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PHYSIOCHEMICAL ASSESSMENT OF PHARMACEUTICAL SALT FORMS: A QUALITY ATTRIBUTE

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ABSTRACT

Salt formation is a simple way of modifying the properties of a drug having ionisable functional groups in order to overcome some undesirable characteristic of the parent drug. An active pharmaceutical ingredient often has suboptimal physicochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug molecule with a counterion to create a salt version of the drug. Physicochemical characteristics of a drug can be dramatically altered by salt formation. Around 50%of drug administered as salts. The chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Salt-forming agents are often chosen empirically. They can be selected by

INTRODUCTION

The term pharmaceutical salt is used to refer to an ionisable drug that has been combined with a counterion to form a neutral complex. Converting a drug into a salt through this process can increase its chemical stability, render the complex easier to administer and allow manipulation of the agent's. Salt selection is now a common standard operation performed with small ionisable molecules during drug development, and in many cases the drug salts display preferential properties as compared with the parent molecule. As a consequence, there has been a rapid increase in the number of drugs produced in salt form, so that today almost half of the clinically used drugs are salts.

This, combined with the increase in generic drug production, means that many drugs are now produced in more than one salt form. In almost all cases where multiple drug salts of the same agent exist, they have been marketed as therapeutically equivalent and clinicians often treat the different salt forms identically. Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions. Theoretically, every compound that exhibits acid or base characteristics can participate in salt formation. Particularly important is the relative strength of the acid or base-the acidity and basicity constants of the chemical species involved. These factors determine whether or not formation occurs and are a measure of the stability of the resulting salt. The number of salt forms available to a chemist is large; surveys of patent literature show numerous new salts being synthesized annually. Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect dissolution rate and, hence, bioavailability. Ideally, it would be desirable if one could predict how a pharmaceutical agent's properties would be affected by salt formation.

ADVANTAGES

- Altered solubility and dissolution rate
- Controlled release potential
- Improved thermal, hydrolytic and photostability
- Reduce hygroscopicity
- Improved permeability
- Improved drug efficacy
- Altered melting point resulting in improved milling and formulation properties
- Improved compactability
- Ease of purification and handling

DISADVANTAGES

- Only suitable for ionisable compound
- Reduces the percentage of active content
- Increased chance of poor solid-state stability at microenvironment pH of salt

Pharmaceutical Salts

The term pharmaceutical salt is used to refer to an ionisable drug that has been combined with a counter-ion to form a neutral complex. Converting a drug into a salt through this process can increase its chemical stability, render the complex easier to administer and alter the pharmacokinetic profile. Salt selection is now a common standard operation performed with small ionisable molecules during drug development, and in many cases the drug salts display preferential properties as compared

with the parent molecule. As a consequence, there has been a rapid increase in the number of drugs produced in salt form, so that today almost half of the clinically used drugs are salts. This, combined with the increase in generic drug production, means that many drugs are now produced in more than one salt form.

In almost all cases where multiple drug salts of the same agent exist, they have been marketed as therapeutically equivalent. However, in many cases this may not be justified.

Potentially Useful Salts

Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. Ideally, it would be desirable if one could predict how a pharmaceutical agent's properties would be affected by salt formation. One salt form imparts greater water solubility, is less toxic, or slows dissolution rate would greatly benefit chemists and formulators. In general, salt combinations with monocarboxylic acids are insoluble in water and lend themselves to repository preparations, while those of dicarboxylic acids confer water solubility if one carboxylic group is left free. Pamoic acid, an aromatic dicarboxylic acid, is an exception since it is used as a means of obtaining prolonged action by forming slightly soluble salts with certain basic drugs.

The appropriate choice of a salt form has been found to reduce toxicity. It can be rationalized that any compound associated with the normal metabolism of food and drink must be essentially nontoxic. The approach of choosing organic radicals that are readily excreted or metabolized opened up a new class of substances from which to select a salt form. For example, certain salts of the strong base choline have proven to be considerably less toxic than their parent compound. Amino acids and acid vitamins also have been used as salt-forming agents. The vitamins most commonly used for forming salts exhibiting reduced toxicity.

