PP - 009

Identifying and localizing molecular polarities as a basic process to predict compatible drug mixtures

A. Dubied, Hospital Pharmacist – Retired, Gebenstorf AG, Switzerland

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So far – and today

1) Looking up the pH-values of two not buffered drug solutions:
They should not differ more than 2 pH-unities. Buffered solutions should not differ more than 1 pH-unit (carefully attend the presence of protondonors / protonacceptors as ingredients).

References:
W.Felis, Kompatibilitätsstudie (german!), MPS Mainz, 1981, out of stock,
www.kingguide.com, www.micromedexsolutions.com (Trissel)

2) A knowledge respected in biology, biochemistry and water sciences, is not consequently adopted in pharmaceutical considerations:

Two basic forces determine the water structure: electrostatics (**water's dipole interacting with ions**), hydrogen bonding (**water interacting with neighboring waters**).
Charge densities govern the extent of both types of interactions.

Reference e.g.: Wiggins P (2008) Life depends on two kinds of water DOI: 10.1371/journal.pone.0001406

Diagnose compatibilities

Two drug solutions applied by y-site administration are compatible, if:

1) They do not differ more than 2 pH-unities if no buffering ingredients are present.
2) Buffered solutions do not differ more than 1 pH-unit (check the presence of protondonors/protonacceptors as ingredients).
3) The pPol-values lay in corresponding ranges (the numeric scope remains actually to be settled more precisely)
4) All values of all ingredients were considered respecting their impacts (inorganic salts, mostly tha anions are decisive

Figure2 illustrates the statement of point 3. Please allow that the bars are indicating the values of the starting or the endpoint of a value range and not the range itself.

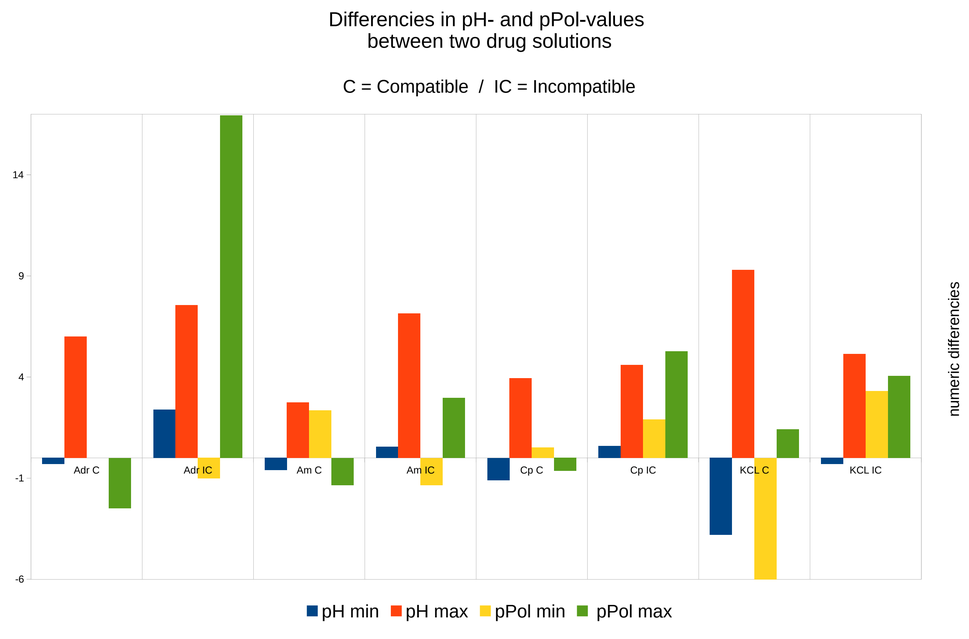

Figure 2: Initial and endpoints of the indicated parameter ranges in relation to the values of the agent chosen as reference

Idea 1

Examining compatible and incompatible drug solutions let us incorporate the following established facts:

- We have to know possible polar contacts between a chemical substance and water (see figure 1 below).
- All solutes appear to partition selectively into either high density water (HDW, non-tetrahedral O-O-O angles and a collapsed second coordination shell) or low density water (LDW, open hydrogen-bonded tetrahedral structure), generating osmotic pressure gradients: The solutes are solved in clusters not evenly distributed. DOI:http://dx.doi.org/10.1103/PhysRevLett.84.2881
- If water can move to abolish an osmotic pressure gradient, it does so: Reorganisation of a new water structure equilibrium.

