

PHARMACEUTICAL CHEMISTRY

Major Intra and Extra Cellular Electrolytes

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Keywords

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Introduction

About 56% of the adult human body is fluid. Although most of this fluid is inside the cells and is called intracellular fluid, about one third is in the space outside the cells and is called extracellular fluid. The extracellular fluid is in constant motion throughout the body. In the extracellular fluid are the ions and nutrients needed by the cells for the maintenance of cellular life. Therefore, all the cells live in essentially the same environment, the extracellular fluid, for which reason the extracellular fluid is called internal environment of the body.

The body fluids are solutions of inorganic and organic solutes. The concentration balance of the various components is maintained in order for the cell and tissue to have a constant environment. In order for the body to maintain this internal homeostasis, (homeostasis means maintenance of static or constant conditions in the internal environment) there are regulatory mechanisms which control pH, ionic balance, osmotic pressure etc. The volume and composition of the body fluids vary tremendously from one compartment to another, and are maintained remarkably constant despite the vicissitude of daily life and the stress imposed by disease. Disturbance of fluid and electrolyte metabolism involve four properties of the body fluid-volume, osmolarity, hydrogen ion concentration (pH) and the concentration of other specific ions. The total body water is divided into three compartments 1) the intercellular compartment 2) the extracellular compartment, which consists of the plasma and the interstitial fluid and 3) the transcellular compartment, which includes the fluid within the gastrointestinal tract, humor of the eye and the excretory system of the kidneys and glands, pericardial, peritoneal, synovial, cerebrospinal fluid.

All the body fluids intracellular, extracellular (interstitial, plasma or vascular) contains electrolytes. The electrolyte concentration varies in these fluids, it is 45-50% of body weight in intercellular fluid, interstitial fluid makes 12-15 % and plasma makes 4-5% of body weight. About 40% of intracellular fluid (4lts) is dense connective tissue i.e. bone and cartilage and does not take part in quick exchange of electrolytes with the remaining body. The rest of the interstitial fluid IF (6.6lts) and plasma (3.5lts) comprise the active part of the extracellular fluids. These fluid compartments are separated from each other by membranes which are permeable to water and many organic and inorganic solutes. They are nearly impermeable to macromolecules e.g. proteins and selectively permeable to certain ions e.g. Na^+ , K^+ and Mg^{2+} as a result, each of these fluid compartments has distinct solute pattern and the solution in each compartment is ionically balanced. For electro neutrality to exist in extracellular fluid, the sum of the concentration of cations must be equal to the sum of the concentration of anions.

The extracellular fluid contains large amounts of sodium, chloride and bicarbonate ions, plus nutrients for the cell such as oxygen, glucose, fatty acids and amino acids. The intracellular fluid contains large amounts of potassium, magnesium and phosphate ions. Measurement of electrolyte concentrations (plasma) is usually limited to Na^+ , K^+ , Cl^- , and HCO_3^- . The sum of the concentration of sodium and unmeasured cations (Ca^{2+} , Mg^{2+} , K^+) equals the sum of the concentration of Cl^- and HCO_3^- and unmeasured anions (phosphates, proteins, sulphates, derivatives of organic acids). The difference between the concentration of unmeasured cations and anion is known as anionic gap. Variation in this gap is a useful diagnostic indication to disorders of acid base balance.

The electrolyte balance of the body is maintained by a regulation between the intake and output of water. The intake of water includes the fluid taken orally and the release of water during the oxidation and other metabolic process in body.

Water is eliminated from body by urine, expiration (lungs), perspiration and feces. Excessive loss of water results in concentration of body fluids which causes rise in osmotic pressure, as a result water moves out from intracellular compartment to maintain the osmotic pressure in extracellular fluid. This results in dehydration of cells. Loss of water above 20% may prove to be fatal.

Calcium

About 99% of body calcium is found in bones and the remaining is present in extracellular fluid compartment. Only 10% of the ingested calcium is absorbed from the intestinal tract and the remainder is excreted with feces. The concentration of calcium in plasma averages about 9.4mg/dl, (9-10mg/dl). The calcium level in plasma is regulated within narrow limits by parathyroid hormone. The calcium in plasma is present in three forms 1. About 40% is combined with plasma proteins and is non diffusible through the capillary membrane. 2. About 10% is combined with other substances of plasma and interstitial fluid (citrate, phosphate for instance) and is diffusible through the capillary membrane in such a manner that it is not ionized. 3. The remaining 50% calcium present in plasma is diffusible through the capillary membrane and ionized. The plasma and interstitial fluid have a normal calcium ion concentration of about 1.2mmole/l (or 2.4mEq/l because it is a divalent ion), a level only half of the total plasma calcium concentration.

Calcium is important for blood clotting and contraction of various smooth muscles. In cardiovascular system (CVS) Calcium is essential for contraction coupling in cardiac muscles as well as for the conduction of electric impulse in certain regions of heart. Calcium also plays role in maintaining the integrity of mucosal membrane, cell adhesion and function of the individual cell membrane as well.

Hypercalcemia: When the level of Calcium rises above normal, the nervous system is depressed, and the reflex action of CNS can become sluggish. It also decreases the QT interval of the heart which can lead to cardiac arrhythmia. It causes constipation and lack of appetite and depresses contractility of the muscle walls of the GIT. The depressive effect begins to appear when blood Calcium level rises above 12mg/dl and beyond 17 mg/dl calcium phosphate crystals are likely to precipitate throughout the body. This situation occurs due to hypoparathyroidism, vitamin D deficiency, Osteoblastic metastasis, steatorrhea (fatty stools), Cushing syndrome (hyper active adrenal cortex), acute pancreatitis and acute hypophosphatemia.

Hypocalcemia: Change in blood pH can influence the degree of calcium binding to plasma proteins. With acidosis less calcium is bound to plasma proteins. When calcium ion concentration falls below normal, the excitability of the nerve and muscle cells increases markedly.

Sodium

The sodium and its associated anions, mainly chloride, account for more than 90% of the solute in extracellular fluid compartment. The concentration of sodium is 142mEq/l in extracellular fluid, and 10 mEq/l in intracellular fluid. Plasma sodium is a reasonable indicator of plasma osmolarity under many conditions. When plasma sodium is reduced below normal level a person is said to have hyponatremia. When plasma sodium is elevated above normal level a person is said to have hypernatremia.

