\_\_\_DIURETICS\_\_\_\_

\_ \_\_\_\_\_\_\_\_\_

**1. INTRODUCTION**

**Diuretics** are drugs that promote the output of urine excreted by the kidneys.

The increased excretion of water and electrolytes by the kidneys is dependent on three different

processes, *viz.,* glomerular filtration, tubular reabsorption (active and passive) and tubular secretion.

Every normal human being essentially bears a daily rhythm in the excretion of water and

electrolytes, being minimum during night and maximum in the morning. This may be a reflection of

intra-cellular metabolism. Alteration prevailing in the diurnal rhythm is normally characterized by initial

symptoms of disturbance of fluid balance of the body as evidenced in heart failure (Addison’s disease),

hepatic failure and renal diseases.

**Diuretics** are very effective in the *treatment of cardiac oedema, specifically the one related with*

*congestive heart failure.* They are employed extensively in various types of disorders, for example, *nephrotic*

*syndrome, diabetes insipidus, nutritional oedema, cirrhosis of the liver, hypertension, oedema of pregnancy*

*and also to lower intraocular and cerebrospinal fluid pressure.* In some instances where oedema is not

present, the diuresis may be specifically indicated and effected by certain highly specialized diuretics as in

hypertension, epilepsy, migraine, glaucoma, anginal syndrome and bromide intoxication.

In its simplest explanation the formation of urine from the blood mainly comprises of *two* cardinal

processes taking place almost simultaneously, namely : (*a*) **glomerular filtration ;** and (*b*) **selective**

**tubular reabsorption, and subsequent secretion.** It has been duly observed that as the **‘glomerular**

**filtrate’** gets across through the tubules, substances that are absolutely essential to the blood and tissues,

such as: water, salts, glucose, and amino acids are reabsorbed eventually.

However, under perfect normal physiologic circumstances the glomerular filtration rate is

approximately 100 mL min– 1. And from this volume about 99 mL of the fluid is sent back to the blood

pool, and thus only 1 mL is excreted as urine. From these critical and vital informations one may infer that

the *‘diuretics’* may enhance the rate of urine-formation by either of the *two* following phenomena, *viz.,*

(*a*) Increasing glomerular filtration, and

(*b*) Depressing tubular reabsorption.

**2. CLASSIFICATION**

**Diuretics** may be broadly classified under the following *two* categories :

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(*a*) Mercurial Diuretics,

(*b*) Non-mercurial Diuretics.

**2.1. Mercurial Diuretics**

The **mercurial diuretics** essentially contain Hg++ in an organic molecule. They usually inhibit

sodium reabsorption in the proximal tubuler and ascending loop of Henle. There may be slight effect in

the distal tubule where inhibition of chloride reabsorption also occurs. The mercurials have been found

to enhance K+ excretion though potassium loss is less than that produced by many other diuretics.

However, the overall action of **mercurial diuretics** is invariably increased by acidification of urine. The

mercurial diuretics are not very much used in clinical practices due to their pronounced and marked

side-effects *viz.,* mercurialism, hypersensitivity and excessive diuresis which may lead to electrolyte

depletion and vascular complications. Most of the **mercurials** are administered by intramuscular route

and the availability of orally active diuretics has limited their use.

The **mercurial diuretics** has the following general formula :

*Y*—CH2—CH—CH2—Hg—*X*

|

OR

where *X* = OH, halide, or heterocyclic moiety,

*Y* = Subsituted side chain or substituted aromatic function,

and *R* = Methyl group.

**Examples : Chlormerodrin Hg 197 ; Meralluride ; Mercaptomerin sodium ; Merethoxylline**

**procaine ; Mersalyl ;** and **Mercumatilin sodium.**

**A. Chlormerodrin Hg 197 USAN. Chlormerodrin BAN, Chlormerodrin (197 Hg) INN,**

H2NCONH—CH2CHCH2—HgCl

|

OCH3

Chloro (2-methoxy-3-uriedopropyl) mercury– 197 Hg ; Mercury197 Hg, [3-(aminocarbonyl) amino]

2-methoxypropyl] chloro-USP ; BPC (1959) ;

Neohydrin-197(R) (Abbott).

**Synthesis**

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It may be prepared by the interaction of N-allyl urea with mercuric acetate in the presence of

methanol when the former gets acetoxymercurated. The saturation also takes place simultaneously when

the methoxy group is introduced at position 2. Metathesis occurs on the addition of aqueous NaCl

resulting in the precipitation of **chlormerodrin** which is subsquently filtered, washed and dried.

**Chlormerodrin197 Hg** is used in the *treatment of oedema of congestive heart failure. It has also*

*been employed in the management of chronic nephritis, ascites of liver disease and nephrotic oedema.*

**Dose :** *Usual, oral, 18.3 to 73.2 mg per day* (≡to 10 to 40 mg of mercury per day).

**B. Meralluride INN, BAN, USAN,**

[3-[3-(3-Carboxypropionyl) ureido]-2-methoxypropyl]-hydroxy-mercury mixture with

theophylline ; Mercury [3[[[(3-carboxy-1-oxopropyl) amino] carbonyl] amino]-2-methoxypropyl]

(1, 2, 3, 6-tetrahydro-1, 3-dimethyl-2, 6-dioxo, 7H-purin-7-yl)-; BPC (1959) ; NFXIV ;

Mercuhydrin(R) (Merrell Dow).

**Synthesis**

(*Contd...*)

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**Cyclic diacylurea** is prepared by the condensation of succinimide and allyl isocyanate which

upon acid hydrolysis affords the cleavage of the ring of the succinimide. Oxymercuration of the terminal

olefin bond in the presence of mercuric acetate in methanol solution gives [3-[3-(3-caboxy-propionyl

ureido]-2-methoxypropyl]-hydroxy mercury. This on condensation with an equimolar portion of

theophylline gives the official compound.