Physiochemical Studies

Biological activity of a drug molecule is influenced by two factors: its chemical structure and effect at a specific site and its ability to reach-and then be removed from the site of action. Thus, a knowledge of the physicochemical properties of a compound that influence its absorption, distribution, metabolism, and excretion is essential for a complete understanding of the onset and duration of action, the relative toxicity, and the possible routes of administration. The salt form is known to influence a number of physicochemical properties of the parent compound including dissolution rate, solubility, stability, and hygroscopicity. These properties, in turn, affect the availability and formulation characteristics of the drug.

Consequently, the Pharmaceutical industry has systematically engaged in extensive preformulation studies of the physicochemical properties of each new drug entity to determine the most suitable form for drug formulation.

Dissolution Rate

The dissolution rate of a pharmaceutical agent is of major importance to the formulator. In many cases, particularly with poorly soluble drugs, this characteristic best reflects the bioavailability of the compound As a rule, a pharmaceutical salt exhibits a higher dissolution rate than the corresponding conjugate acid or base at an equal pH, even though they may have the same equilibrium solubility. The explanation for this result liesin the processes that control dissolution. Dissolution can be described by a diffusion layer Modellin terms of an equation developed by Nernst and Brunner,

$$dW/dt = Ds/h (Cs-C) \qquad \textbf{(Eq.1)}$$

where, *W* is the mass of the solute dissolved at time *t,d Wldt* is the rate of mass transfer per unit time, *D* is the solute molecule diffusion coefficient, S is the surface area of the dissolving solid, *h* is the diffusion layer thickness, C is the concentration of the drug in the bulk solution at time *t,* and C,s is the saturation solubility of the solute in the diffusion layer. The driving force for dissolution in Eq. 1 is the difference between the saturation solubility of the drug and the concentration of the drug in the bulk fluid. If the drug is not rapidly absorbed after it dissolves, then C, the concentration in the bulk solution, approaches C, and the dissolution rate is retarded. When this occurs, absorption is "absorption rate" limited (or "membrane transport" limited). If the absorption rate is rapid (or if the absorption mass transfer coefficient is much larger than *DSlh* of Eq. 1)' however, C becomes negligible compared to ***C,*** and dissolution occurs under "sink" conditions. Absorption is then said to be dissolution rate limited, which is what occurs with most poorly soluble drugs. In either case, an increase in *C,*,as in salt formation, increases dissolution.

Salts often speed dissolution by effectively acting as their own buffers to alter the pH of the diffusion layer, thus increasing the solubility of the parent compound. Some consideration must be given to the influence of salt formation on oral toxicity, which often reflects the relationship between the *IN-VIVO* dissolution rate and the appearance of drug in the circulation.

Solubility

Knowledge of the solubility characteristics of a pharmaceutical agent is essential, because solubility is usually an important factor in the pharmacokinetic profile, the chemical stability, and, ultimately, the formulation of the drug. The solubility of a compound depends basically upon the physical and chemical properties of the solute; *e.g.***,** a lower melting point for a compound within a series reflects a decreased lattice energy, which would suggest a higher solubility. Solubility depends on temperature, pressure, solvent

properties (such as resulting pH), and, to a lesser extent, the state of subdivision of the solute. An important solvent property which is often overlooked involves the common ion effect.

Salt formation is perhaps one of the first approaches considered as a means of increasing a compound's water solubility. As with dissolution rates, however, salt formation does not always confer greater solubility.

Organoleptic Properties

Modern medicine requires that a pharmaceutical formulation be efficacious, safe, stable, and acceptable to the patient. Primary importance in the development of oral dosage forms is taste acceptability. This factor presents no major problems when the drug is to be administered as a tablet or a capsule and swallowed as a unit but is clearly a prominent factor in patient acceptability when it is to be administered as a liquid, chewable tablet, or lozenge. Taste is a chemical sense; a substance must be dissolved if it is to elicit a taste sensation-either by taking it as a solution or by its dissolving in the saliva. Therefore, one method used to minimize undesirable organoleptic properties of pharmaceuticals involves the preparation of a poorly soluble salt form of the drug.