Hyponatremia: Decreased plasma sodium concentration can result from loss of sodium chloride from the extracellular fluid. Conditions that cause hyponatremia owing to loss of sodium chloride include excessive sweating, diarrhea and vomiting and over use of diuretics that inhibit kidney to conserve sodium. Addison's disease, which results from decreased secretion of hormone aldosterone (impairs the ability of kidneys to reabsorb sodium) can be one of the causes of hyponatremia .

Hypernatremia: Hypernatremia is increased plasma sodium level which also increases osmolarity, can be due to excessive water loss from extracellular fluid, secretion of sodium-retaining hormone aldosterone (cushing syndrome) excessive treatment with sodium salts.

Potassium

Potassium is major intracellular cation present in a concentration approximately 23 times higher than the concentration of potassium present in Extracellular fluid compartment. Extracellular fluid potassium concentration is normally precisely regulated at 4.2mEq/l. This is because many of the cell functions are sensitive to change in the extracellular fluid potassium concentration. Increase in potassium concentration can cause cardiac arrhythmias and higher concentrations can lead to cardiac arrest by fibrillation. About 95% of body potassium is contained in the cells and only 2% in extracellular fluid. Maintenance of potassium balance depends primarily on its excretion by kidney because only 5-10 percent is excreted in feces. Both, elevated and low levels of potassium, can be fatal,

Hypokalemia occurs due to high intake of potassium or in kidney damage while **Hyperkalemia** due to vomiting, diarrhea, burns, diabetic coma, over use of thiazide diuretics, alkalosis etc.

Chloride

Chloride major extracellular anion is principally responsible for maintaining proper hydration, osmotic pressure, and normal cation anion balance in vascular and interstitial compartment. The concentration of chloride is 103mEq/l in extracellular fluid, and 4 mEq/l in intracellular fluid.

Decreased chloride concentration can be the result of salt losing nephritis, leading to lack of tubular reabsorption of chloride, metabolic acidosis such as found in diabetes mellitus, in renal failure and prolonged vomiting. Increased concentration of chloride may be due to dehydration, decreased renal blood flow found with congestive heart failure (CHF) or excessive chloride uptake.

Phosphate

Phosphate is the principal anion of intracellular fluid compartment. Inorganic phosphate in the plasma is mainly in two forms HPO_4^{2-} and H_2PO_4^- . The concentration of HPO_4^{2-} is 1.05 mmole/L and the concentration of H_2PO_4^- 0.26 mmole/L. When the total quantity of the phosphate in extracellular fluid rises so does the concentration of each of these ions. When pH of the extracellular fluid becomes more acidic there is relative increase in H_2PO_4^- and decrease in HPO_4^{2-} and vice versa. Phosphorous is essential for proper metabolism of calcium, normal bone and tooth development. HPO_4^{2-} and H_2PO_4^- makes an important buffer system of body.

Bicarbonate

Bicarbonate is the second most prevalent anion in extracellular fluid compartment. Along with carbonic acid it acts as body's most important buffer system. Each day kidney filters about 4320 milliequivalents of bicarbonate and under normal conditions all of this is reabsorbed from the tubules, thereby conserving the primary buffer system of the extracellular fluid. When there is reduction in the extracellular fluid hydrogen ion concentration (alkalosis) the kidneys fail to reabsorb all the filtered bicarbonate thereby increasing the excretion of bicarbonate. Because bicarbonate ions normally buffer hydrogen in the extracellular fluid, this loss of bicarbonate is as good as adding a hydrogen ion to the extracellular fluid. Therefore, in alkalosis, the removal of bicarbonate ions raises the extracellular fluid hydrogen ion concentration back towards normal. In acidosis the kidneys do not excrete the bicarbonate in the urine but reabsorb all the filtered bicarbonate and produces new bicarbonate which is added back to the extracellular fluid. This reduces the extracellular fluid hydrogen ion concentration back towards normal.

Replacement Therapy

The basic objective of replacement therapy is to restore the volume and composition of the body fluids to normal one. Volume contraction is a life threatening condition because it impairs the circulation. Blood volume decreases, cardiac output falls and the integrity of microcirculation is compromised. In volume depletion of sufficient magnitude to threaten life, a prompt infusion of isotonic sodium chloride solution is indicated. In an extreme case, intravenous therapy at the rate of 100 ml per minute for the first 1000ml has been considered necessary for the successful treatment of cholera. A general rule is to replace one half of the estimated volume loss in the first 12-24 hours of treatment.

Sodium Replacement

Sodium Chloride: NaCl (MW 58.44)

I.P. Limit. Sodium chloride contains not less than 99.5 % and not more than 100.5 % calculated with reference to dried substance. It contains no added substances. It occurs as colorless cubic crystals or as white crystalline powder having saline taste. It is freely soluble in water, and slightly more soluble in boiling water, soluble in glycerin and slightly soluble in alcohol.

Test for identification:

For Sodium: To sample solution add 15 % w/v potassium carbonate heat, no precipitate. Add potassium antimonite solution, heat to boiling, cool and if necessary scratch the inside of test tube with a glass rod, a dense white precipitate is produced.

For Chloride: Dissolve sample in water, acidify with dilute nitric acid and add silver nitrate solution shake, and allow to stand, a curdy white precipitate is formed which is insoluble in nitric acid but, soluble after being well washed with water, in dilute ammonium hydroxide solution from which it is reprecipitated by the addition of dilute nitric acid.

Preparation: On commercial scale it is prepared by evaporation of sea water in shallow pans. It contains impurities of sodium carbonate, sodium sulphate, magnesium chloride, magnesium sulphate, calcium chloride etc. these impurities are removed by dissolving the salt in water in a cemented tank; some alum and lime are added. The suspended impurities are allowed to settle down. The clear solution is decanted into iron pans and concentrated. The crystals of sodium chloride settle down which are then collected and dried.

Assay: The assay of sodium chloride is dependent on the modified Volhard's method in which indirect volumetric precipitation titration is involved. An acidified solution of sodium

chloride with nitric acid is treated with a measured excess amount of standard solution of silver nitrate in the presence of nitrobenzene. Some of the silver nitrate is consumed in the reaction with sodium chloride. The remaining unreacted AgNO_3 is determined by titration with standard solution of ammonium thiocyanate using ferric alum (ferric ammonium sulphate) as indicator. The end point is obtained as a permanent brick red color due to formation of ferric thiocyanate.

