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Thermodynamic and analytical studies of drugs binary systems of paracetamol mixed with pseudoephedrine.HCl, dextropropoxyphene.HCl and tramadol.HCl

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ABSTRACT

In this paper, we report a DSC investigation of solid–liquid equilibria in three binary mixtures of paracetamol, namely with pseudoephedrine, dextropropoxyphene and tramadol, resulting in a temperature-composition phase diagrams with eutectic equilibrium. Eutectic mole fractions, temperatures and enthalpies were determined and reported for each system.

The study reports also a direct exploitation of the DSC results for the quantification purpose, which were in good agreement with those obtained by a standard analytical method namely high performance thin layer chromatography (HPTLC), used in this work for comparison purpose.

1. Introduction

Acetaminophen, collectively called paracetamol is one of the traditional, better tolerated, and active ingredients for short- and fast acting analgesics that act through different pathways from opioids [1]; it is an aniline derivative, having antipyretic properties but no anti-inflammatory effect.

Paracetamol is often combined with other drugs to enhance its therapeutic efficacy. These combinations are often prescribed for acute pain management as they have been shown to yield pain relief superior to single agents by either acting synergistically or targeting more than one physiological cause of the pain simultaneously [2]. In addition, combination products allow for lower dosing of the individual components, which can decrease the severity of adverse events associated with each agent. Reduced toxicity, together with the simplified dosing regimens associated with combination strategies, has been shown to increase patient compliance [2].

For the treatment of the range of symptoms associated with upper respiratory tract infection (URTI), the combination of paracetamol and a decongestant such as pseudoephedrine hydrochloride is widely used [3]. Paracetamol has been shown to be more effective than placebo in treating symptoms associated with URTI such as sore throat [4], headache [5] and fever [6], and pseudoephedrine has been shown to be more effective than placebo in treating the nasal symptoms associated with URTI [7–9]. The combination of paracetamol and pseudoephedrine used for up to 6 days has been shown to be more effective than placebo in treating the symptoms of URTI requiring the use of an analgesic and a decongestant [10].

Analgesics are also combined with paracetamol in order to combine the two substances with synergic effects obtaining rapid analgesic effect; In addition, safety is expected to improve due to the lower total dose of each of the two substances compared with either substance given at its currently recommended maximum daily dose [11–13].

Clinical evidence has shown that paracetamol combined with weak opioids (dextropropoxyphene or tramadol hydrochlorides) can serve as a first-line analgesic for postoperative pain [14–17]. Combination of these two sorts of analgesic agents with complementary mechanisms of action may enhance analgesia and at the same time reduce the risk of adverse events [18]. These combi-

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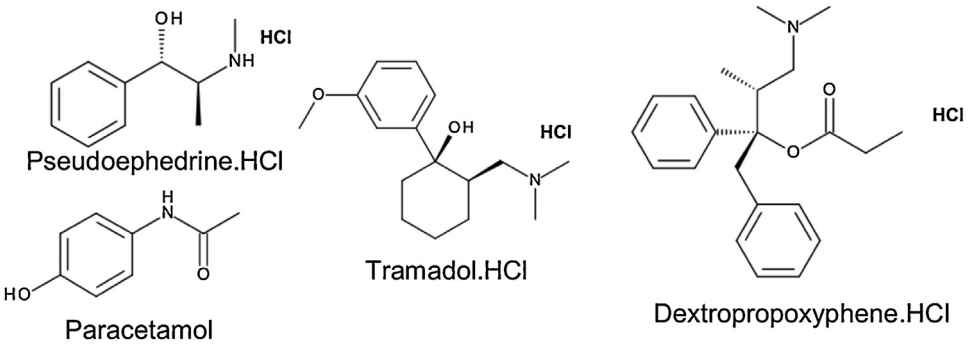

Fig. 1. Structures of the studied drugs.

Table 1
Chemicals used in this work.

Compound	Batch N°	Source	Purity on anhydrous basis (PA) (mass fraction)	Purity as basis (PB) (mass fraction)
Pseudoephedrine.HCl	003522AX20	BASF PharmaChemikalien GmbH & CO.KG. (Germany)	0.998[a]	0.997[b]
Dextropropoxyphene.HCl	DP20090518	Hy-gro Chemicals Pharmtek Private Limited. (India)	0.998[a]	0.996[b]
Tramadol.HCl	TRC0460410	Elder Pharmaceuticals Ltd. (India)	0.993[a]	0.991[b]
Paracetamol (Form I)	1550032	Anqiu Lu'an Pharmaceutical Co.Ltd. (China)	0.997[a]	0.996[b]

[a] According to the suppliers.
[b] Calculated by using the formula: Purity as basis (PB) = [Purity on anhydrous basis (PA) x (100- water content (%))]/100.
•Purity as basis corresponds to the raw purity of the substance, while purity on anhydrous basis implies that the water content has been taken into account.

nation drugs can provide a safe and effective analgesic option for ambulatory surgery.