Stability

The chemical and physical stability of a pharmaceutical must be known, because it can influence the choice of dosage form, the manufacturing and packaging, and the therapeutic efficacy of the final preparation. Systematic determination' of the thermal stability, solution stability (at various pH's), and light sensitivity of a drug and its derivatives, both alone and in the presence of common additives, provides essential input toward selecting the most suitable derivative and dosage form. Depending on the route of degradation, different salt forms impart different stability characteristics to the parent drug by various mechanisms.

Most commonly used are sparingly soluble salts which, when used in the formulation of suspensions, reduce the amount of drug in solution and, hence, its degradation. Differences in hygroscopicity of several salts influence the stability of the drug in the dry state. In some cases, the salt-forming radical itself enhances the stability of the parent agent.

Miscellaneous Properties

The salt form has been reported to influence other physicochemical properties of a drug substance. Studies illustrating the effect of the salt-forming radical on surface tension, deaggregation behavior, and ion-pair extraction have appeared.

Bioavailability

Most drugs prescribed in the United States are administered in solid and polyphasic dosage forms. Consequently, dissolution of the drug must precede the absorption process.

Since the dissolution rate is generally slow for drugs with poor solubility, Step 1 is frequently rate limiting in the overall absorption process. As a result, the onset, intensity, duration of pharmacological activity, and, hence, bioavailability are affected by changes in dissolution rate. As discussed previously, administering a salt of the parent drug often proves to be an effective means of altering dissolution rate and absorption.

Formulation Effects

Choice of the salt form of a drug may have a pronounced effect on the formulation of the parent compound. For example, Fenton and Warren (194) found there was no release of medicament from proflavine cream BPC, a water-in-oil emulsion containing 0.1% proflavine as the hemisulfate salt.

Pharmacokinetics

Because of the various new properties that are usually imposed on a compound by salt formation, the pharmacokinetics of the drug necessarily change as a function of these properties. Regardless of formulation, the area under the plasma concentration-time curve of un metabolized drug from free acid administration was less than that for the salts.

Toxicological Considerations

Toxicity of salt

Ion-Any discussion regarding the toxicity of salts of a drug must consider the pharmacological properties of the cation or anion used to form the salt as well as those of the free drug, since any of these may produce toxic effects. The toxicology of several ions that are commonly used to form salts.

Toxicity of salt form

Provided the salt-forming agents are nontoxic, the relative toxicities of a series of salts of a compound are often observed to reflect directly their absorption rates.

Principles of salt formation and salt solubility

The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts or not and, if salts are formed.

pH–Solubility Interrelationship Of Free Base And Its Salt

Kramer and Flynn, demonstrated that the pH–solubility profile of a basic drug may be expressed by two independent curves, one where the free base is the saturation or equilibrium species and the other where the salt is the equilibrium species.

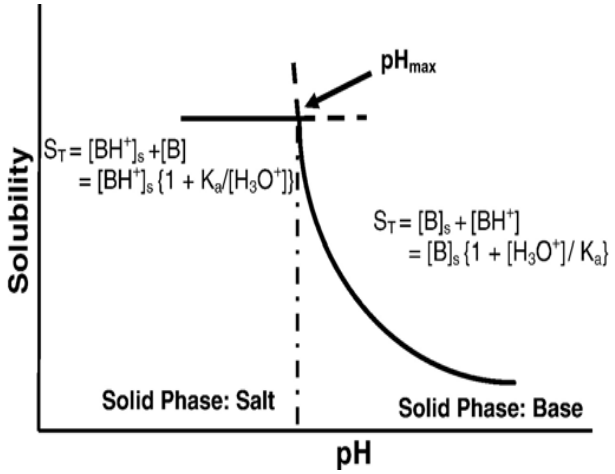

Fig 1: Schematic representation of the pH–solubility profile of a basic drug indicating that the solubility's may be expressed by two independent curves and that the point where two curves meet is the pHmax.

pH–Solubility Interrelationship Of Free Acid And Its Salt

The free acid would be the equilibrium species at a pH below pHmax, and it would convert to a salt only if it is equilibrated with a solution at a pH above pHmax by adding a sufficient quantity of an alkali or organic counterion.