Procedure: Accurately weigh the substance (0.1 gm) and dissolve in 50 ml water. Add 50 ml of 0.1N AgNO_3 , 3 ml HNO_3 , 5 ml nitro benzene, 2 ml ferric ammonium sulphate and mix thoroughly. The solution is titrated with ammonium thiocyanate until the color becomes brick red.

1ml of 0.1N $\text{AgNO}_3 \equiv 0.005844$ gm NaCl

Use:

Used as fluid and electrolyte replenisher, manufacture of isotonic solution, flavor enhancer.

- Isotonic solutions are used in wet dressings, for irrigating body cavities or tissues
- Hypotonic solutions are administered for maintenance therapy when patients are unable to take fluids and nutrients orally for one to three days.
- Hypertonic solution/injection are used when there is loss of sodium in excess.
- Official preparations of Sodium chloride

Sodium Chloride Injection I.P.

Sodium chloride injection is a sterile isotonic solution of sodium chloride in water for injection. It contains not less than 0.85 % and not more than 0.95 % w/v of sodium chloride. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 4.5-7.0.

Sodium Chloride Hypertonic Injection I.P. (Hypertonic saline)

It is a sterile solution of sodium chloride in water for injection. It contains not less than 1.52 % and not more than 1.68 % w/v of sodium chloride. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 5-7.5.

It complies with the test for pyrogens.

Compound Sodium Chloride Injection I.P. (Ringer injection)

It contains not less than 0.82 % and not more than 0.9 % w/v of sodium chloride, not less than 0.0285 %, not more than 0.0315 % w/v of potassium chloride and not less than 0.03 % and not more than 0.036% w/v of calcium chloride in water for injection. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 5-7.5.

Sodium Chloride and Dextrose Injection

It is a sterile solution of sodium chloride and dextrose in water for injection. It contains not less than 95% and not more than 105 % w/v of the stated amount of sodium chloride and dextrose as given below:

Combinations of Sodium Chloride and Dextrose

%of Sodium Chloride	%of Dextrose	%of Sodium Chloride	%of Dextrose
0.11	5	0.45	5
0.18	5	0.45	10
0.20	5	0.90	2.5
0.225	5	0.90	5
0.3	5	0.90	10
0.33	5	0.90	25
0.45	2.5		

It is clear colorless or faintly straw colored solution with pH between 3.5-6.5.

Potassium Replacement

Potassium Chloride: KCl (MW 74.56)

I.P. Limit. Potassium chloride contains not less than 99 % calculated with reference to dried substance. It occurs as sylvine (KCl) and Carnallite (KCl, MgCl₂)6H₂O contaminated with magnesium sulphate and chlorides. It occurs as white crystalline solid, cubic crystals. It is less soluble in water than sodium chloride, and slightly more soluble in boiling water, soluble in glycerin and insoluble in alcohol.

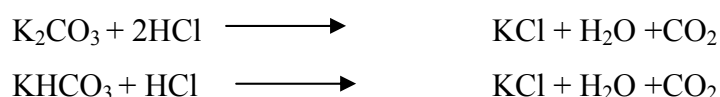
Test for Identification:

For potassium: To 1ml of solution add 1ml dilute acetic acid and 1ml of 10 % w/v sodium cobalt nitrite, a yellow color is produced.

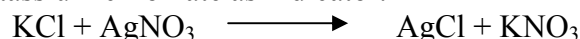
For Chloride: Substance in water is added with dilute solution of silver nitrate, shake the solution and allow to stand, on standing white precipitate is obtained which is insoluble in nitric acid but soluble after being washed with water; in dilute ammonium hydroxide, from which it is reprecipitated by the addition of dilute nitric acid.

Preparation:

1. It is prepared by fusing carnallite whereby liquefied magnesium chloride hexahydrate is separated from the solid potassium chloride.
2. The crushed carnallite is dissolved by boiling with liquor leaving other impurities undissolved. These are filtered off and the filtrate is crystallizes to get cubic crystals of potassium chloride.
3. It is also prepared in laboratory by reacting HCl with potassium carbonate or bicarbonate

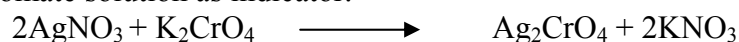


Assay: The assay is based on Mohr's method of direct volumetric precipitation titration. An aqueous solution of the substance is titrated against a standard solution of silver nitrate using solution of potassium chromate as indicator.



When whole of potassium chloride has been precipitated as AgCl, further addition of silver nitrate solution gives brick red color with the indicator. The end point is change of color from yellow to red.

Procedure: Accurately weigh the specified (0.25g) amount of potassium chloride and dissolve in 50 ml of water. Titrate the solution with 0.1N silver nitrate solution using potassium chromate solution as indicator.



1ml of 0.1N silver nitrate $\equiv$ 0.007455g of KCl

Use: Electrolyte replenisher in potassium deficiency, familial periodic paralysis, Meniere's syndrome (disease of inner ear), antidote in digitalis intoxication, myasthenia gravis.

Contraindication: renal impairment with oligouria, acute dehydration.

Potassium Chloride injection: Ringer injection

Calcium Replacement

Calcium Lactate: $C_6H_{10}CaO_6 \cdot xH_2O$

MW 308.30 (Pentahydrate)

I.P. Limit. Potassium chloride contains not less than 97% and not less than 103% of Calcium Chloride dihydrate. It occurs as white odorless powder. The pentahydrate effloresces and becomes anhydrous at 120° . Aqueous solutions are prone to become moldy. It is soluble in water, practically insoluble in alcohol.

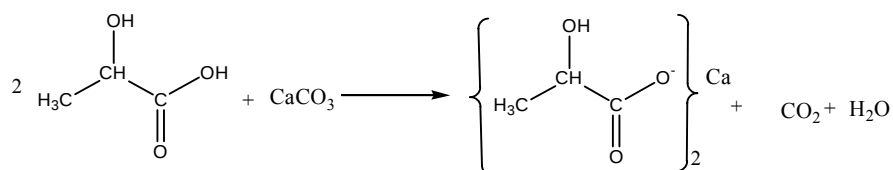
Test for Identification:

For Calcium: Dissolve substance in 5 M acetic acid and add 0.5 ml of potassium ferrocyanide solution. The solution remains clear. Add ammonium chloride white crystalline precipitate is formed.

