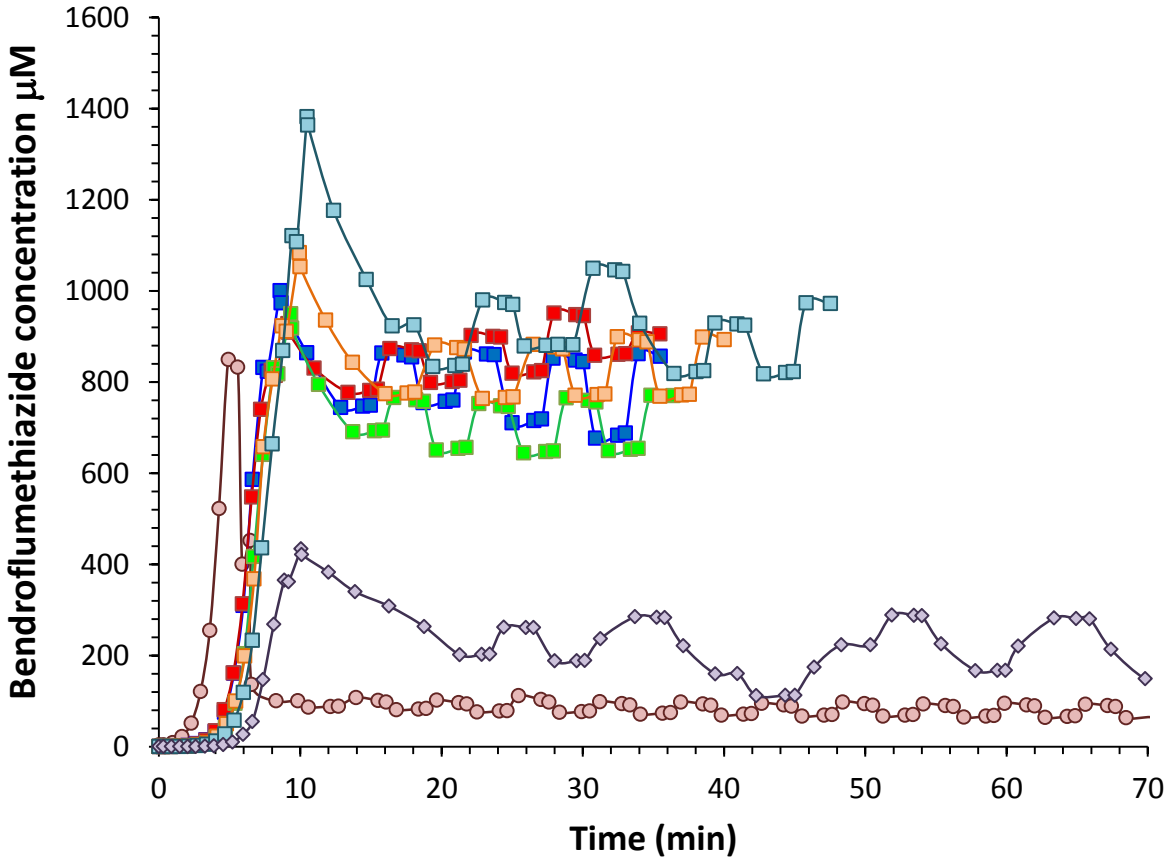


Figure 3

Figure(s)