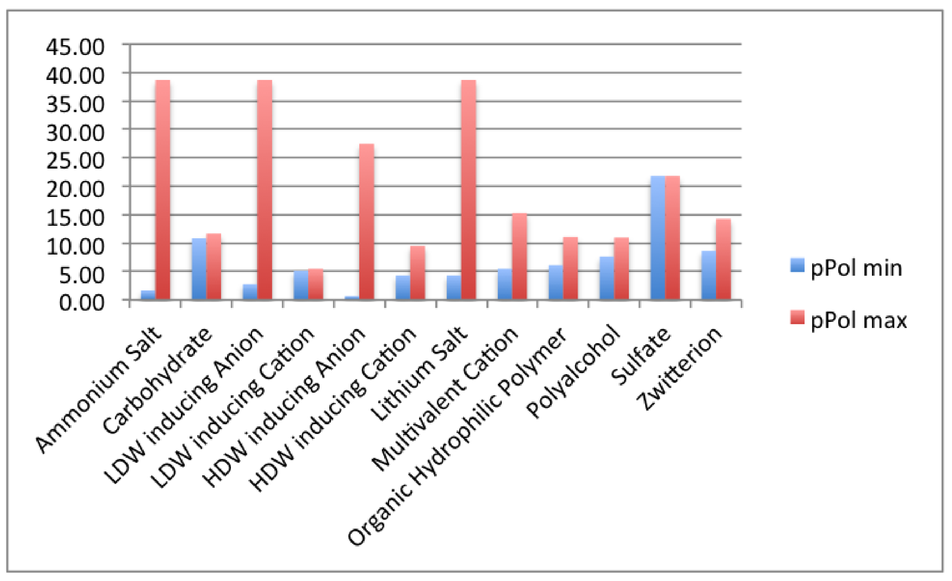

Figure 1: pPol values of several chemical classes of adjuvants

Idea 2

Let us define the polar (and nonpolar) properties of an ingredient. All chemical ingredients govern the appropriate water structure of the solution through the polarities of their chemical functional groups:

Amide > Acid > Alcohol > Ketone ~ Aldehyde > Amine > Ester > Ether > Alkane (examples listed in decreasing order of polarity) not to forget the not localisable excited π-electrons in aromatic structures.

PSA = Polar surface area (Å2) is the molecular parameter depicting polar areas of the molecular surface. Its reference value is the **SASA** = Solvent accessable surface area (Å2).

Furthermore the molecular polarisabilities **mPol** (Å3) can be calculated. The corresponding values can be downloaded from databases free of charge: www.chemspider.com or www.chemicalize.org.

With these three parameters at hand we assume that water molecules adress their dipol-inducing power at the very moment of mutual contact **preferentially to the nonpolar surface.**

Thus, we can calculate a **potential polarisation (pPol)** of a molecule in aqueous solution with the following equation:

$$pPol = (mPol / (SASA - PSA) \times f$$

Dimension = (Å); f = Factor adjusting the display format

Now, please list all ingredients of the drug solution und their pPol values. The pPol values of the inorganic salts are decisive since they are strongly influencing the water structure (HDW, LDW).

DISCLAIMER Nothing to disclaim.

Most data required may be found and verified at no charge in the public domain. See also www.pharmamind.ch, the dedicated database and author system under construction).
The model presented is still evolving. All ideas, corrections and complements are welcome!

Contact the author: ***andre.dubied(at)gmail.com***