For Lactate: To sample solution add bromine water, 1 M H_2SO_4 and heat on water bath stirring occasionally until the color is discharged. Add ammonium sulphate mixture of 10% solution of sodium nitroprusside in ammonia solution. Allow to stand for 10 mins, a dark ring appears at the interface of two liquids.

Preparation:

1. It is obtained by neutralizing a hot solution of lactic acid with calcium carbonate in slight excess. The hot liquid is filtered and filtrate is evaporated to crystalline product.



2. It is also obtained by fermenting hydrolyzed starch with a suitable mold in the presence of calcium carbonate
3. Or by fermentation of mother liquor resulting from the production of milk sugar and chalk. The mixture is digested for a week at about 30° . The product is purified by crystallization.

Assay: The assay is based on complexometric method of titration wherein disodium EDTA as titrant and calcon mixture as indication. The end point is change of color from pink to blue.

Procedure: Accurately weigh specified amount of sample and dissolve in water (50 ml), titrate the solution with 0.05 M disodium EDTA to within few ml of the expected end point. Add sodium hydroxide solution and calcon mixture and continue titration till end point is observed. The color of solution changes from pink to blue.

1ml of 0.05 M disodium EDTA $\equiv$ 0.005004 gm of calcium

Use: An excellent source of calcium in oral treatment of calcium deficiency.

Physiological Acid Base Balance

Abnormalities of the pH of body are frequently encountered and are of major clinical importance. Acidemia and alkalemia refer respectively to an abnormal decrease or increase in the pH of the blood. Acidosis and alkalosis refer respectively to clinical states that can lead to either acidemia or alkalemia. However in each condition the extent to which there is an actual change in pH depends in part on the degree of compensation which varies in most clinical disturbances. It is most convenient to evaluate clinical disturbances of pH by reference to $\text{HCO}_3^- - \text{H}_2\text{CO}_3$ System

Because it is in buffer system of extracellular fluid, this results from a number of factors:

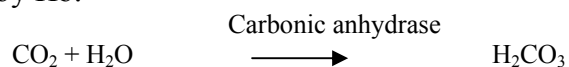
1. There is considerably more bicarbonate present in extracellular fluid than any other buffer component.
2. There is a limitless supply of carbon dioxide
3. Physiological mechanisms operate to maintain the extracellular pH function by controlling fluid
4. The bicarbonate – carbonic acid buffer system operates in conjunction with haemoglobin.

Acids are constantly being produced during metabolism. Most metabolic reactions occur only within narrow pH range of 7.38-7.42. Therefore the body utilizes several buffer systems, two of them are bicarbonate and carbonic acid ($\text{HCO}_3^- : \text{H}_2\text{CO}_3$) present in plasma and kidney and monohydrogen phosphate/dihydrogen phosphate ($\text{HPO}_4^{2-} : \text{H}_2\text{PO}_4^-$) found in cells and kidney.

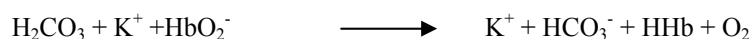
RBC's have hemoglobin buffer system which is most effective single buffer system for buffering the carbonic acid produced during metabolic process. For each millimole of oxygen that dissociates from hemoglobin (Hb) 0.7 millimole of H^+ are removed.

Carbon dioxide, the acid anhydride of carbonic acid is continuously produced in the cells. It diffuses into the plasma and reacts with water to form carbonic acid. The increased carbonic acid is buffered by plasma proteins. Most CO_2 enters the erythrocytes where it either rapidly forms H_2CO_3 by the action of carbonic anhydrase or combines with Hb.

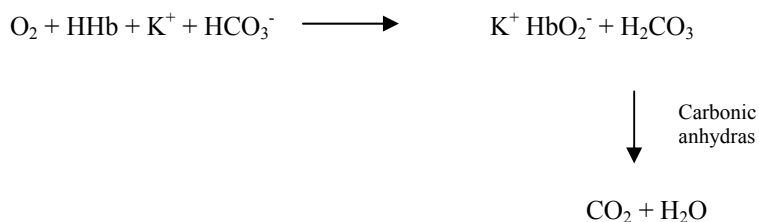
The tendency to lower the pH of the erythrocytes due to increased concentration of H_2CO_3 is compensated by Hb.



The bicarbonate anion then diffuses out of erythrocytes and chloride anion diffuses in. This has been named as chloride shift. The bicarbonate in plasma, along with the plasma carbonic acid now acts as efficient buffer system



The normal $\text{HCO}_3^- / \text{H}_2\text{CO}_3$ ratio is 27/1.35 meq/l (20:1) corresponding to pH 7.4. In lungs there is reversal of the above process due to the large amount of O_2 present. Oxygen combines with the protonated deoxyhemoglobin releasing proton. These combine with HCO_3^- forming H_2CO_3 which then dissociates to CO_2 and water. The carbon dioxide is exhaled by the lungs. Thus by regulating breathing it is possible for the body to exert a partial control on the $\text{HCO}_3^- / \text{H}_2\text{CO}_3$ ratio.



The phosphate buffer system is also effective in maintaining physiological pH. At pH 7.4 the $\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$ ratio is approximately 4:1. In kidney, the pH of urine can drop to 4.5-4.8 corresponding to $\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$ ratio of 1:99- 1:100. The acid is excreted from kidney as follows:

1. sodium salt of mineral or organic acids are removed from the plasma by glomerular filtration
2. Sodium is preferentially removed from the renal filtrate or tubular fluid in the tubular cells. The process known as sodium hydrogen exchange.
3. The sodium bicarbonate returns to plasma (eventually being removed in the lungs as CO_2) and protons enter tubular fluid, forming acids of the anions that originally were sodium salts.

Factors altering the pH of Extra Cellular Fluid

1. Acidosis: Acidosis is defined as increase in either potential and/or nonvolatile hydrogen ion (H^+) content of body. Increase in the H^+ concentration of plasma is known as acedemia and is manifested by fall in the pH of blood. In case there is no rise in H^+ concentration of plasma, such state of acidosis (without acedemia) is known as **compensated acidosis**.