**Meralluride** is employed for the *treatment of oedema secondary to congestive heart failure, the*

*nephrotic state of glomerulonephritis and hepatic cirrhosis.*

**Dose :** *Usual, 1 ml (*≡*to 39 mg of Hg and 43.6 mg of anhydrous theophylline) 1 or 2 times a*

*week, parenteral 1 to 2 ml.*

**C. Mercaptomerin Sodium BAN, USAN, Mercaptomerin INN,**

[3-(3-Carboxy-2, 2, 3-trimethylcyclopentane-carboxamide)-2-methoxypropyl] (hydrogen

mercaptoacetate)-mercury disodium salt ; Mercury, [3-[[(3-carboxy-2, 2, 3-trimethylcyclopentyl)

carbonyl] amino]-2-methoxypropyl] (mercapto-acetate-S)-, disodium salt ; USP. ; Ind. P. ;

Thiomerin(R) (Wyeth).

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**Synthesis**

**Camphoric acid** on condensation with ammonia and subsequent treatment with allyl isocyanate

affords an intermediate which on reaction with mercuric acetate in methanol gives rise to the corresponding

mercury derivative as acetate. This on treatment with sodium chloride followed by sodium thioglycollate

in aqueous NaOH solution yields the official compound which may be obtained either by evaporation or

by precipitation with an appropriate solvent.

The uses of mercaptomerin sodium are similar to those of **meralluride.**

**Dose :** *Usual, 125 mg once daily ; parenteral 15 to 250 mg daily to weekly*

**D. Merethoxylline Procaine BAN, USAN,**

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The **procaine merethoxylline** is an equimolar mixture of **procaine** and **merethoxylline,** the

latter being the inner salt of [*o*-[[3-(hydroxymercuri)-2-(2-methoxyethoxy)-propyl]-carbamoyl] phenoxy]

acetic acid. A mixture of the procaine merethoxylline and theophylline in the molecular proportion of

1 : 1.4 is available as a solution. **Dicurin Procaine(R) (Lilly, USA).**

It has been used effectively in the *treatment of oedema and ascites in cardiac failure and also in*

*ascites due to cirrhosis of the liver. The procaine component helps in reducing the discomfort of local*

*irritation which may be caused by the mercurial compound when injected into tissues.*

**Dose :** *Usual i.m., subcutaneous, daily 0.5 to 2.0 ml (containing 100 mg of merethoxylline procaine*

*and 50 mg of theophylline per ml)*

**E. Mersalyl INN, USAN, Mersalyl Sodium BAN,**

Sodium salt of *o*-[(3-hydroxymercuri-2-methoxypropyl) carbamoyl]-phenoxy-acetic acid ; BPC.

1959 ; NF. XI ;

Salygran(R) (Winthrop).

**Mersalyl** is *used to increase the output of oedema fluid in such typical conditions as renal disease,*

*heart failure etc. It is also employed in the treatment of nephrotic oedema and in ascites due to cirrhosis*

*of the liver.*

**Dose :** *After assessing patient’s tolerance by giving i.m. injection of 0.5 ml (10% m/v) ; 0.5 to*

*2 ml i.m. on alternate days.*

**2.1.1. Mechanism of Action**

The mechanism of action of the **‘mercurial diuretics’** described under Section 13.2.1 are stated

as under :

**2.1.1.1. Chlormerodrin**

**Mercury-197** has been used in the form of **chlormerodrin (197Hg)**, but has been largely

superseded by other agents, such as : **Technetium-99 m.** It mainly survived as the **197Hg isotope** (*t*1/2 =

64 hr.) employed for the exact visualization of renal parenchyma.

**2.1.1.2. Meralluride**

Organic mercurial diuretics were widely employed prior to the introduction of ***‘thiazides’***

and a host of other potent non-mercurial diuretics, but now have been virtually superseded by these

orally active drugs that are found to be both potent and less toxic.

**2.1.1.3. Mercaptomerin Sodium**

The statement given under Section 2.1.1.2. also holds good for this *‘drug’.*

**2.1.1.4. Merethoxylline Procaine**

The statement provided under Section 2.1.1.2. also holds good for this *‘drug’.*

**2.1.1.5. Mersalyl Sodium**

The **‘drug’** is a powerful diuretic that acts on the renal tubules specifically, thereby enhancing

the excretion of Na+ and Cl– ions, in almost equal amounts, and of water.

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**Salient Features of Organomercurials :** The exact mechanism of action pertaining to the

*organomercurials* is still quite a mystery. However, a few important salient features are as stated under :

(1) They breakdown usually to ionic mercury at the acidic urinary pH.

(2) Bonding of a Hg-atom to the organic residue overwhelmingly lowered the degree of toxicity

of the corresponding **‘inorganic compounds’** to an appreciable **‘acceptable’** levels *in*

*vivo.*

(3) Besides, it may be suggested that as an **‘organic ligand’** the chances of legitimate cellular

penetration to the specific **sulfhydryl enzymes** present in the proximal tubules is significantly

improved thereby inactivating the renal enzymes directly involved with the tubular

reabsorption processes, causing *diuresis* ultimately.