In the pharmaceutical field, the knowledge of the drugs behavior toward the temperature is essential for the manufacture of various forms of medication, such as tablets and capsules. These forms of medicines represent heterogeneous systems consisting of one or more active pharmaceutical ingredients and a number of excipients, which can interact forming, for example, low-temperature eutectic melts or stable chemical compounds (cocrystals) [19]. Information on possible interactions among components of pharmaceutical formulations should be extract from equilibrium phase diagrams, which can be obtained experimentally or theoretically by the use of input thermodynamic data. Differential scanning calorimetry (DSC) is one of the appropriate methods for determination of equilibrium phase diagrams of binary systems comprising low-temperature melting organic substances [20–22].

Thermal analysis of pure paracetamol has been widely studied [23–27], and many binary systems comprising paracetamol, have been investigated by using DSC or other thermoanalytical methods, including systems of paracetamol with ascorbic acid and citric acid [19], theophylline [28], caffeine [19,29], phenazone [30], propyphenazone [31], 4-aminobenzoic acid [32], *p*-aminophenol [33], urea [34], acetylsalicylic acid [35], cellulose and hydroxypropylmethylcellulose [36], cloperastine hydrochloride [37], lactose, magnesium stearate and stearic acid [38], polyvinylpyrrolidone, magnesium stearate, citric acid, aspartame, mannitol, cellulose, starch [39], and phenobarbital [40].

The aim of this work is a DSC study of three binary systems of paracetamol (PAR), namely PAR–Pseudoephedrine hydrochloride (PSE.HCl), PAR–Dextrpropoxyphene hydrochloride (DXP.HCl) and PAR–Tramadol hydrochloride (TRM.HCl). The chemical structures of the studied substances are presented in Fig. 1.

Furthermore, because of the psychoactive nature of the studied drugs (pseudoephedrine, dextropropoxyphene and tramadol), the medicines made from the studied mixtures are often trafficked and as are highly sought by drug abusers, reason why these drugs are often seized by police forces and sent to laboratories for analysis and expertise. Therefore, another objective of this work was the use of DSC as alternative simple, rapid, reliable and precise method for the simultaneous determination of the studied drugs in seized materials.

Table 2
Physical properties of pure compounds: melting temperature, T_m; enthalpy of fusion, ΔH_m, at pressure $p = 0.1$ MPa[a].

Compound	T_m/K	ΔH_m/J g^{-1}
Pseudoephedrine.HCl	458.0[b]	135.6[b]
	456.4[c]	139.3[c]
Dextropropoxyphene.HCl	441.0[b]	84.6[b]
	(435.5–441.5)[d]	
Tramadol.HCl	457.2[b]	98.6[b]
	455.7[e]	
Paracetamol (Form I)	443.4[b]	180.3[b]
	(440.9–442.0)[f]	(179.7–186.0)[f]
	(440.0–445.1)[g]	(172.0–225.6)[g]
	(441.0–444.0)[h]	(178.6–185.9)[h]
	(442.2–443.6)[i]	(179.3–185.9)[i]
	(441.9–443.2)[j]	(172.0–185.6)[j]

[a] Standard uncertainties u are $u(\Delta H) = 2.0$ J g^{-1}, $u(T) = 1.0$ K, $u(p) = 10$ kPa.
[b] Our experimental Values.
[c] Ref. [47].
[d] Ref. [48].
[e] Ref. [49].
[f] Ref. [19].
[g] Ref. [23].
[h] Ref. [50].
[i] Ref. [51].
[j] Ref. [52].

Differential scanning calorimetry was suggested in the past for the direct analysis of some illicit drugs such as cocaine [41], and amphetamine type stimulants (ATS) [42], and was also used for purity determination of some drugs and organic compounds [43–46]. However, in the present work, an original methodology was adopted by using a total enthalpy (combination of the eutectic and the melting enthalpies) for plotting the DSC calibration curves, which will be then exploited for the quantification study. The results will be compared to those obtained by a classical analytical method, namely High Performance Thin Layer Chromatography (HPTLC).