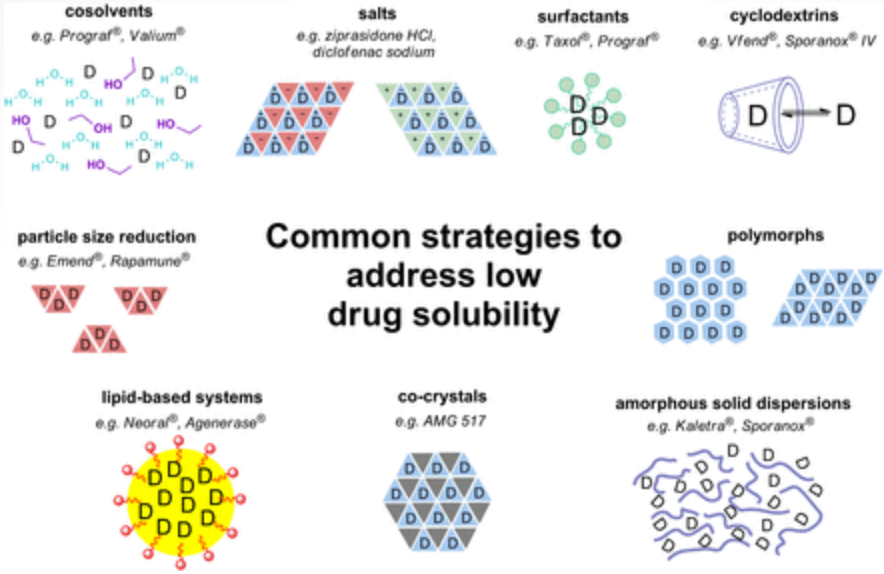

Biopharmaceuitcs lab 7

PH and Solvent Effect on Drug Solubility

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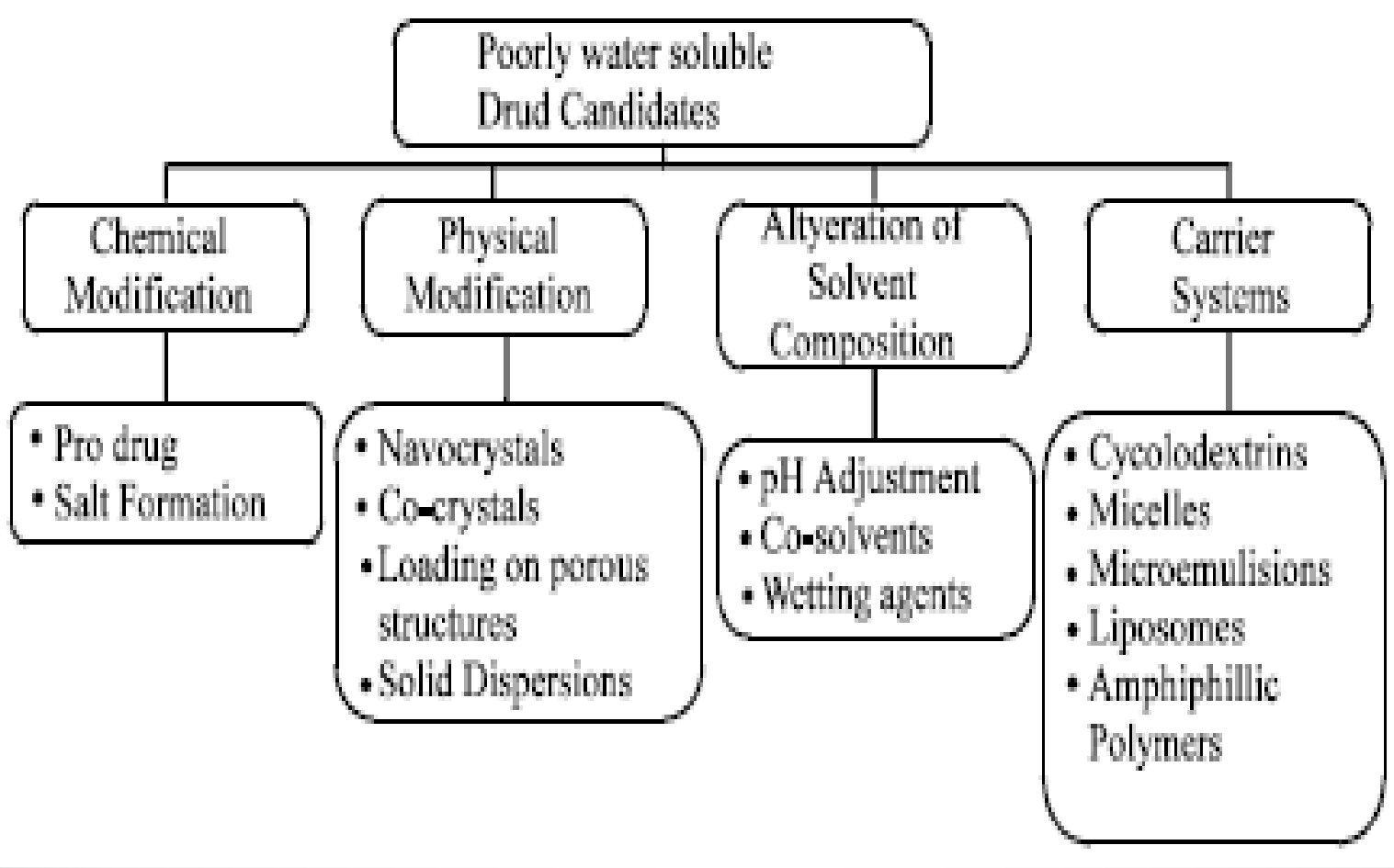
- The emerging trends in the combinatorial chemistry and drug design have led to the development of drug candidates with greater lipophilicity , high molecular weight and poor water solubility.