**2.2. Non-Mercurial Diuretics**

The **non-mercurial diuretics** usually are predominant in terms of their significant clinical

effectiveness and wider applications. They, in general, possess fewer side-effects and are much less

toxic than the corresponding mercurial diuretics. They are used as adjunct specifically in the *treatment*

*of either poisoning or drug over-dosage during which they increase the process of elimination of poisons*

*or drugs through the kidneys. These diuretics are also employed to counter water and salt retention*

*caused by various drug treatments.*

The most commonly used **diuretics** are invariably classified by their respective chemical class,

mechanism of action, site of action, or effects on the *urine* contents. Nevertheless, these drugs normally

exert their action rather widely with regard to their prevailing efficacy as well as their definite site of

action located within the nephron. The real efficacy of a diuretic is often measured by its ability to

enhance the rate of excretion of Na+ ions filtered usually at the glomerulus (*i.e.,* the filtered load of

sodium) and hence, must not be misunderstood with the potency, that is the actual amount of the *‘diuretic’*

essentially needed to cause a specific diuretic response. In other words, the efficacy of a diuretic is

invariably estimated in portion by the site of action of the diuretic.

The **non-mercurial diuretics** may be classified on the basis of their chemical structures together

with their physical characteristics as follows :

1. Thiazides (Benzothiadiazines),

2. Carbonic-Anhydrase Inhibitors,

3. Miscellaneous Sulphonamide Diuretics,

4. Aldosterone Inhibitors,

5. ‘Loop’ or ‘High-Ceiling’ Diuretics,

6. Purine or Xanthine Derivatives,

7. Pyrimidine Diuretics,

8. Osmotic Diuretics,

9. Acidotic Diuretics, and

10. Miscellaneous Diuretics.

**2.2.1. Thiazides (Benzothiadiazines)**

A major breakthrough in diuretic therapy was the introduction of **chlorothiazide** as a reliable,

oral and non-mercurial diuretic in 1955 by Nouello and Spagne in the research laboratories of Merck,

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Sharp and Dohme. A number of **benzothiadiazines (I),** having the following general chemical formula :

were subsequently synthesized and found to possess varying degree of diuretic actions. The

**benzothiadiazines** are frequently known as **thiazides** or **benzothiazides.**

It has been amply observed that the **thiazide diuretics** enhance urinary excretion of both Na and

H2O by specifically inhibiting Na reabsorption located in the cortical (thick) portion of the ascending

limb of Henle’s loop\* and also in the early distal tubules. Besides, they also progressively cause an

increase in the excretion of Cl–, K+ and HCO3

– (to a lesser extent) ions. However, the latter effect is

predominantly by virtue of their mild carbonic anhydrase-inhibitory action. Importantly, due to their site

of action, they invariably interfere with the dilution ; whereas, the concentration of urine is not affected

appreciably.

In general, the **thiazide diuretics** minimise the glomerular filtration rate. Furthermore, this specific

action fails to contribute to the diuretic action of such drugs, and this would perhaps put forward a

logical explanation of their observed lower efficacy in instances having *impaired-kidney function.*

**Examples : Chlorothiazide ; Hydrochlorothiazide ; Hydroflumethiazide ;**

**Bendroflumethiazide ; Benzthiazide ; Cyclothiazide ; Cyclopenthiazide ; Methylclothiazide ;**

**Trichlormethiazide ; Polythiazide ; Altizide**

**A. Chlorothiazide INN, BAN, USAN,**

6-Chloro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-

7-sulphonamide, 6-Chloro-1, 1-dioxide ; BP., USP., Int. P.

Diuril(R) (Merck Sharp and Dohme) ; SK-Chlorothiazide(R) (Smith Kline and French).

**Synthesis**

It may be prepared by the chlorination of 3-chloroaniline with chlorosulphonic acid to yield 3-

chloroaniline-4, 6-disulphonyl chloride, which is then amidated with ammonia to give the corresponding

4, 6-disulphonamide analogue. This on heating with formic acid affords cyclization through double

condensation.

\*The U-shaped portion of a renal tubule lying between the proximal and distal convoluted portions. It consists of a

thin-descending limb and a thicker ascending limb.

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**Chlorothiazide** is used in the *treatment of oedema associated with congestive heart failure and*

*renal and hepatic disorders. It is also employed in hypertension, either alone or in conjunction with*

*other antihypertensive agents. It is also used in oedema associated with corticosteroid therapy thereby*

*increasing the potassium-depleting action of the latter.*

**Dose :** *Antihypertensive, 250 to 500 mg ; usual, antihypertensive, 250 mg 3 times per day ;*

*diuretic 500 mg to 1g ; usual, diuretic, 500 mg 1 or 2 times per day.*

**B. Hydrochlorothiazide INN, BAN, USAN,**

6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-

Benzothiadiazine-7-sulphonamine, 6-chloro-3, 4-dihydro-1, 1-dioxide ; BP ; USP ; Int. P ;

Esidrix(R) (Ciba-Geigy) ; Hydro DIURIL(R) (MS and D) ; Thiuretic(R) (Parke-Davis) ; Oretic(R)

(Abbott).

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**Synthesis**

*The route of synthesis is more or less identical with that for chlorothiazide described earlier*

*except that formaldehyde is used instead of formic acid in the final cyclization step from 3-chloroaniline-*

*4, 6-disulphonamide.*

Its diuretic actions are similar to those of **chlorothiazide** but it is ten times more potent than the

latter. However, when the treatment is prolonged loss of K+ causes hypokalemia which may be prevented

by supplementation with potassium salts.

**Dose :** *25 to 200 mg per day ; usual, 50 mg 1 or 2 times daily.*

**C. Hydroflumethiazide INN, BAN, USAN,**

3, 4-Dihydro-6-(trifluoromethyl)-2H-1, 2, 4-benzothiadiazine-7-sulphonamide, 1, 1-dioxide ; 2H-

1, 2, 4-Benzothiadiazine-7-sulphonamide, 3, 4-dihydro-6-(trifluoromethyl)-1, 1-dioxide ; Trifluoromethylhydrothiazide

; BP. USP ; Int. P ;

Diucardin(R) (Ayerst) ; Saluron(R) (Bristol).