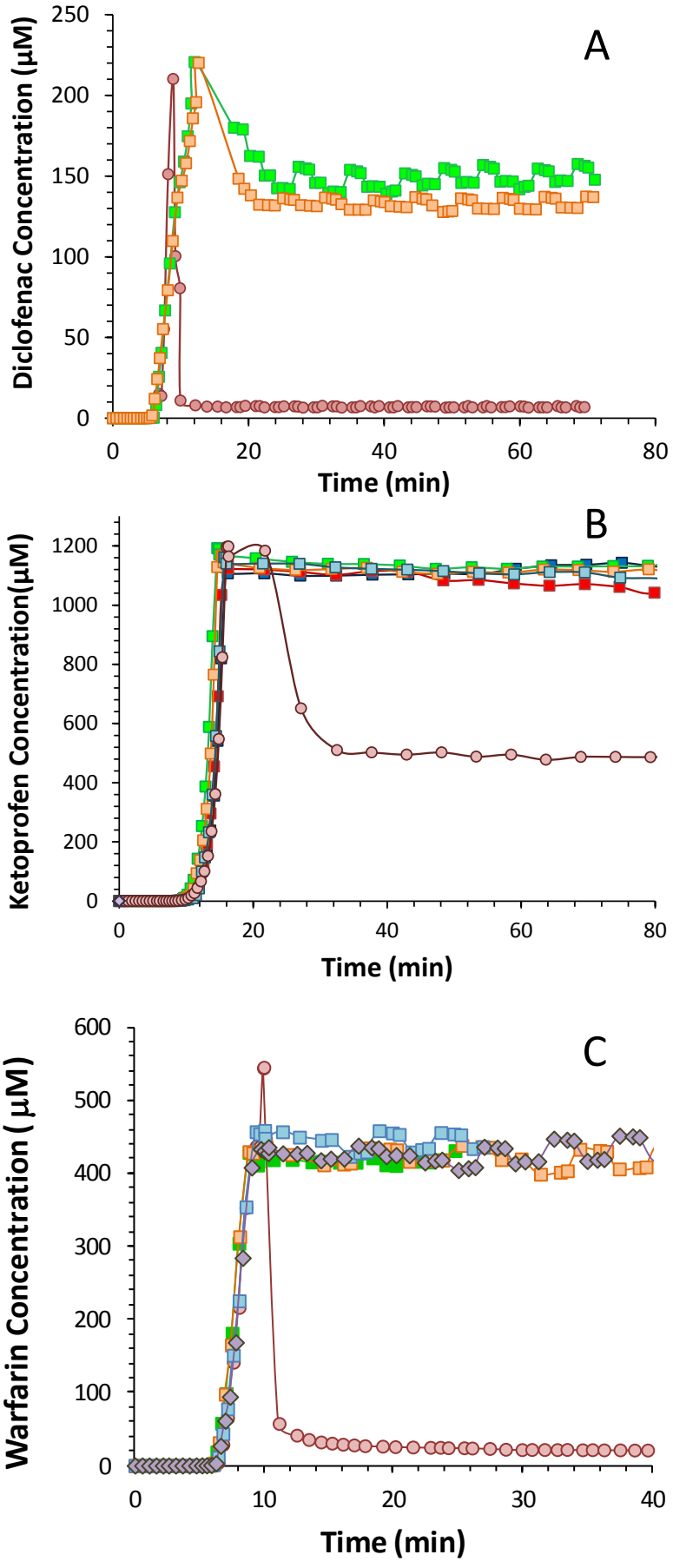


Figure 4

Figure(s)