- Majority of the failures in new drug development have been attributed to poor water solubility of the drug. Issues associated with poor solubility can lead to low bioavailability resulting in suboptimal drug delivery.

- About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble.

Insoluble drug delivery strategies



- In formulating liquid solutions of pharmaceuticals, it is important for the pharmacist to be aware of factors which may affect the solubility of the individual drug constituents .
- Two such factors which can be used to advantage in increasing solubility are the effect attributable to **PH and solvent**.

❖ pH modification and salt forms :

Nearly 70% of drugs are reported to be ionizable , of which a majority are **weakly basic.** A pH-dependent solubility is exhibited by ionizable drugs, wherein weakly acidic drugs are more soluble at pH> pKa (ionization constant)and weakly basic drugs are soluble at pH< pKa. This pH dependent solubility was explored extensively to formulate insoluble drugs.

Examples for pH – dependant solubility

- Ciprofloxacin is a classic drug which is weakly basic and practically insoluble in water at neutral pH . However it exhibits pH-dependent solubility with higher solubility at acidic condition.
- Most of the intravenous formulations contain **lactic acid as pH modifier** to improve solubility. Intravenous ciprofloxacin infusions are essential for
- treating different kinds of severe bacterial infections.

- Insoluble drugs are mostly formulated using the salt forms of weakly acid and basic drugs.

- The soluble **aspirin-D,L-lysine salt** was formulated for intravenous injection(IV).

- Recently FDA approved Advil®, **a sodium salt of ibuprofen** .This product is superior in terms of its rapid onset of action as compared to Advil Liqui-Gels capsules containing ibuprofen .

❖ **Co-solvency**

- Formulation of insoluble drugs using co-solvents is also one of the oldest and widely used technique, especially for liquid formulation intended for oral and intravenous administration.

- At a certain PH , the relative concentration of ionic and the molecular moieties of a drug are given by the Henderson- Hassel Balch equation.

For a weak acid HA , which ionizes according to equation 1:

$$HA + H_2O = H_3O^+ + A^- \quad \text{eq(1)}$$

The following relation is obtained:

Ka: dissociation constant
A^- : molar concentration of the acidic anion
HA: molar concentration of the undissociated acid.

$$PH = pka + \log \frac{A^-}{HA}$$

Eq (2)

- As seen from eq 2 ,**the concentration of ionic moiety of weak acid increases with increasing the PH of the aqueous solution** (i.e. for acidic drugs ,the lower the pka ,the stronger the acid).

- If we consider the example of certain weak acid , barbiturates , sulfonamides, etc)which are not highly soluble in distilled water alone.

- We find that an increase in PH and alcohol concentration lead to increase solubility of the drug. Such changes in formulation ,must be used **with caution** , since at extremes of high pH and high alcohol concentration ,**undesirable side effects** become apparent. For example the salts of barbiturates are subject to **decomposition** in aqueous solutions particularly above pH 8.