**Synthesis**

(*Contd.*..)

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Treatment of 3-amino-trifluoromethyl benzene with chlorosulphonic acid yields the corresponding

4-disulphonyl chloride derivative which on reaction with ammonia gives rise to 3-amino-trifluoro methyl

benzene 4, 6-disulphonamide. This on heating with formaldehyde in an environment of sulphuric acid

affords a concomitant condensation and finally cyclization to the official compound.

**Hydroflumethiazide** is a potent diuretic employed in the management of oedema associated

with cardiac failure, steroid administration, premenstrual tension and hepatic cirrhosis.

**Dose :** *25 to 200 mg ; usual, 50 to 100 mg daily.*

**D. Bendroflumethiazide INN, USAN, Bendrofluazide BAN,**

3-Benzyl-3, 4-dihydro-6-(trifluoromethyl)-2H, 1, 2, 4-benzo-thiadiazine-7 sulphonamide 1, 1-

dioxide ; 2H, 1, 2, 4-Benzothiadiazine-7-sulphonamide, 3, 4-dihydro-3-(phenylmethyl)-6-

(trifluoromethyl)-, 1, 1-dioxide ; BP., USP., Int. P. ;

Naturetin(R) (Squibb) ; Neo-Naclex(R) (Glaxo).

**Synthesis**

It consists of cyclization of 3-amino-trifluoromethyl benzene 4, 6-disulphonamide through

condensation with phenylacetaldehyde.

**Bendroflumethiazide** is used in the *control and management of oedema, nephrosis and nephritis,*

*cirrhosis and ascites, congestive heart failure, and other oedematous states. It is also employed as an*

*antihypertensive agent.*

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**Dose :** *Initial, diuretic, 5 to 20 mg per day ; maintenance, 2.5 to 5 mg daily ; as antihypertensive,*

*initial, 5 to 20 mg per day, maintenance, 2.5 to 15 mg per day.*

**E. Benzthiazide INN, BAN, USAN,**

S

N

NH

CH SCH 2 2 —

O O

H NSO 2 2

C l

3-[(Benzylthio) methyl]-6-chloro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-

1, 2, 4-Benzothiadiazine-7-sulphonamide-6-chloro-3-[[(phenylmethyl) thio] methyl]-, 1, 1-dioxide ;

BPC ; (1963), USP ;

Exna(R) (Robins) ; Aquatag(R) (Tutag).

**Synthesis**

3-Chloroaniline-4, 6-disulphonamide is prepared in the same manner as described for

**chlorothiazide** which is then made to condense and cyclize by treatment with benzyl thioacetyl chloride

in the presence of sodium hydroxide to yield **benzthiazide.**

*It is used as a diuretic and an antihypertensive agent with pharmacological actions similar to*

*those of* ***chlorothiazide.***

**Dose :** *Usual, diuretic, initial, 50 to 200 mg per day ; maintenance, 50 to 150 mg per day ; usual,*

*antihypertensive, initial, 50 mg 2 times a day ; maintenance, maximal dose of 50 mg 3 times daily.*

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**F. Cyclothiazide INN, BAN, USAN,**

6-Chloro-3, 4-dihydro-3-(5-nor-bornen-2-yl)-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-

dioxides ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 3-bicyclol [2, 2, 1] hept-5-en-2-yl-6-

chloro-3, 4-dihydro-, 1, 1-dioxide ; USP ; NF ;

Anhydron(R) (Lilly) ; Fluidil(R) (Adria).

**Synthesis**

The synthesis of **cyclothiazide** is analogous to that for **chlorothiazide,** except that 5-nonbornene-

2-carboxaldehyde is used in the cyclization process in place of formic acid.

It possesses both diuretic and antihypertensive actions. It is often *used as an adjunct to other*

*antihypertensive drugs, such as reserpine and the ganglionic blocking agents.*

**Dose :** *Usual, initial, diuretic, 1 to 2 mg per day ; maintenance, 1 to 2 mg on alternate days, or*

*2 or 3 times per week ; usual, antihypertensive, 2 mg 1 to 3 times daily*

**G. Cyclopenthiazide INN, BAN, USAN,**

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6-Chloro-3-(cyclopentylmethyl)-3, 4-dihydro-2H, 1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-

dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3-(cyclopentylmethyl)-3, 4-

dihydro, 1, 1-dioxide ; BP ;

Navidrex-K(R) (Ciba, U.K.).

**Synthesis**

The process is similar to that for **chlorothiazide,** except that cyclopentyl acetaldehyde is used in

the cyclization to yield the official compound.

**Cyclopenthiazide possesses actions and uses similar to those of chlorothiazide.**

**Dose :** *For oedema, usual, initial, 0.5 to 1 mg per day, reduced to 250 to 500 mcg per day or 500 mcg*

*on alternate days ; For hypertension, usual, 250 to 500 mcg per day either alone, or in conjunction with*

*other antihypertensive agents.*

**H. Methyclothiazide INN, BAN, USAN,**

6-Chloro-3-(chloromethyl)-3, 4-dihydro-2-methyl-2H-1, 2, 4-benzothiadiazine-7-sulphonamide-1, 1-

dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3-(chloromethyl)-3, 4-dihydro-

2-methyl, 1, 1-dioxide ; USP ;

Enduron(R) (Abbott).

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**Synthesis**

It may be prepared by a method analogous to **chlorothiazide** when 4-amino-6-chloro-N3-methyl*m*-

benzenedisulphonamide is caused to condense with monochloroacetaldehyde.