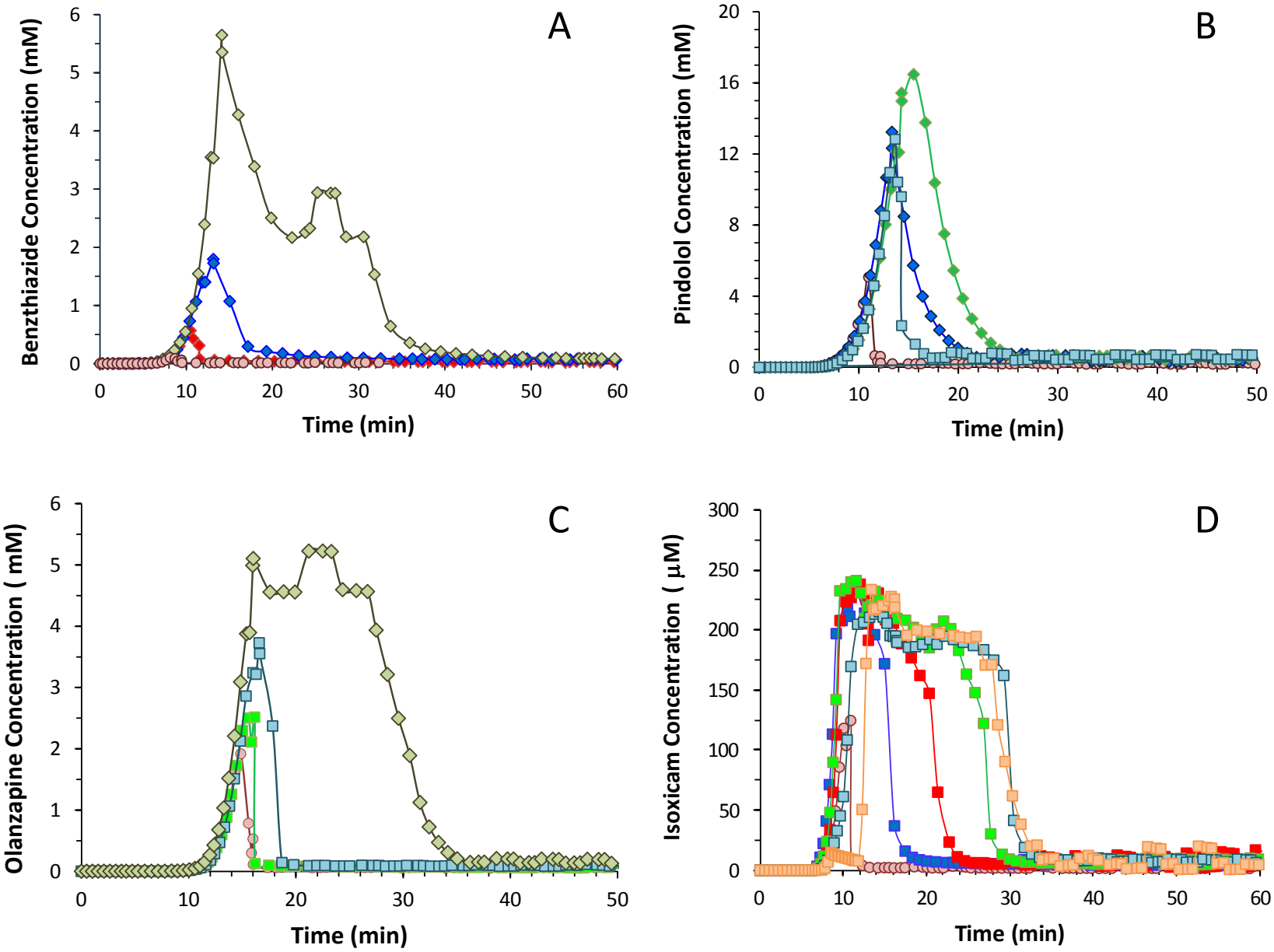


Figure 5

Figure(s)