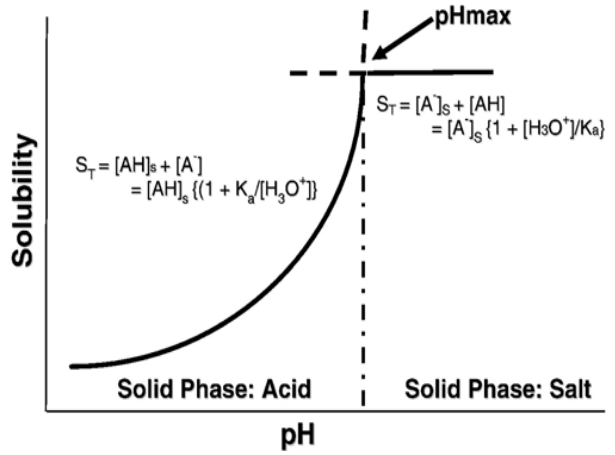

Fig.2: Schematic representation of the pH–solubility profile of an acidic drug indicating that the solubility may be expressed by two independent curves and that the point where the two curves meet is the pHmax.

Effect Of Counterion On Salt Solubility:

Salt-forming agents used to prepare salts, such as acids to form salts of basic drugs and bases to form salts of acidic drugs, exert influences on salt solubility by exerting common-ion effects in solution.

Effects of solubility, pKa and ksp on pH max

The concept of pHmax is an important one in the physical chemistry of salts. PHmax plays a major role in determining whether a salt would be formed or not. Deviation of pH–solubility interrelationship from ideality organic compounds often undergoes self-association in solution because of their amphiphilic nature**.** Bile salts are great examples of how organic compounds exhibit surface activity and undergo self-association in aqueous solutions because of their amphiphilic properties. It has been reported that salt forms of many drug molecules undergo similar aggregation in solution. Because of self-aggregation, activities of saturated solutions of many salts and even non-salts are lower than their measured concentrations in solution, resulting in non-ideal pH–solubility behavior.

Structure–Solubility Relationships

Aqueous solubility's of haloperidol salts differed depending on salt-forming agents used. For example, solubility's of terfendine salts formed with phosphoric acid, hydrochloric acid, methanesulfonic acid and lactic acid showed up to 10-fold differences, ranging from 0.5 mg/mL to 5 mg/mL. It may be noted that acidities and structures of acids used to form the salts in this study differed greatly.

Effect Of Organic Solvent On Salt Solubility

Pharmaceutical salts are usually synthesized either from organic solvents or from organic–water cosolvents Organic solvents are used not only in the preparation of salts; they are also used in parenteral and other liquid dosage forms. Organic solvents may influence the solubility f a drug candidate by (a) increasing solubility of unionized species (S0), (b) decreasing its protonation or ionization, and (c) decreasing solubility of the salt form.

Principles Of Salt Dissolution

The dissolution is the process by which a solid dissolves in a liquid, and the rate at which the dissolution takes place is referred to as the dissolution rate.

General Solubility–Dissolution Rate Relationships

The relationship between dissolution rate (J) and solubility (Cs) may be expressed by the.

Noyes–Whitney equation

$J = K A(Cs-C)$

Where, K is a constant, A is the surface area of the dissolving solid, and C is the concentration in the dissolution mediummay be modified according to the Nernst–Brunner diffusion layer model , which implies that the outermost layer of the solid drug dissolves instantly into a thin film of solvent to form a saturated solution of concentration Cs, and the transfer of the dissolved drug to the bulk solution occurs by diffusion of drug molecules through this layer. If the diffusion layer thickness may be denoted by h and the diffusion coefficient of the solute in this layer by D, then K becomes equivalent to D/h, and the equation may then be rewritten as.