Types and Causes of Acidosis:

Metabolic acidosis: it occurs due to excess production of proton in the body which may be because of

- i) Acceleration of normal metabolic process i.e. excessive catabolism e.g. in fever
- ii) Administration of drugs which are proton donors e.g. salicylates, chlorides
- iii) Excessive loss of alkaline fluid from the intestine, as in diarrhea
- iv) Administration of large quantity of saline.

Metabolic acidosis is treated with sodium salts of bicarbonate, lactate, acetate and occasionally citrate. When there is bicarbonate deficit, administration of bicarbonate increases the $\text{HCO}_3^-/\text{H}_2\text{CO}_3$ ratio. Lactate, acetate and citrate ions are normal components of metabolism and are degraded to carbon dioxide and water by TCA cycle (Citric acid cycle or Krebs cycle).

Renal Acidosis: where increase in H^+ is due to defective renal excretion of H^+ . Seen in Tubular disorders, Addisons disease, drugs which interfere with tubular secretion of H^+ e.g. carbonic anhydrase inhibitors

Respiratory Acidosis: is due to increase in retention of carbon dioxide leading to rise in plasma carbonic acid content. It occurs due to chronic lung disease, respiratory muscle paralysis, by drugs that depress respiratory center.

2. Alkalosis: Alkalosis is reduction in the total hydrogen ion content of the body. Alkalemia is reduction of hydrogen ion content in plasma and is manifested by increase in the pH of

blood. In case there is no decrease in H^+ concentration of plasma, such state of alkalosis (without alkalemia) is known as **compensated alkalosis**.

Metabolic alkalosis: Due to renal damage that cannot excrete an appreciable amount of alkali. Occurs due to alkali ingestion in presence of renal damage, excessive vomiting which causes loss of H^+ and Cl^- ions. Metabolic alkalosis has been treated with ammonium salts. Its action is in kidney where it retards the $Na^+ - H^+$ exchange.

Contraction alkalosis: seen following administration of mercurial diuretics which cause excessive loss of Cl^- and sodium.

Respiratory alkalosis: Respiratory alkalosis is caused by hyperventilation which washes away large amount of carbon dioxide formed in metabolism causes lowering of arterial pCO_2 and reduction in ratio of bicarbonate ion and carbonic acid with fall in hydrogen ion concentration. It Occurs due to high altitude, fever, encephalitis, hypothalamic tumor, drugs like salicylate, hot bath

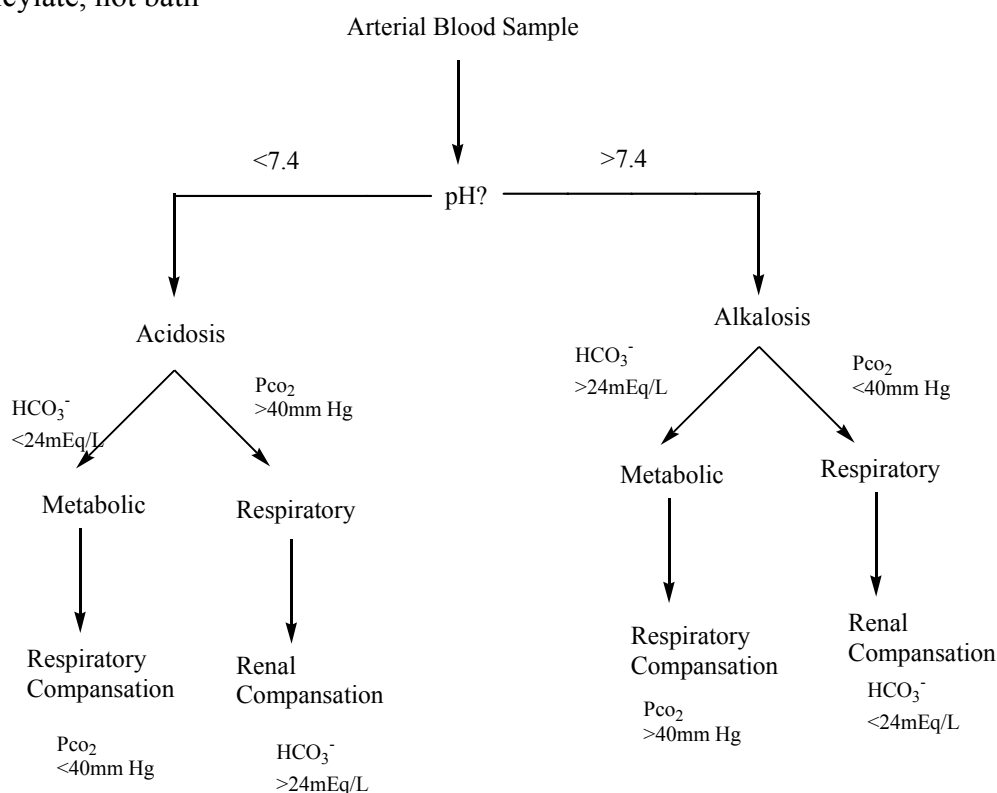


Figure: Analysis of acid base disorder.

If the compensatory responses are markedly different than those shown at the bottom of the figure, one should expect a mixed acid base disorder

Sodium bicarbonate (Sodabicarb): $NaHCO_3$; (M.W. 84.01)

I.P. limit: Sodium bicarbonate contains not less than 99.0 % and not more than 101 % of sodium bicarbonate.

Sodium bicarbonate occurs as a white odourless crystalline powder or granules. It begins to lose carbon dioxide at 50° and at 100° it is converted into sodium carbonate. It is soluble in

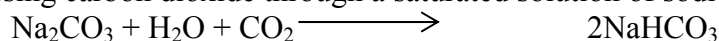
water (1 in 12); partially soluble in alcohol. The aqueous solution is alkaline to litmus; alkalinity increases on standing, agitation or heating. It is stored in well closed containers.

Sodium bicarbonate when mixed with calcium or magnesium salts, cisplatin, dobutamine hydrochloride or oxytetracyclin forms insoluble precipitates. The following drugs are susceptible to inactivation on mixing with sodium bicarbonate; adrenaline hydrochloride, benzyl penicillin potassium, carmustine, glycopyrronium bromide; isoprenaline hydrochloride and suxamethonium chloride.