- **At very high alcohol concentrations, the taste of the vehicle becomes objectionable to the patient.**
- In order to avoid these difficulties, it is possible to determine an **optimal combination of pH and alcohol concentrations**, where solubility ,stability and patient acceptance are maximal.
- An analogous form of eq 2 can be derived for calculating the pH below which the undissociated form of weak organic acid begins to separate from solution

pHp : pH below which the drug separates from solutions as the undissociated acid.
S: total solubility for both dissociated and undissociated forms.
S^o: molar solubility of undissociated form .

$$pH_p = pK_a + \log \frac{S - S_0}{S_0}$$

Key Concept

Solvents and Weak Electrolytes

The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways: (*a*) The addition of alcohol to a buffered aqueous solution of a weak electrolyte increases the solubility of the un-ionized species by adjusting the polarity of the solvent to a more favorable value. (*b*) Because it is less polar than water, alcohol decreases the dissociation of a weak electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased (pK_a is increased).

Combined Effect of pH and Solvents

- Edmonson and Goyan investigated the effect of alcohol on the solubility of phenobarbital.
- The results of Edmonson and Goyan are shown in Figure 1, where one observes that the pKa of phenobarbital, 7.41, is raised to 7.92 in a hydroalcoholic solution containing 30% by volume of alcohol.
- Furthermore, as can be seen in Figure 2, the solubility, So, of un-ionized phenobarbital is increased from 0.12 g/100 mL or 0.005 M in water to 0.64% or 0.0276 M in a 30% alcoholic solution.