$J = DA/h (Cs-C)$

For a constant surface area A and under sink condition. (Cs≫C), where the left side of may remain constant under a particular experimental condition, that is, when D and h remain constant may be modified according to the Nernst–Brunner diffusion layer model, which implies that the outermost layer of the solid drug dissolves instantly into a thin film of solvent to form a saturated solution of concentration Cs, and the transfer of the dissolved drug to the bulk solution occurs by diffusion of drug molecules through this layer.

If the diffusion layer thickness may be denoted by h and the diffusion coefficient of the solute in this layer by D, then K becomes equivalent to D/h, and the equation may then be.
J = DACs/h

Where the left side of Eq. may remain constant under a particular experimental condition, that is, when D and h remain constant. Dissolution rate is proportional to both solubility and surface area, the increase in Cs is the more effective way of improving the dissolution rate of a solid dosage form.

Dissolution In Reactive Media
Four situations may arise due to possible conversion of salts to relatively less soluble free acid/base forms under GI pH conditions.

1. The salt continues dissolving in the dissolution medium without any conversion to free form either because the drug concentration is below the saturation limit or a supersaturated solution has been formed.
2. The drug concentration reaches saturation limit (or forms a transient super saturation) after initial dissolution in the medium and the excess salt dissolving from the solid surface converts to its free form and precipitates out in a finely divided state.
3. The free acid or base may precipitate out at the surface of dissolving salt as an insoluble layer.
4. In this situation, the precipitated acid or base forms an impermeable layer at the surface of dissolving salt. Further dissolution is controlled by the solubility of the free from of the drug rather than the salt. Although the salt may exist below the surface layer, it is not available for dissolution.

It has been reported that dissolution rates of a hydrochloride salt decrease as the pH of an aqueous medium is lowered by adding HCl or if NaCl is added to the medium. Similarly, the dissolution rate of sodium salt decreases in the presence of added NaCl in the medium. Such decreases in dissolution rates are due to the common-ion effect.

Characterization of salt form
Weather salt form formed or not is confirmed by the characterization of prepared salt form. It was confirmed by powder X-ray diffraction, differential scanning calorimetry, infrared spectroscopy and elemental analysis.

Powder x-ray diffraction
These methods are based on the scattering of X-rays by crystals. By these methods, one can identify the crystal structures of various solid compounds. These methods are extremely important as compared with X-ray absorption and X-ray flurescence methods.

Differential scanning calorimetry
Differential scanning calorimetry is a technique for measuring the energy necessary to establish a nearly zero temperature difference between a substance and an inert reference material, as the two specimens are subjected to identical temperature regimes in an environment heated or cooled at a controlled rate. There are two types of DSC system in common use first is power compensation DSC and second is heat-flux DSC.

Thermogravimetric analysis
Thermogravimetric analysis is an analytical technique used to determine a material's thermal stability and its fraction of volatile components by monitoring the weight change that occurs as a specimen is heated. The measurement is normally carried out in air or in an inert atmosphere, such as Helium or Argon, and the weight is recorded as a function of increasing temperature. Sometimes, the measurement is performed in a lean oxygen atmosphere (1 to 5% O2 in N2 or He) to slow down oxidation.

Thermomicroscopy
Thermomicroscopy is indispensable in the study of solid state kinetics. First of all, it is essential to interpret kinetic observations with due consideration of the possibility that the material may undergo a loss of structural order at elevated temperature. The melting may be local, temporary or partial within a reacting condensed phase .

Secondly, TM observations are also required to supplement conventional kinetic data in the formulation or determination of a reaction mechanism or model . Such model is needed in the mathematical model fitting methods to calculate the kinetic parameters.

Karl fischer titration
Karl Fischer titrations (KFT), for the determination of water content, were carried out on powdered samples using Metrohm 701 KF Titrino linked to a Metrohm 703 Ti stand. All analyses were performed in triplicate. Prepared by compressing 200 mg of powder in a Perkin–Elmer hydraulic press, for 5 min less than 8 ton of pressure, using a 13 mm punch and die set. Analysis of the compressed discs by XRD confirmed that the crystal form of the original powderWas retained following the compression procedure. Paraffin wax was used to mount the discs in stainless steel disc holders, leaving one face exposed (surface area, 1.327 cm2).