It is stable in dry air, but slowly decomposes in moist air.

Preparation:

1. It is prepared by passing strong brine containing high concentration of ammonia through a carbonating tower where it is saturated with carbon dioxide under pressure. The ammonia and CO_2 reacts to form ammonium bicarbonate which is allowed to react with sodium chloride to precipitate sodium bicarbonate. It is then separated by filtration
2. By passing carbon dioxide through a saturated solution of sodium carbonate.

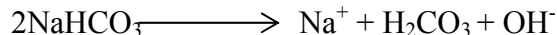


Chemical Properties:

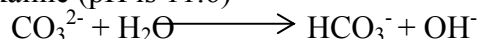
1. When sodium bicarbonate is heated, it is decomposed into the normal carbonate, carbon dioxide and water.



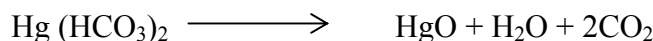
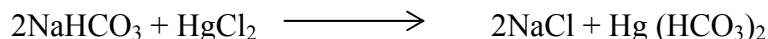
2. A solution of sodium bicarbonate is alkaline due to hydrolysis (pH 8.2)



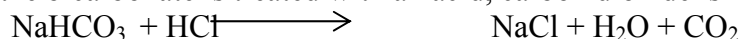
Sodium bicarbonate is slightly alkaline and fails to turn phenolphthalein red. On the other hand, in sodium carbonate the carbonate ion is so extensively hydrolyzed that the solution is quite alkaline (pH is 11.6)



3. When a mercuric chloride solution is added to a solution of sodium bicarbonate there is no immediate formation of precipitate. After some time a reddish precipitate of HgO is formed.



4. When the bicarbonate is treated with an acid, carbon dioxide is liberated;



Test for purity : Tests for alkalinity; aluminum; calcium; insoluble matter; arsenic; iron; lead; chloride; sulphate; ammonium compounds.

- For detecting the presence of aluminum, calcium and insoluble matter an aqueous solution is boiled with ammonia solution and filtered. The residue is ignited and weighed.
- An aqueous solution after addition of nitric acid complies with the limit test for chloride.

- An aqueous solution after addition of hydrochloric acid complies with the limit test for sulphates.
- Evolution of ammonia on heating the substance with sodium hydroxide indicates the presence of ammonium compound.
- An aqueous solution after addition of hydrochloric acid complies with the limit test for iron.
- Heavy metals are determined by comparing the colour produced with the substance and with standard lead solution after treatment with hydrogen sulphide solution.
- Simultaneous administration of sodium bicarbonate with other drugs inhibits the activity of the drug. Such a therapeutic incompatibility is found when sodium bicarbonate and sodium salicylate are used in equivalent amounts.

Test for identification: It gives the reactions of sodium, and of bicarbonates.

For Sodium: To sample solution add 15 % w/v potassium carbonate, heat, no precipitate, add potassium antimonite solution, heat to boiling, cool and if necessary scratch the inside of test tube with a glass rod, a dense white precipitate is produced.

For bicarbonate: to sample add magnesium sulphate no precipitate is produced. On boiling a white colored precipitate is formed.

Assay: A solution of weighed amount of sample dissolved in water is titrated with 0.5 N hydrochloric or sulphuric acid, using methyl orange as indicator.

Each ml of 0.5 N hydrochloric acid is equivalent to 0.042 g of NaHCO_3 .

It is a direct titration method, the end point is yellow to pink. The equivalence point of this titration is at about pH 3.6 which corresponds to the colour change of methyl orange (pH 2.8 - 4.0, red-yellow). The reaction at the equivalence point is acidic because of the presence of carbonic acid.

Uses : Sodium bicarbonate is an electrolyte replenisher, and systemic alkalinizing agent used in the treatment of metabolic acidosis (increase in acidity) , diarrhoea, acute poisoning from acidic drugs (phenobarbitone and salicylates) , and as an antacid to relieve dyspepsia. Solutions of sodium bicarbonate are used as eye lotions, to aid the removal of crusts in blepharitis, as eardrops, to soften and remove ear wax, and as lubricating fluid for contact lenses.

Administration of sodium bicarbonate by mouth can cause stomach cramps and flatulence. Its large quantities may cause systemic alkalosis, vertigo (loss of power of balancing) and jerky muscular movement.

Sodium bicarbonate is available as mint-flavored soda-mint tablets. It is self-medicated, inexpensive and easily available drug. It is absorbed from the intestine which produces effects all over the body. It produces carbon dioxide gas in stomach and may cause perforation of a deep ulcer. Its onset of action is quick but the duration of action is short. It may cause rebound acidity due to short duration of action and systemic effects. When taken with milk it may cause milk alkali syndrome, characterized by deposition of calcium of milk on the kidney and increased blood urea.

Sodium acetate: $\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$

I.P. Limit. Sodium acetate contains not less than 99.0 per cent of $\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$.

Preparation: It is prepared by neutralization of acetic acid with sodium carbonate or sodium hydroxide, and then crystallizing the product.

Characters: it occurs as colourless, transparent crystals or a white granular powder or white flakes: odourless or with a slight odour of acetic acid; m.p. 58° ; becomes anhydrous at 120° , decomposes at highertemperature. It effloresces in warm dry air. It is soluble in water (1 in 0.8), and alcohol (1 in 19). A 5 % solution in water has a pH of 7.5 to 9.2. It is kept in airtight containers.

Tests for purity : Tests for arsenic; calcium and magnesium; heavy metals; iron; chloride; sulphate; reducing substances; pH; clarity and colour of solution ; loss on drying.

For determining calcium and magnesium, a mixture of dilute ammonia buffer solution, mordant black 11 is itrated with 0.05 M EDTA. When reducing substances are absent, the pink colour is not entirely discharged on treatment of potassium permanganate with an acidified solution of the substance with dilute sulphuric acid.

Incompatibility: Aqueous solutions of substance react with oxygen to produce slight pink colour. It can be prevented by addition of a solution of sodium metabisulphite.

Test for identification: it gives the reactions of sodium and of acetates.

For Sodium: To sample solution add 15 % w/v potassium carbonate heat, no precipitate, add potassium antimonite solution, heat to boiling, cool and if necessary scratch the inside of test tube with a glass rod, a dense white precipitate is produced.