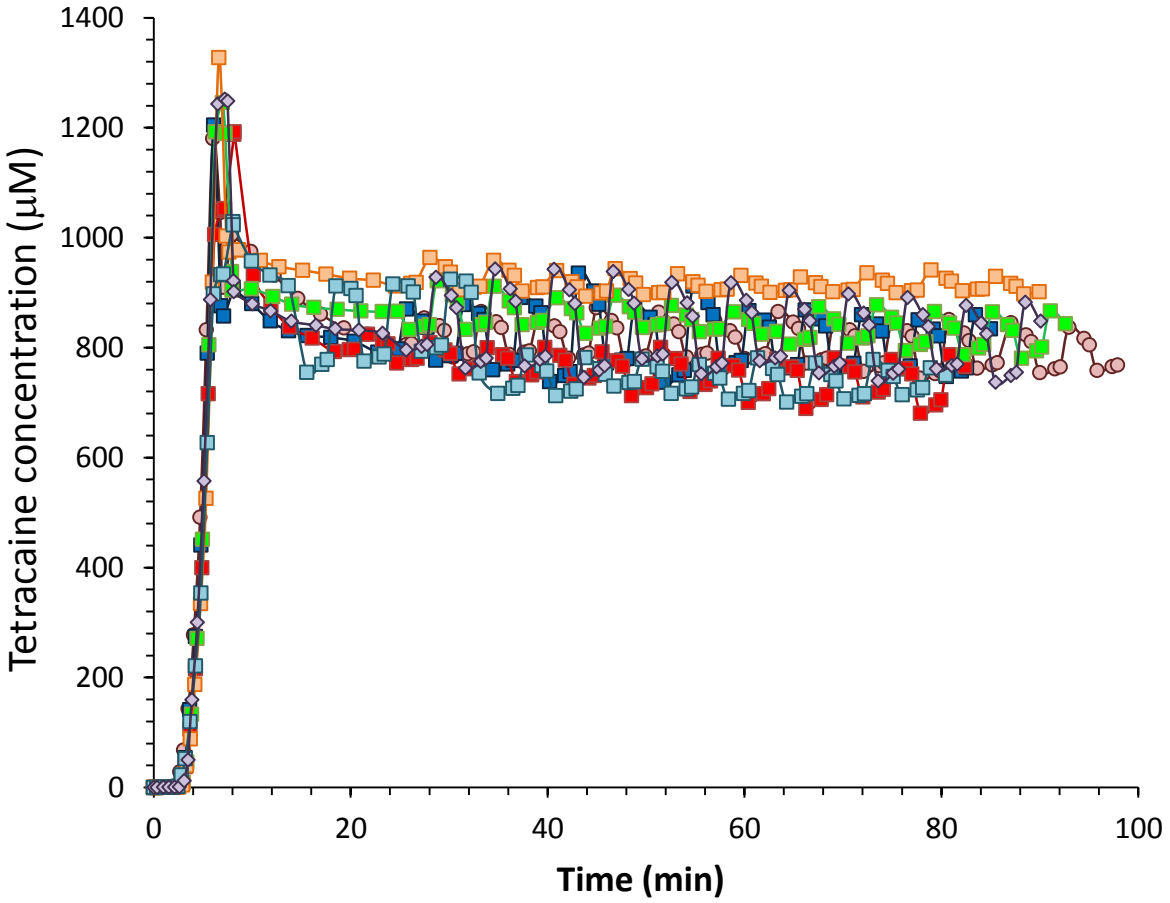
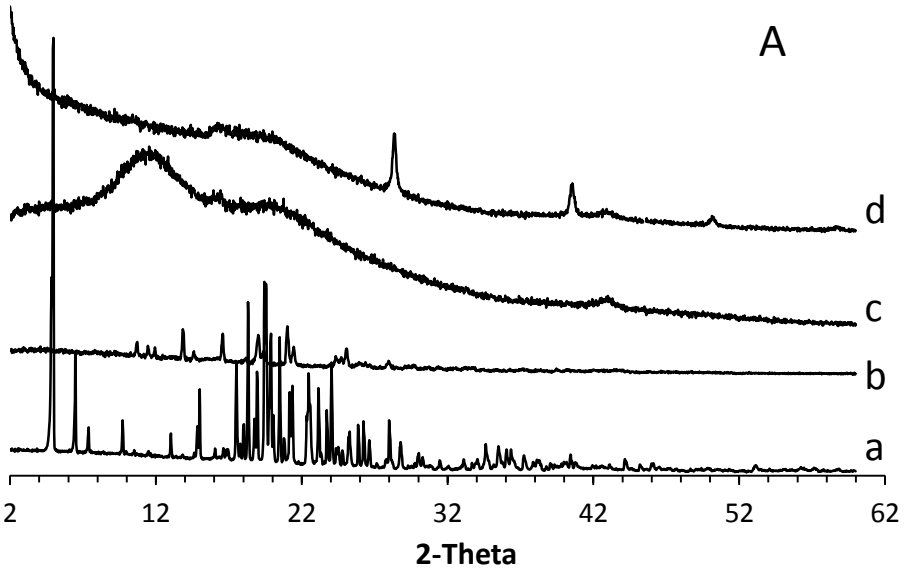


Figure 6

Figure(s)



