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Application of machine learning in prediction of hydrotrope-enhanced solubilisation of indomethacin

Safa A. Damiati[a], Luigi G. Martini[b], Norman W. Smith[c], Jayne M. Lawrence[a,*,1], David J. Barlow[a,*]

[a] Institute of Pharmaceutical Science, Faculty of Life Sciences & Medicine, Franklin-Wilkins Building, King's College London, 150 Stamford Street, London, SE1 9NH, UK
[b] Roche Products Ltd. (Pharmaceuticals), Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW, UK
[c] Analytical and Environmental Science Division, Faculty of Life Sciences & Medicine, King's College London, 150 Stamford Street, London, SE1 9NH, UK

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ABSTRACT

Systematic *in-vitro* studies have been conducted to determine the ability of a range of 10 potential hydrotropes to improve the apparent aqueous solubility of the poorly water soluble drug, indomethacin. Solubilisation of the drug in the presence of the hydrotropes was determined experimentally using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. These experimental data, together with various known and computed physicochemical properties of the hydrotropes were thereafter used *in silico* to train an artificial neural network (ANN) to allow for predictions of indomethacin solubilisation. The trained ANN was found to give highly accurate predictions of indomethacin solubilisation in the presence of hydrotropes and was thus shown to provide a valuable means by which hydrotrope efficacy could be screened computationally. Interrogation of the network connection weights afforded a quantitative assessment of the relative importance of the various hydrotrope physicochemical properties in determining the extent of the enhancement in indomethacin solubilisation. It is concluded that *in-silico* screening of drug/hydrotrope systems using artificial neural networks offers significant potential to reduce the need for extensive laboratory testing of these systems, and could thus provide an economy in terms of reduced costs and time in drug formulation development.

1. Introduction

The task of optimising drug solubility remains a major concern for the formulator of pharmaceutical dosage forms. Approximately 40% of drugs with market approval and almost 90% of compounds in the development pipeline fail to reach the market because of problems of poor aqueous solubility (Kalepu and Nekkanti, 2015; Zhang et al., 2014). It is well known that poor aqueous solubility can significantly limit a drug's bioavailability and ultimately,

* Corresponding authors.
E-mail address: dave.barlow@kcl.ac.uk (D.J. Barlow).
[1] Current address: Division of Pharmacy & Optometry, University of Manchester, Stopford Building, Oxford Road, Manchester, M13 9PT, UK.

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therefore, its efficacy, thereby necessitating the administration of higher doses and increasing the chance of side effects as well as costing more per patient (Williams et al., 2013). There are numerous formulation strategies that have been proposed and used to overcome this problem, and one such strategy involves the use of hydrotropes (Kunz et al., 2016).

The term of hydrotropy was used to describe the increase of the apparent aqueous solubility of insoluble or slightly soluble organic substances in water by the addition of large concentrations of some organic acid salts of alkali metal such as sodium benzoate (Neuberg, 1916). Hydrotropes are modestly amphiphilic organic compounds that possess only a relatively small hydrophobic moiety which were considered as non-micelle forming compounds (Elworthy et al., 1968). Unlike surfactants, however, – which can also be used to enhance drug solubilisation – hydrotropes achieve their solubilisation effects only at quite high concentration, generally, in the molar rather than the millimolar range (Balasubramanian et al., 1989; Hopkins Hatzopoulos et al., 2011).

The phenomenon of hydrotropy was first recognised by Carl Neuberg back in 1916 (Neuberg, 1916) but there has been relatively little work since that time performed to explore – in a detailed and systematic manner – the ability of different hydrotropes to increase the apparent (drug) solubility. A variety of mechanisms have been proposed for hydrotropic solubilisation including: increased drug solubilisation as the result of hydrotrope self-aggregate formation (Badwan et al., 1983; Balasubramanian et al., 1989; Cui et al., 2010), hydrotrope-induced alteration of the water structure (Coffman and Kildsig, 1996), formation of solute-hydrotrope complexes (Sanghvi et al., 2007), and more recently, solubilisation driven by an accumulation of hydrotrope around the drug (Abbott et al., 2017; Booth et al., 2015; Shimizu and Matubayasi, 2014).

As a consequence of our incomplete understanding of the phenomenon, the task of selecting an appropriate hydrotrope for a given poorly water-soluble drug is generally approached simply by trial-and-error screening of a large number of potential hydrotropic agents. Such selection, however, might be much more conveniently made *in silico* using artificial neural networks (ANNs). ANNs are biologically inspired computational models capable of simulating the brain's ability to learn by example; they provide particularly powerful tools to aid in the modelling of non-linear relationships and have found numerous applications in the pharmaceutical sciences (Gawehn et al., 2016; Marsland, 2015; Sutariya et al., 2013).