**Methyclothiazide** is effective both *as a diuretic and an antihypertensive agent. It is about 100*

*times more potent than chlorothiazide. In prolonged treatment it is absolutely necessary to supplement*

*with potassium to avoid hypokalemia.*

**Dose :** *Usual, maintenance, as diuretic and antihypertensive, 2.5 to 10 mg once per day.*

**I. Trichlormethiazide INN, BAN, USAN,**

6-Chloro-3-(dichloromethyl)-3, 4-dihydro-2H-1, 2, 4-benzo-thiadiazine-7-sulphonamide 1, 1-

dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3-(dichloromethyl)-3, 4-dihydro-

1, 1-dioxide USP ;

Metahydrin(R) (Merrell Dow) ; Naqua(R) (Schering)

**Synthesis**

It may be prepared by the condensation of 4-amino-6-chloro-*m*-benzene disulphonamide with

dichloroacetaldehyde.

Trichlormethiazide belongs to the class of *long-acting diuretic and antihypertensive thiazide*.

**Dose :** *Usual, 2 to 4 mg twice daily ; maintenance 2 to 4 mg once per day.*

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**J. Polythiazide INN, BAN, USAN,**

6-Chloro-3, 4-dihydro-2-methyl-3-[[2, 2, 2-trifluoroethyl) thio] methyl]-2H-1, 2, 4-benzothiadiazine-

7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3, 4-

dihydro-2-methyl-3-[[(2, 2, 2-trifluoroethyl) thio] methyl]-, 1, 1-dioxide ; BP ; USP ; NF ;

Renese(R) (Pfizer).

**Synthesis**

A heterocycle intermediate is prepared by the condensation of 4-amino-6-chloro-*m*-benzene

disulphonamide with urea which on treatment with methyl iodide in a basic medium yields the corresponding

methylated heterocycle. This on hydrolysis in the presence of a base affords N-methylated

aminosulphonamide which on condensation with dimethylacetal of 2, 2, 2-trifluoroethylmercaptoacetaldehyde

yields the official compound.

**Polythiazide** is a *potent long-acting diuretic and anti-hypertensive agent.*

**Dose :** *As diuretic, usual, 1 to 4 mg per day ; as antihypertensive, 2 to 4 mg as required.*

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**K. Altizide INN, Althiazide USAN,**

3-[(Allythio) methyl]-6-chloro 3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-

dioxide ;

Althiazide(R) (Pfizer).

**2.2.1.1. Mechanism of Action**

The mechanism of action of the **thiazide diuretics** shall now be discussed individually in the

pages that follows :

**2.2.1.2. Chlorothiazide**

The epoch making era of wonderful **‘drug discovery’** of **benzothiadiazines** commenced with

the synthesis (1957) and the remarkable valuable diuretic characteristic features of this **‘drug’** *i.e.,*

**chlorothiazide (CTZ)**. It acts by depliting Na and followed by reduction in the plasma volume. Besides,

it also reduces in the peripheral resistance. Refractoriness of the *‘drug’* is comparatively uncommon,

even after a prolonged span of continuous usage.

**2.2.1.3. Hydrochlorothiazide (HCTZ)**

Slightly more soluble in water than chlorothiazide, but its mode of action is practically the same

as that of **chlorothiazide**.

**2.2.1.4. Hydroflumethiazide**

The replacement of the Cl-atom at C-6 with trifluoromethyl function (CF3) renders the **‘drug’**

more potent in its therapeutic activity.

**2.2.1.5. Bendroflumethiazide**

Additional benzyl moiety at C-3 of **hydroflumethiazide** attributes far better potency than the

parent drug in terms of its diuretic profile.

**2.2.1.6. Benzthiazide**

Additional benzyl thiomethyl group at C-3 of **chlorothiazide** renders the drug more broad-spectrum

in its therapeutic values *i.e.,* it serves both as a diuretic and also as an antihypertensive agent.

**2.2.1.7. Cyclothiazide**

The only glaring difference between this **‘drug’** and **chlorothiazide** is the presence of 5-norboren-

2-yl lipid-soluble moieties strategically located at the C-3 position which renders the drug both orally

effective as a diuretic and antihypertensive *i.e.,* the two pharmacological characteristics desirably present

in the same drug molecule.

**2.2.1.8. Cyclopenthiazide**

The **‘drug’** exhibits its activitiy quite similar to those of **HCTZ**. However, in suceptible patients

potassium supplements or a potassium-sparing diuretic may be absolutely important and necessary.

**2.2.1.9. Methyclothiazide**

The dosage regimen of clinically used compounds invariably ranges between 1 to 2000 mg.

Besides, there exists one more important and clinically useful variable within which a choice is obviously

preferable is the duration of action. **Methyclothiazide** possesses a range of 24+ hours in comparison to

**CTZ** having as much a low range of 6 hours.

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**2.2.1.10. Trichlormethiazide**

The **‘drug’** is an orally effective as well as long-acting thiazide diuretic and antihypertensive. It

resembles **CTZ** with respect to its pharmacologic actions, therapeutic uses and untoward effects.

**2.2.1.11. Polythiazide**

It is also a long-acting diuretic and antihypertensive agent that causes diuresis within 2 hr,

attains a peak in 6 hr and lasts 24 to 48 hr. The mean plasma half-lives for absorption and elimination

are 1.2 and 25.7 hour respectively. It has been observed that nearly 20% of the drug gets excreted

unchanged in the urine. On being compared on a milligram basis, 2 mg of **polythiazide** has almost

nearly the same diuretic activity as produced by 500 mg of **CTZ**.

**2.2.1.12. Altizide (Althiazide)**

It is a **thiazide diuretic** having action very similar to **hydrochlorothiazide (HCTZ)**. It is invariably

administered in combination with spironolactone.