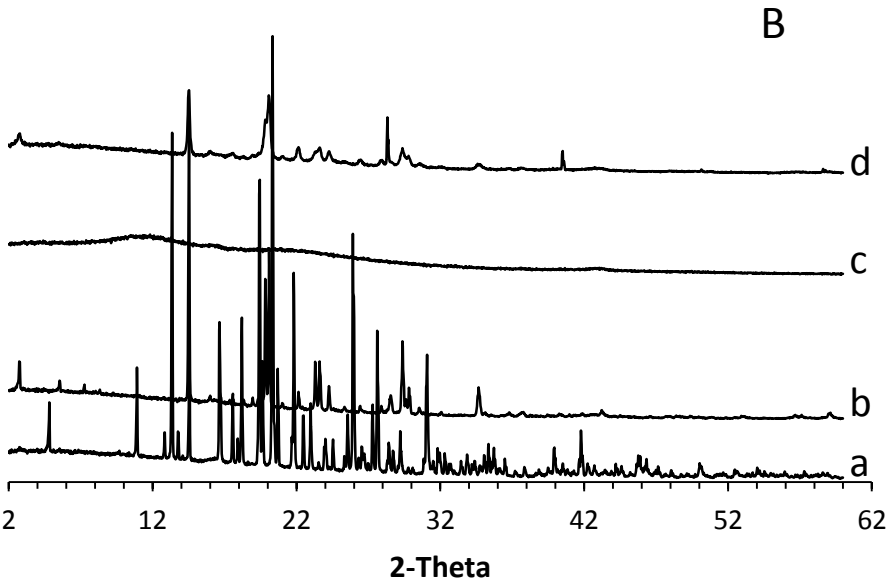
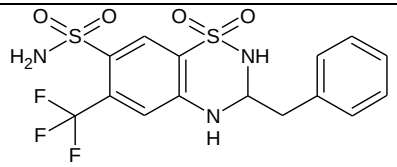
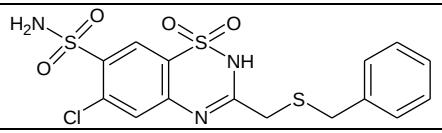
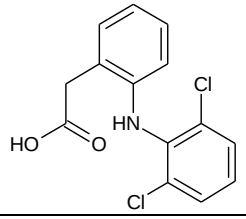
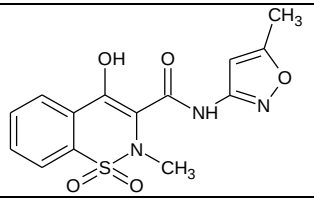
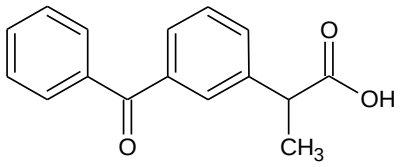
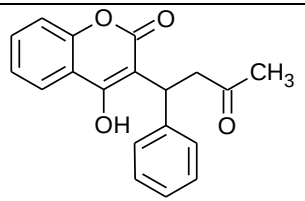
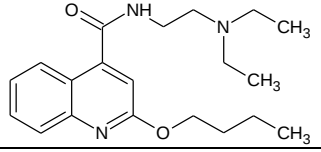
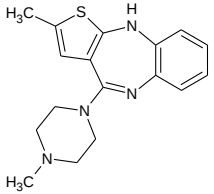
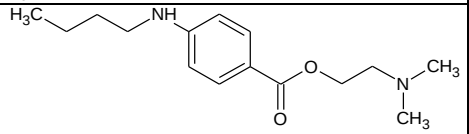
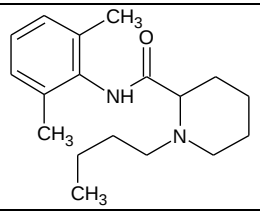