In the studies reported here our aim was to explore the potential for using ANNs to predict the effects of likely hydrotropic agents on the apparent aqueous solubility of poorly water-soluble drugs. In order for such *in-silico* predictions to provide significant benefit to drug formulators, the ANN ultimately produced would need to cater for *any* poorly water-soluble drug, and be able to provide reliable predictions of the solubility enhancements achieved using *any* potential hydrotrope. In the initial studies reported here, however, we aimed only to establish proof of principle, seeking only to determine whether an ANN could be trained to give reliable predictions of the solubility enhancements achieved using different hydrotropic agents for just a *single* drug. The drug chosen for the studies was the non-steroidal, anti-inflammatory agent, indomethacin (Fig. 1). This particular drug was chosen in part because of the interest in producing aqueous formulations for injection and ophthalmic use (Elsaman and Ali, 2016; Halim Mohamed and Mahmoud, 2011; Sostres et al., 2013), and partly because there have been some experimental studies reported in which hydrotropes have been explored as a means to improve its aqueous solubility (Jain, 2008).

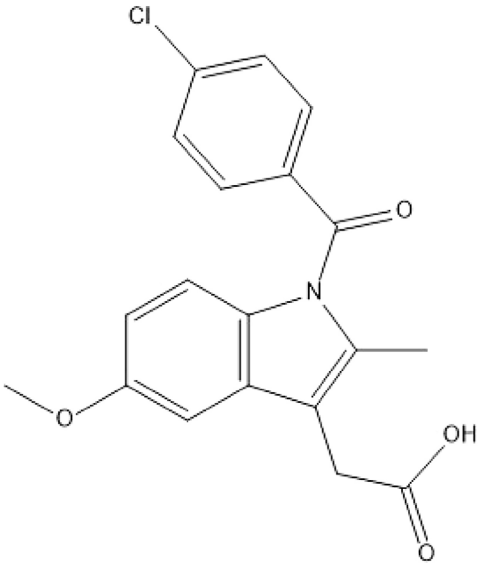

Fig. 1. Chemical structure of indomethacin.

Experimental data were obtained on the solubilisation of the drug using a systematically chosen range of 10 potential hydrotropes, each possessing a simple (phenyl or pyridinyl) aromatic hydrophobe and a hydrophilic group comprising a carboxylate, sulfonate, or amide moiety. The chosen compounds included, sodium nicotinate, sodium benzoate, sodium salicylate, sodium gentisate, sodium benzenesulfonate, sodium *p*-toluenesulfonate, benzamide, *N,N*-dimethylbenzamide, nicotinamide, and *N,N*-diethylnicotinamide (Fig. 2). The drug solubilisation data obtained were taken along with various known and computed physicochemical descriptors of the hydrotropes and were used to train an ANN to allow for prediction of new hydrotropes for indomethacin.

2. Materials and methods

2.1. Chemicals and reagents

Indomethacin (purity ≥99%, confirmed as the λ polymorph, and used as received), sodium nicotinate, sodium benzoate, sodium salicylate, sodium gentisate, sodium benzenesulfonate, sodium *p*-toluenesulfonate, benzamide, *N,N*-dimethylbenzamide, nicotinamide, *N,N*-diethylnicotinamide, pyridoxine, and formic acid were all purchased from Sigma-Aldrich Ltd. (Dorset, U.K.). Caffeine was supplied from Alfa Aesar (Lancashire, U.K.). Both water and acetonitrile were HPLC-grade and were obtained from Fisher Scientific UK Ltd. (Leicestershire, U.K.). All chemical reagents were ≥95% pure and used as received. Water at 18.2 mΩ.cm (25 °C) was purified by an ultra-pure water system (ELGA, UK).

2.2. Instrumentation and chromatographic conditions

Chromatographic analysis of indomethacin was performed using an HP 1050 series liquid chromatography system (Agilent Technologies, UK), equipped with HP 1050 quaternary pump, DAD detector, autosampler, and column oven, and a G1379A vacuum degasser. The system was controlled by ChemStation Software (version A10.02). Chromatography was performed using an XTerra 3.5 μm C18 column, 2.1 mm ID X 150 mm length (Waters, Milford, USA). The mobile phase was 45:55% (v/v) acetonitrile:water with 0.1% formic acid at a flow rate of 0.3 mL/min. The injection volume was 5 μL and the wavelength set at 320 nm. All measurements were made in triplicate and averaged for all experiments. The total