The dissolution runs were carried out at 25 °C in 900 ml Deionised water at 50 rpm .Aliquots (5 ml) were withdrawn at 5, 10, 15, 20 and 25 min intervals, filtered through a 0.45 _m filter diluted if necessary and assayed for drug content. The withdrawn sample was replaced with 5 ml of deionised water. All dissolution runs were carried out in triplicate, in sink conditions. The initial linear portion of each dissolution profile (0–15 min) was used to derive the intrinsic dissolution rate.

Fourier transforms infrared spectroscopy

FT-IR stands for Fourier Transform Infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample. Like a fingerprint no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis.

FTIR is used to indentify unknown compound, to determine the quality of a sample and also to determine amount of components in mixture.

Uv assay for the determination of Gabapentin concentration

An accurate and validated spectrophotometric method was developed for the determination of gabapentin. This is simple, sensitive and low cost UV spectrophotometric method. The method is based on the direct measurement of the native absorbance of the drug. The detection was done at 210 nm. The method was linear in the range of 0.25 - 3.5 µ g/mL with correlation coefficient of 0.9999. It is validated according to the ICH guidelines with respect to linearity, selectivity, accuracy and precision, limit of quantitation and limit of detection. The method has been applied to assess gabapentin in pharmaceutical formulations with good accuracy and precision and relatively free of interference from coexisting substances.

Solubility studies

Equilibrium solubility's were determined using a modification of the sealed ampoule method of Mooney et al. (1981). Excess solid (approximately 2–3 times the estimated solubility) was placed in 5 ml deionised water in a 10 ml glass ampoule, which was then heat-sealed. Ampoules were placed in a shaker water bath (Precision Scientific) at 25 °C and agitated at 150cycles/min. At 24, 48 and 72 hours, samples were withdrawn from the ampoules, filtered through a 0.45 _m filter, diluted appropriately and assayed for the drug content. The pH of the filtered solution was determined using an Orion Model 520A pH meter.

Solubility determinations were carried out in triplicate. Where relevant, at the end of a solubility determination, the solid was recovered for powder XRD analysis, to ascertain any possible phase changes.

Intrinsic dissolution rate determination

Intrinsic dissolution rate (IDR) studies were performed using the USP 24 paddle method (United States Pharmacopeia, 2000). Discs were prepared by compressing 200 mg of powder in a Perkin–Elmer hydraulic press, for 5 min under 8 ton of pressure, using a 13 mm punch and die set. Analysis of the compressed discs by XRD confirmed that the crystal form of the original powder was retained following the compression procedure.

Paraffin wax was used to mount the discs in stainless steel disc holders, leaving one face exposed (surface area, 1.327 cm2). The dissolution runs were carried out at 25 °C in 900 ml deionised water at 50. Aliquots (5 ml) were withdrawn at 5, 10, 15, 20 and 25 min intervals, filtered through a 0.45 _m filter, diluted if necessary and assayed for drug content. The withdrawn sample was replaced with 5 ml of deionised water. All dissolution runs were carried out in triplicate, in sink conditions. The initial linear portion of each dissolution profile (0–15 min) was used to derive the intrinsic dissolution rate.

CONCLUSIONS

Salt formation is a means of altering the physical, chemical, and biological characteristics of a drug without modifying its chemical structure. Clearly, the salt form can have a dramatic influence on the overall properties of the parent compound. At present, selecting a salt form that exhibits the desired combination of properties is a difficult. Pharmaceutical scientists now recognize these facts and are beginning to study the effects of different salt forms on the physicochemical properties, bioavailability, and toxicity of drug substances.

Although now only a few generalizations are available to predict the effect of particular salt forms on the characteristics of a drug, perhaps in time it will be possible to evolve increasingly more powerful generalizations regarding the effect of a salt on the properties of its parent compound, In addition, we predict that polymer-drug salts will have a revolutionary effect on future trends in drug therapy, particularly in the areas of reducing drug toxicity and in controlling the release profile of novel drug delivery systems.

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