For acetate:

1. Heat the sample with equal quantity of oxalic acid, acidic vapours with the characteristic odour of acetic acid are liberated.
2. To 1 gm of sample add sulphuric acid, add ethanol, warm, ethyl acetate is evolved which is recognizable by its odour.

Assay: Accurately weighed amount of sample (0.25 g) is dissolved in glacial acetic acid (50 ml.), acetic anhydride (5 ml) and kept for 30 minutes and titrated with 0.1N perchloric acid using 1-naphtholbenzein solution as indicator. The end point is change of colour from yellowish green to dark green. A blank determination is also performed and necessary correction made.

Each ml of 0.1 N perchloric acid is equivalent to 0.01361 of $\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$.

Uses: An effective buffer in metabolic acidosis. It is used as pharmaceutical aid (for peritoneal dialysis fluid); acidulant in food; and as an effective buffer in metabolic acidosis.

Potassium acetate: CH_3COOK ; M W = 99.14

I.P. Limit: Potassium acetate contains from 99 to 101.0% of CH_3COOK . It occurs as colourless crystals or a white crystalline powder; odourless with a faint acetic acid like odour. It is deliquescent in moist air. It is soluble in water and alcohol. A 5 % solution in water has a pH of 7.5 to 9.5.

Potassium acetate should be kept in a well-closed container.

Tests for purity : Tests for aluminium: arsenic; calcium; heavy metals; magnesium; sodium; chloride; nitrate; sulphate; readily oxidizable substances; loss on drying; and alkalinity

For determining nitrate, an aqueous solution is treated with sodium chloride, indigo carmine solution and nitrogen-free sulphuric acid. A blue colour is produced which persists for at least 10 minutes.

Test for identification: it gives reactions characteristic of potassium salts and of acetates.

For potassium: To 1ml of solution add 1ml dilute acetic acid and 1ml of 10 % w/v sodium cobalt nitrite, a yellow color produced.

For acetate:

1. Heat the sample with equal quantity of oxalic acid, acidic vapours with the characteristic odour of acetic acid are liberated.
2. To 1 gm of sample add sulphuric acid, add ethanol, warm, ethyl acetate is evolved which is recognizable by its odour.

The presence of readily oxidizable substances is found out by treating an aqueous solution with sulphuric acid and potassium permanganate. The pink colour is not completely discharged. The salt complies with the limit test for arsenic, calcium, heavy metals, magnesium and chloride.

Assay: Non –aqueous titration is carried out using perchloric acid and crystal violet solution as indicator. Accurately weighed amount of sample is dissolved in glacial acetic acid (50 ml.), acetic anhydride (5 ml) and kept for 30 minutes and titrated with 0.1N perchloric acid using 1-naphtholbenzein solution as indicator. The end point is change of colour from yellowish green to dark green. A blank determination is also performed and necessary correction made.

Each ml of 0.1 N perchloric acid is equivalent to 9.814 mg of CH_3COOK .

Uses: It is used in solutions for hemodialysis and peritoneal dialysis as an alkalizer. It is also used as a food preservative.

Sodium citrate: $\text{C}_6\text{H}_5\text{O}_7\text{Na}_3$

I.P. Limit: Sodium citrate is trisodium 2-hydroxypropane- 1,2,3,-tricarboxylate dihydrate. It contains about 99% of $\text{C}_6\text{H}_5\text{Na}_3\text{O}_7$.

Preparation: It is prepared by mixing of calculated amounts of hot solution of citric acid and sodium carbonate and crystallizing the product.



Characters: it occurs as white, granular crystals or a white crystalline powder; slightly deliquescent in moist air. It is freely soluble in water; practically insoluble in ethanol. It is stored in air-tight containers. Sterilized solutions of sodium citrate on keeping cause separation of small solid particles from a glass container. A solution containing such particles must not be used.

Tests for purity: Tests for heavy metals; oxalate; sulphate; readily carbonizable substances; water; acidity or alkalinity; clarity and colour of solution.

- Acidity or alkalinity is determined by neutralizing an aqueous solution with hydrochloric acid or sodium hydroxide using phenolphthalein as indicator.
- For determining oxalate, zinc and phenylhydrazine are treated with acidified solution. Hydrochloric acid and potassium hexacyanoferrate solution are added. Any pink color produced is not more intense than that obtained by treating at the same time and in same manner a reference solution of oxalic acid.
- Readily carbonisable substances are detected by heating the salt with sulphuric acid at about 90° for one hour. On cooling, the solution is not more intensely colored than a reference solution.
- Sodium citrate complies with the limit test for chloride and sulphate

Test for identification: Aqueous solution gives reactions characteristic of sodium salts and citrates.

For Sodium: To sample solution add 15 % w/v potassium carbonate, heat, no precipitate, add potassium antimonite, solution heat to boiling, cool and if necessary scratch the inside of test tube with a glass rod, a dense white precipitate is produced.

For Citrate: To a neutralized solution of sample add calcium chloride solution no precipitate is produced, boil the solution white precipitate, soluble in 6M acetic acid is produced.

Assay: A solution of the accurately weighed substance in anhydrous acetic acid is heated and after cooling to room temperature titrated with 0.1N perchloric acid using 1-naphtholbenzein solution as indicator, until a green color is produced. A blank determination is also performed.

Each ml of 0.1 N perchloric acid is equivalent to 8.602mg of $C_6H_5Na_3O_7$.

Uses: It is used as systemic alkalizing substance. Sodium citrate has anticlotting properties and is employed in mixtures as the acid citrate in the anticoagulation and preservation of blood for transfusion purposes. It is also used for dentifrices as desensitizing agent and added to milk for infant feeding to prevent the formation in the stomach of large curds. It also has a diuretic effect due to increased body salt concentration.

Potassium Citrate: $KOOC.CH_2 CH(OH)COOK CH_2 COOK H_2O$; $C_6H_5O_7 K_3.H_2O$
MW 324.42

I.P. Limit: Potassium citrate is the monohydrate of tripotassium 2-hydroxy-propane- 1,2,3,-tricarboxylate. It contains about 99% of $K_3C_6H_5O_7$.

Preparation: It is prepared by mixing of calculated amounts of hot solution of citric acid and potassium carbonate and crystallizing the product.