**2.2.1.13. SARs of Thiazide Diuretics**

The SARs of these **benzene disulphonamide structural analogues** yielded a broad-spectrum of

compounds having a relatively high degree of diuretic activity, which are summarized as stated under :

(1) **Thiazide diuretics** are found to be weakly acidic in nature having a

benzothiadiazine 1, 1-dioxide nucleus.

(2) **Chlorothiazide (CTZ)** being the simplest member of this series of

structural analogues having two pKa (dissociation constant) values

of 6.7 and 9.5. The two acidic zones in **CTZ** are virtually due to the

presence of : (*a*) presence of a H-atom at the 2-N that essentially

attributes the most acidic character by virtue of the influence of the

prevailing electron withdrawing effects of the neighbouring

sulphone moiety ; and (*b*) presence of the sulphonamide (–SO2NH2) functional moiety

strategically located at C-7 position which affords an additional environment (zone) of

creating acidity in the molecule ; however, its acidic influence is much less than the 2-N

proton. Importantly, these acidic protons enable the formation of the corresponding water-

soluble sodium salt which may be gainfully used for IV-administration of the diuretics

as shown below :

(3) Presence of an electron-withdrawing moiety at C-6 is an absoluble necessity for the diuretic

activity. A few important and vital observations are as enumerated below :

(*a*) Practically negligible diuretic activity is obtained by having a H-atom at C-6 ;

(*b*) Substitution with a chloro or trifluoromethyl moiety at C-6 are quite active

pharmacologically.

(*c*) Further, the CF3 moiety renders the resulting diuretic compound more lipid-soluble

and also with a much longer duration of action in comparison to its chloro-substituted

derivatives ;

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(*d*) Presence of electron-releasing moieties, namely : *methyl* or *methoxyl* at C-6 position

attributes significantly reduced diuretic activity.

(4) Removal or possible replacement of the sulphonamide function at C-7 results into such

compounds possessing either little or almost no diuretic activity.

(5) Saturation of the prevailing double-bond between 3 and 4 positions to give rise to a

corresponding 3, 4-dihydro structural analogue which is observed to be having nearly 10

times more diuretic activity than the unsaturated analogue.

(6) Introduction of a lipophilic functional moiety at C-3 position renders a marked and

pronounced enhancement in the diuretic potency. For instance : aralkyl, haloalkyl, or

thioether substitution, enhances the lipoidal solubility of the molecule to a considerable

extent thereby producing compounds with a much longer duration of action.

(7) Alkyl substitution on the N-2 position is observed to lower the polarity and ultimately

enhancing the duration of the ensuing diuretic action.

**2.2.2. Carbonic Anhydrase Inhibitors**

In early 1940s, attempts were made towards the synthesis and subsequent screening of

**sulphonamides** possessing carbonic anhydrase inhibitory characteristics of sulphanilamide which

resulted in the production of a variety of heterocyclic sulphonamides. When the enzyme is

inhibited, the generation of carbonic acid (H2CO3) that usually dissociated into HCO3

– and H3O+,

is also inhibited. Thus in glomerular filtrate, a deficiency of H3O+ which normally exchanges for

Na+ occurs. The Na+ remains in the renal tubule together with the HCO3

– plus an osmotic

equivalent of water, which ultimately results in the excretion of a large quantity of urine and

hence diuresis. These compounds which inhibit carbonic anhydrase, besides acting as diuretics,

also cause acidosis because of the elimination of HCO3

– and Na+ ions. The acidosis tends to limit

its diuretic activity.

A most logical H-bonding mechanism which is believed to act competitively perhaps

explains the action of some sulphonamide carbonic anhydrase inhibitors which predominantly

exhibit both diuretic and antiglaucoma activities. It is, however, assumed that carbonic acid

being the normal substrate which not only fits into a cavity but also complexes with the corresponding

enzyme **carbonic anhydrase (CA)** as illustrated in Fig. 14.1(*a*). Consequently, this

complex is strongly stabilized by **four** H-bonds.

**Fig. 14.1. Interactions Occurring at the Hypothetical Reactive Sites**

**of Enzymes Carbonic Anhydrase.**

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Interestingly, the **sulphonamide moiety** which essentially possesses a **geometric structural**

**entity** thus allowing an equally perfect fit compatible into the cavity of the enzyme CA also get bound

quite securedly and effectively, perhaps to the same four areas by H-bonds as depicted in Fig. 14.1(*b*).

Therefore, one may safely draw an inference that these **sulphonamide structural analogues**

competitively prevent the carbonic acid from getting bound at this specific site. Consequently, such an

action shall obviously inhibit the prvailing action of the enzyme CA, thereby giving rise to an apparent

acid-base imbalance that would ultimately cause diuresis.

It is, however, pertinent to state here that the **sulphonamides** of the type wherein the possibilities

for H-bonding having been lowered from *four* to *three* usually render the compounds **inactive**.

A few typical examples of this class of **diuretics** are described here.

**Examples : Acetazolamide ; Methazolamide ; Ethoxzolamide ; Diclofenamide ; Disulfamide**

**A. Acetazolamide INN, BAN, USAN,**

N-(5-Sulfamoyl-1, 3, 4-thiadiazol-2-yl) acetamide ; Acetamide, N-[5-(amino-sulphonyl)-1, 3, 4-

thiadiazol-2-yl]- ; BP ; USP ; Ind. P. ;

Diamox(R) (Lederle).

**Synthesis**

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Reaction between hydrazine hydrate and ammonium thiocyanate yields 1, 2-*bis* (thiocarbamoyl)

hydrazine which on treatment with phosgene undergoes molecular rearrangement through loss of ammonia

to yield 5-amino-2-mercapto-1, 3, 4-thiadiazole. This on acylation gives a corresponding amide

which on oxidation with aqueous chlorine affords the 2-sulphonyl chloride. The final step essentially

consists of amidation by treatment with ammonia.