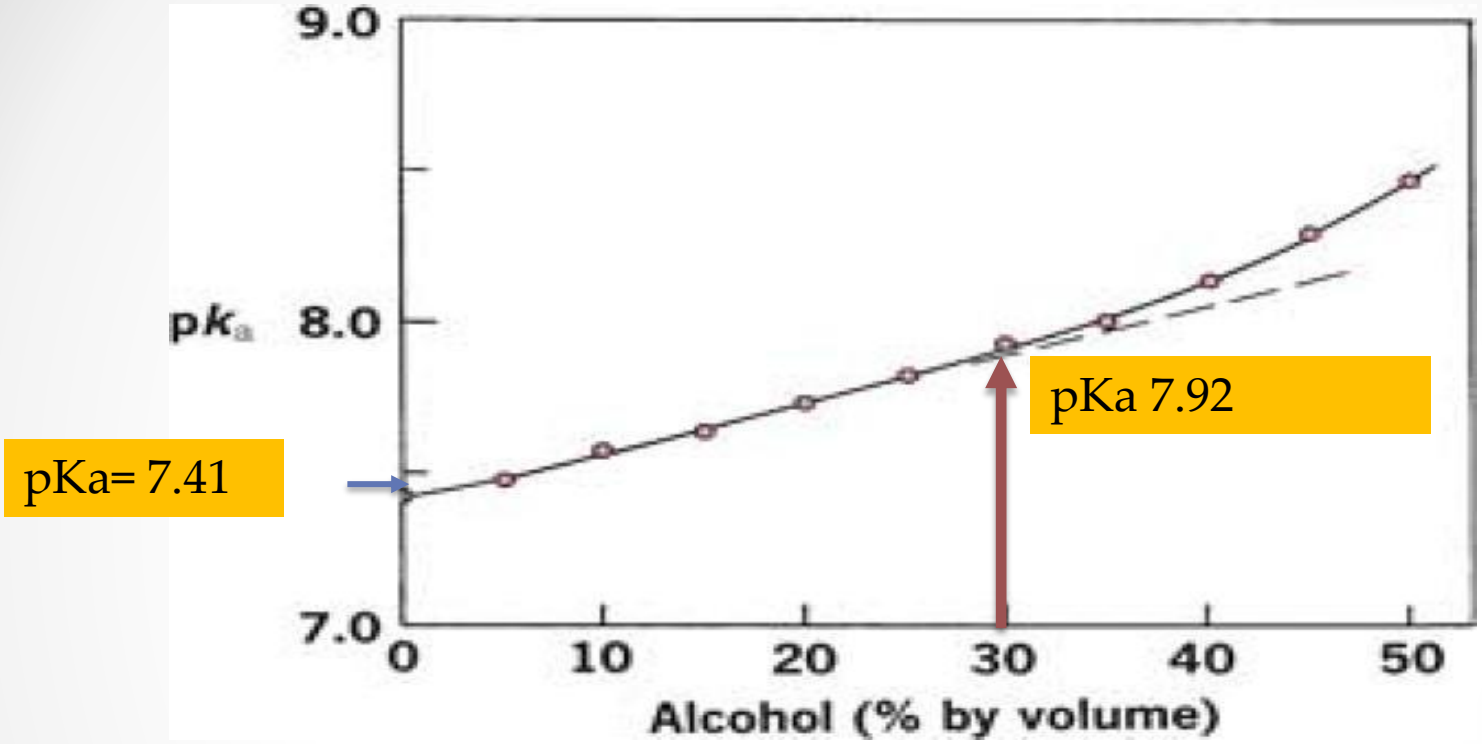
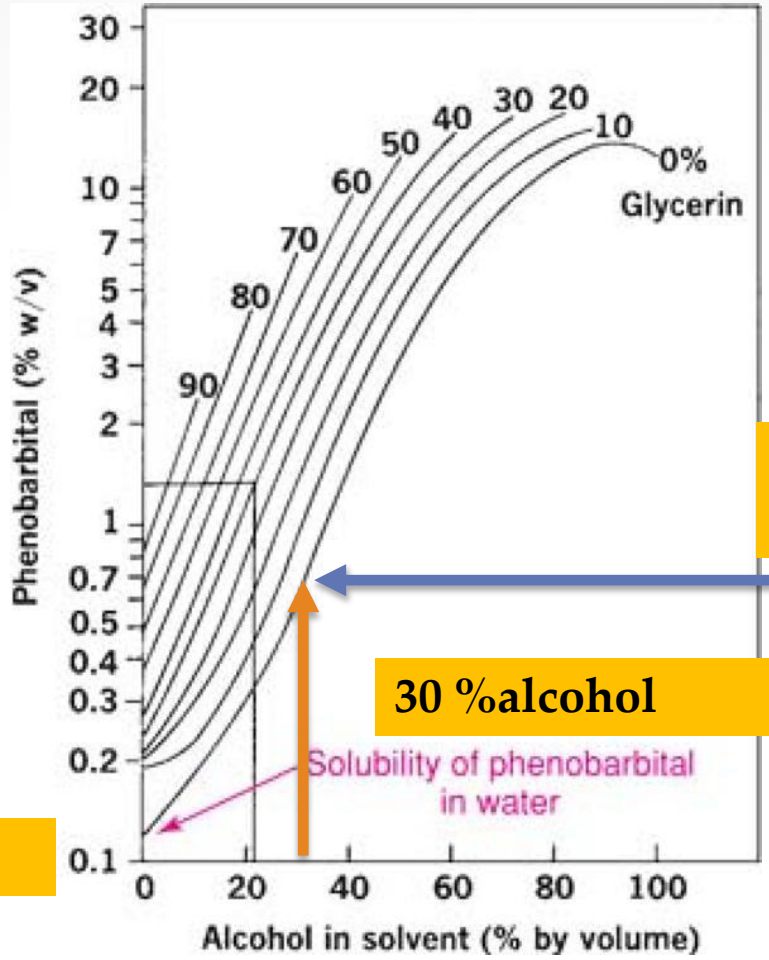


Fig 1



So = 0.64%=0.0276M ≈ 0.028 M

30 %alcohol

S0= 0.12%=0.005 M

Fig 2

- The calculation of solubility as a function of pH involving these results is illustrated in the following example

6gm/254=0.0236 mol/100 ml
0.0236 mol/100 ml
X /1000 ml=
0.236mol/L

Example 9-3

Minimum pH for Complete Solubility

What is the minimum pH required for the complete solubility of the drug in a stock solution containing 6 g of phenobarbital sodium in 100 mL of a 30% by volume alcoholic solution?

From equation (9-9),

$$pH_p = 7.92 + \log \frac{0.236 - 0.028}{0.028}$$

$$pH_p = 7.92 + 0.87 = 8.79$$

For comparison, the minimum pH for complete solubility of phenobarbital in an aqueous solution containing no alcohol is computed using equation (9-9):

$$pH_p = 7.41 + \log \frac{0.236 - 0.005}{0.005} = 9.07$$

- From the calculations of Example 9-3, it is seen that **although the addition of alcohol increases the pKa, it also increases the solubility of the un-ionized form of the drug over that found in water sufficiently so that the pH can be reduced somewhat before precipitation occurs.**