Potassium citrate occurs as transparent, odorless, hygroscopic crystals or a white granular powder, taste is saline. It is soluble in water (1 in 1) and glycerol (1 in 25), practically insoluble in alcohol. Aqueous solutions are slightly alkaline and may be incompatible with acidifying agents. It is stored in airtight containers.

Test for purity: Tests for acidity or alkalinity; arsenic; heavy metals; lead, sodium chloride, sulphates, oxalates, readily carbonizable substances and water

- Acidity or alkalinity is determined by neutralizing aqueous solution with either 0.1N sulphuric acid or 0.1N sodium hydroxide to thymol blue solution. A clear solution obtained after addition of potassium antimonite solution to the aqueous solution indicated the absence of sodium.
- For determining oxalate an aqueous mixture of the substance, hydrochloric acid, alcohol and calcium chloride remains clear. Readily carbonisable substance are detected by heating the substance with sulphuric acid for a few min at 80-90°; the solution is not intensely colored, than a mixture of ferric chloride, copper sulphate, cobalt chloride and hydrochloric acid.

Test for identification: A solution (1 in 20) gives the reactions of potassium and of citrate

For potassium: To 1ml of solution add 1ml dilute acetic acid and 1ml of 10 % w/v sodium cobalt nitrite a yellow color produced.

For Citrate: To a neutralized solution of sample add calcium chloride solution, no precipitate is produced, boil the solution, white precipitate soluble in 6M acetic acid is produced.

Assay: A weighed amount (0.15gm) dissolved in glacial acetic acid is heated to 50° and cooled. To this is added 1-naphtholbenzein solution and titrated with 0.1N perchloric acid until a green color is obtained. A blank determination is performed.

Each ml of 0.1 N perchloric acid is equivalent to 0.01021g of $K_3C_6H_5O_7$.

Uses: it is used as systemic alkalizer and gastric antacid . it is used to relieve painful irritation caused by cystitis (inflammation of gall bladder)

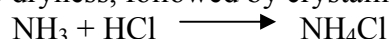
Ammonium Chloride

Ammonium chloride is a sterile solution of ammonium chloride in water for injection

I.P. Limit: It contains not less than 99.5 % and not more than 105 % with reference to dried substance. HCl may be added to adjust pH. The NH_4^+ cation possess certain pharmacological activities

1. acid base equilibrium of the body
 2. diuretic effect
 3. expectorant effect
-
1. Ammonium ion plays important role in maintenance of the acid base equilibrium of the body particularly in combating acidosis. By excreting ammonium ions the kidney saves base i.e. sodium for the body
 2. The diuretic effect of ammonium chloride is produced by conversion of ammonium cation to urea. Ammonium chloride is contraindicated in patients with impaired renal and hepatic functions.

Preparation: It is prepared by neutralizing hydrochloric acid with ammonia and evaporating the solution to dryness, followed by crystallization.



Test for identification

1. Heat a few mg of sample being examined with sodium hydroxide solution. Ammonia is evolved which is recognized by its odor and by its action on moist litmus paper which turns blue

2. Substance in water, is added dilute ammonia solution and silver nitrate, shake the solution and allow to stand, on standing white precipitate is obtained which is insoluble in nitric acid but soluble after being washed with water, in dilute ammonium hydroxide from which it is reprecipitated by the addition of dilute nitric acid.

Test for purity: Test for chloride content, pyrogen is performed and pH between 4-6 is checked.

Assay: The distilled solution, obtained on addition of ammonium chloride and sodium hydroxide solution and heating, is titrated with 0.1N sulphuric acid using methyl red as indicator. A blank determination is also performed.

Each ml of 0.1 N sulphuric acid is equivalent to 0.00549 g of NH_4Cl

OR

Weigh accurately 1gm substance and add water and 5 ml formaldehyde solution previously neutralized to dilute phenolphthalein solution, add 20 ml of water again. After 2 minutes, titrate slowly with 0.1N NaOH using phenolphthalein as indicator.

Each ml of 0.1 N NaOH is equivalent to 0.00549 g of NH_4Cl .

Uses: It is used in acid base therapy, as a diuretic. It is also used to correct hypochloremic alkalosis due to prolonged use of mercurial diuretics.

Electrolyte Combination Therapy

Combinations of glucose and saline solutions are usually sufficient in short term therapy for restoring electrolyte loss. But in severe deficit of electrolytes due to heavy blood loss or chronic diarrhea, solutions containing additional electrolytes are usually required. The combination products are of two types :

1. fluid maintenance therapy
2. electrolyte replacement therapy

Maintenance therapy with intravenous fluids is required to supply normal necessity of water and electrolyte to patient who cannot take them orally. All maintenance therapies should contain at least 5% dextrose. General electrolyte composition of maintenance therapy includes:

Electrolyte	Concentrations (mEq/l)
Sodium	25-30
Potassium	15-20
Chloride	22
Bicarbonate	20-23
Magnesium	3
Phosphorous	3

Replacement therapy is required when there is excess loss of water and electrolytes caused by fever, severe vomiting and diarrhea.

Two types of solutions are used in replacement therapy:

- i) solution for rapid initial replacement
- ii) a solution for subsequent replacement

The electrolyte concentrations in solutions for rapid initial replacement are almost similar to the electrolyte concentrations found in extracellular fluids. The electrolyte concentrations of these solutions are given as

Electrolyte	Concentrations (mEq/l) for rapid initial replacement	Concentrations (mEq/l) for subsequent replacement
Sodium	130 -150	40-121
Potassium	4-12	16-35
Chloride	98-109	30-103
Bicarbonate	28-55	16-53
Calcium	3-5	0-5
Magnesium	3-5	0-13
Phosphorous	-	0-13

Suggested Readings:

- J Bassett, R C Denney, G H Jeffery, J Menndham, Vogel's Textbook of Quantitative Inorganic Analysis, The ELBS and Longman, London
- A H Backett and JB Stenlake, Practical Pharmaceutical Chemistry, Vol I and II, The Athlone Press of the University of London
- Parmacopoeia of India, Govt of India, Ministry of Health, Delhi
- J.C. Block et al, Inorganic Medicinal and Pharmaceutical Chemistry, Lee Febiger, Philadelphia PA