**Acetazolamide** *is employed effectively for adjunctive treatment of drug-induced oedema, oedema*

*caused by congestive heart failure, petit mal and other centrencephalic epilepsies. It has also been used*

*to lower the intraocular pressure prior to surgery in acute conditions of angle-closure glaucoma, besides*

*open-angle and secondary glaucoma.*

**Dose :** *Usual, 250 mg 2 to 4 times per day.*

**B. Methazolamide INN, BAN, USAN,**

N-(4-Methyl-2-sulphamoyl-2-1, 3, 4-thiadiazolin-5-ylidene) acetamide ; Acetamide, N-[5-

(aminosulphonyl)-3-methyl-1, 3, 4-thiadiazol-2 (3H)-ylidene] USP ;

Neptazane(R) (Lederle).

**Synthesis**

(*Contd*...)

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2-Acetamido-5-mercapto-1, 3, 4-thiadiazole is prepared as described under acetazolamide. This

on treatment with *p*-chlorobenzyl chloride forms the corresponding *p*-chloro benzyl mercapto derivative,

which when reacted with methyl bromide in the presence of sodium methoxide yields the acetylamino

thiadiazoline derivative. On oxidation with aqueous chlorine it gives rise to the 2-sulphonyl chloride

derivative which finally yields **methazolamide** on amidation with ammonia.

Its actions and uses are similar to those of **acetazolamide.** However, its action has been found to

be *relatively less prompt but of definitely longer duration than that of the latter, lasting for 10 to 18*

*hours.*

**Dose :** *100 to 600 mg per day ; usual, 50 to 100 mg 2 to 3 times per day.*

**C. Ethoxzolamide BAN, USAN,**

6-Ethoxy-2-bezothiazolesulphonamide ; 2-Benzothiazolesulphonamide, 6-ethoxy- ;

Ethoxyzolamide ; USP ;

Cardrase (Upjohn).

**Synthesis**

It may be prepared by the reaction of 6-ethoxy-benzothiazole with sodium hypochlorite in the

presence of sodium hydroxide and ammonia to yield the corresponding sulphenamide, which upon

oxidation with potassium permanganate in acetone forms the official compound.

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***Ethoxzolamide*** *is mainly used to lower the intraocular pressure prior to surgery in acute angleclosure*

*glaucoma, besides its application in the treatment of chronic simple glaucoma and secondary*

*glaucoma.*

**Dose :** *62.5 mg to 1g daily ; usual, 125 mg 2 to 4 times per day.*

**D. Diclofenamide INN, Dichlorphenamide BAN, USAN,**

4, 5-Dichloro-*m*-benzenedisulphonamide; 1, 3-Benzenedisulphonamide, 4, 5-dichloro- ; 4, 5-

Dichlorobenzene-1, 3-disulphonamide; BP ; USP ;

Daranide(R) (Merck Sharp and Dohme); Oratrol(R) (Alcon)

**Synthesis**

It may be prepared by the interaction of *o*-chlorophenol with chlorosulphonic acid to yield 5-

chloro-4-hydroxy-1, 3-benzene-disulphonyl chloride. This on treatment with PCl5 replaces the 4-hydroxy

with chlorine and the subsequent ammonolysis gives the official compound.

***Diclofenamide*** *is employed to lower intraocular pressure by reducing the rate of secretion of*

*aqueous humor. It is recommended for the treatment of both primary and secondary glaucoma. Though*

*it possesses inherent diuretic properties it is not promoted for this purpose. It produces less acidotic*

*refractoriness to diuretic action than acetazolamide.*

**Dose :** *50 to 300 mg per day ; usual ; 25 to 50 mg 1 to 3 times daily.*

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**E. Disulfamide INN, USAN, Disulphamide BAN,**

5-Chlorotoluene-2, 4-disulphonamide ; BPC (1968) ;

Diluen(R) (Libra, Italy).

**Synthesis**

5-Chlorotoluene-2, 4-disulphonyl chloride is prepared by the interaction of 5-chlorotoluene and

chlorosulphonic acid, which on amidation gives rise to **disulfamide.**

Its actions and uses are simialr to those of **chlorothiazide.** It is invariably employed for the

*treatment of oedema.*

**Dose :** *For oedema, usual, initial, 200 mg per day for 5 days a week or on alternate days,*

*reduced to 100 mg per day.*

**2.2.2.1. Mechanism of Action**

The mechanism of action of certain **carbonic anhydrase inhibitors** used as **diuretics** shall be

discussed in the sections that follows :

**2.2.2.1.1. Acetazolamide**

The **‘drug’** still remanis the most vital carbonic anhydrase inhibitor and being regarded as the

prototype member of this specific category. It gets absorbed appreciably from the GI-tract, bound

extensively to the plasma proteins, and does not undergo biotransformation. It is eliminated almost

completely from the plasma by the kidneys within a span of 24 hr. The drug is subjected to filtration at

the glomeruli, and viable tubular secretion in the proximal tubule. Importantly, it also invariably affords

a varying range of pH-dependent non-ionic back diffusion taking place particularly in the distal segments

of the nephron.

**2.2.2.1.2. Methazolamide**

If has been amply demonstrated *in vitro* that the **‘drug’** is definitely has an edge over the prototype

acetazolamide with regard to its potency as CA inhibitor. Besides, it is also observed to exhibit an

improved penetration into the eye\*, which action strongly recommends its usage in the treatment of

glaucoma.

\*Sprague JM : *Advances in Chemical Series,* American Chemical Society, Washington DC., **45,** 87–101, 1964.

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\*Allen RC : In : Cragoe EJ (ed.) : *Diuretics-Chemistry Pharmacology and Medicine,* John Wiley and Sons, New York,

pp-49–200, 1983.