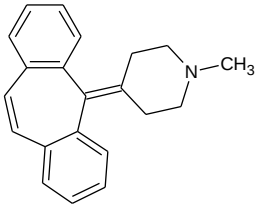
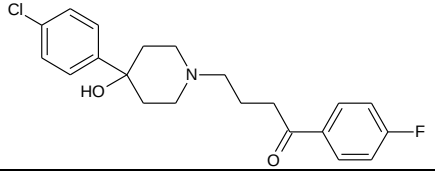
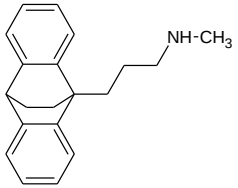
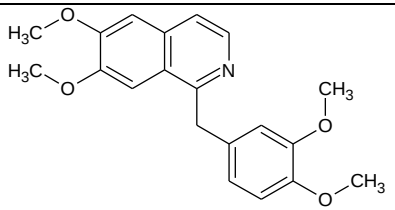
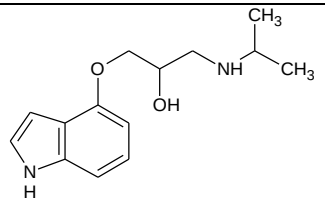
Figure 7

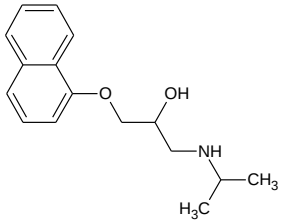
Table(s)

Table 1: Physicochemical parameters of the compounds under study. pK_a values provided are at 0.15M ionic strength and 25 ºC.9

Compound	Molecular structure	Type	pK_a	S_0 (μM)	log S_o	C max (μM)	Supersaturation ratio (R_s)	Time of supersaturation (t_s, min)
Bendroflumethiazide		H_2A	8.46 ± 0.02 9.99 ± 0.01	82 ± 3	-4.09 ± 0.02	1247 ± 405	13 ± 5	12 ± 3
Benzthiazide		H_2A	6.64 ± 0.03 9.22 ± 0.04	12 ± 1	-4.89 ± 0.09	91 ± 11	7 ± 2	4 ± 1
Diclofenac		HA	4.13 ± 0.01	8 ± 2	-5.13 ± 0.10	198 ± 14	27 ± 4	5.1 ± 0.9
Isoxicam		HA	3.84 ± 0.02	2.5 ± 0.8	-5.61 ± 0.14	137 ± 18	55 ± 7	6 ± 2
Ketoprofen		HA	4.00 ± 0.01	585 ± 84	-3.24 ± 0.06	1550 ± 237	2.6 ± 0.2	19 ± 1

Warfarin		HA	4.89 ± 0.01	20 ± 2	-4.70 ± 0.05	395 ± 63	20 ± 3	15 ± 4
Dibucaine		BH_2^{2+}	2.02 ± 0.01 8.64 ± 0.3	96 ± 4	-4.02 ± 0.02	250 ± 17	2.6 ± 0.1	20 ± 13
Olanzapine		BH_2^{2+}	5.59 ± 0.06 8.03 ± 0.01	59 ± 7	-4.23 ± 0.05	1884 ± 30	31.6 ± 0.5	5.6 ± 0.2
Tetracaine		BH_2^{2+}	2.33 ± 0.01 8.53 ± 0.07	819 ± 27	-3.09 ± 0.01	1236 ± 69	1.53 ± 0.07	19.8 ± 0.8
Bupivacaine		BH^+	8.18 ± 0.09	1172 ± 143	-2.93 ± 0.05	1582 ± 315	1.4 ± 0.1	7 ± 2

Cyproheptadine		BH^+	9.40 ± 0.18	10.0 ± 0.9	-5.00 ± 0.04	160 ± 82	16 ± 6	12 ± 3
Haloperidol		BH^+	8.44 ± 0.17	6.81 ± 0.94	-5.22 ± 0.13	303 ± 75	45 ± 9	5 ± 2
Maprotiline		BH^+	10.48 ± 0.1	15.8 ± 0.9	-4.80 ± 0.02	83 ± 13	5.0 ± 0.9	7 ± 2
Papaverine		BH^+	6.44 ± 0.02	39 ± 11	-4.42 ± 0.13	2284 ± 515	59 ± 11	16 ± 5
Pindolol		BH^+	9.48 ± 0.05	256 ± 45	-3.60 ± 0.08	4163 ± 612	15 ± 1	7.5 ± 1.5

Propranolol		BH^+	9.48 ± 0.02	329 ± 15	-3.48 ± 0.02	1976 ± 95	6.0 ± 0.1	17 ± 7