**2.2.2.1.3. Ethoxzolamide**

The **‘drug’** is a **carbonic anhydrase inhibitor** which is found to exert its action by lowering the

intraocular pressure prior to surgery when employed preoperatively in acute angle-closure glaucoma.

**2.2.2.1.4. Dichlorphenamide**

The **‘drug’** acts by lowering the intraocular pressure just like several other CA-inhibitors ; and

hence, may be beneficial in the control, management and treatment of glaucoma *i.e.,* in primary as well

as the acute phase of secondary glaucoma.

Interestingly, the major importance of this **‘drug’** is that it ultimately served as stepping stone far

away from the *‘pure’* CA-inhibiting diuretics ; and, therefore, paved the way towards the development

of the **‘thiazides’** that proved to be extremely useful and effective Na+ and Cl– depleting agents having

almost negligible CA-inhibitory activity.\*

**2.2.2.1.5. Disulphamide**

Its mechanism of action is almost similar to that of **chlorothiazide (CTZ)** in the relief of fluid

retention in the body.

**2.2.3. Miscellaneous Sulphonamide Diuretics**

The actions of these drugs are very similar to the thaizide diuretics, except that these specifically

possess longer duration of action.

In the above **benzothiadiazine (thiazides)** moiety the ‘SO2’ at position 1 has been duly changed

to carbonyl function *i.e.,* the sulphonyl moiety replaced with carbonyl moiety, thereby resulting

into the formation of a series of *‘thiazide isosteres’,* namely : **quinethazone, chlorthalidone, metolazone**

and **indapamide.**

All these compounds grouped together under **‘miscellaneous sulphonamide diuretics’** shall be

treated individually as under :

**A. Quinethazone INN, BAN, USAN,**

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7-Chloro-2-ethyl-1, 2, 4-tetrahydro-4-oxo-6-quinazolinesulphonamide ; 6-Quinazolinesulphonamide,

7-chloro-2-ethyl-1, 2, 3, 4-tetrahydro-4-oxo- ; USP. ;

Hydromox(R) (Lederle)

**Synthesis**

Chlorosulphonation of 4′-chloro-*o*-acetotoluidine yields the corresponding sulphonyl chloride

derivative which on amination forms the sulphonamide derivative. Oxidation of the methyl moiety gives

the respective anthranilamide derivative which on hydrolysis eliminates the acetyl group to yield the

substituted anthranilic acid. Fusion of this amino acid with propionamide first gives rise to an intermediate

by the loss of a mole of water and ultimately helps in the closure of the ring to generate the quinazoline

ring system. Catalytic reduction of this finally produces the official compound.

**Quinethazone** essentially differs from the **benzothiazide type of diuretics** only in the replacement

of a sulphur atom by a carbon at position 4.

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*It possesses both diuretic and antihypertensive properties similar to those of the thiazides.*

**Dose :** *50 to 200 mg per day ; usual, 50 to 100 mg once daily.*

**B. Chlortalidone INN, Chlorthalidone BAN, USAN,**

2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulphonamide ; Benzene sulphonamide, 2-

chloro-5-(2, 3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)- ; BP ; USP ;

Hygroton(R) (USV)

**Synthesis**

**Chlortalidone** is a thiazide-like diuretic agent *which essentially contains an isoindole ring.*

It may be prepared by the diazotization and subsequent treatment with sulphur dioxide in glacial

acetic acid in the presence of cupric chloride of 3-amino-4-chloro-benzophenone-2-carboxylic acid to

yield 4-chloro-2′-carboxy-benzophenone-3-sulphonyl chloride. This on treatment with thionyl chloride

followed by amidation in aqueous ethanol and finally with HCl gives crude **chlortalidone** which is

recrystallized from aqeous ethanol.

**Chlortalidone** *is employed in the treatment of oedema associated with obesity, pregnancy, renal*

*disease, hepatic cirrhosis, premenstrual syndrome and above all the congestive heart failure.*

**Dose :** *As diuretic, 50 to 200 mg per day or alternate day ; usual, 100 mg once daily ; As*

*antihypertensive, 100 mg alternate day or 50 mg every day.*

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**C. Metolazone BAN, USAN**

6-Quinazolinesulphonamide, 7-chloro-1, 2, 3, 4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo- ;

Diulo(R) ; Zaroxolyn(R) ;

It is a **quinazoline-derived nonthiazide diuretic.** It is found to be more effective in comparison

to the thiazide-like diuretics in the treatment of edema in such patients who have a history of compromised

renal function. It is extensively indicated for *hypertension, edema accompanying congestive heart failure,*

*renal disease* including the *nephrotic syndrome* and other *conditions of* retarded renal function.

**Dose :** *Usual, adult, oral, edema of cardiac failure, 5 to 10 mg once daily ; edema of renal*

*disease, 5 to 20 mg once daily ; mild essential hypertension, 2.5 to 5 mg once daily.*

**D. Indapamide BAN, USAN,**

Benzamide, 3-(aminosulphonyl)-4-chloro-N-(2, 3-dihydro-2-methyl-1H-indol-1-yl)- ;

Lozol(R) (Rhone Poulenc Rorer) ;

It is an orally active and effective diuretic acid and anithypertensive drug closely related chemically

to the **indolines.**

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The **‘drug’** undergoes ***keto-enol* tautomerism** and the *‘acid form’* is the active one.

*It is used for the control and management of edema associated with congestive heart failure and,*

*alone or in combination with other such agents, in the treatment of hypertension.*

**Dose :** *Usual, hypertension and edema of congestive heart failure, 2.5 mg as a single daily dose*

*taken in the morning ; if the response is not satisfactory after one (edema) to four (hypertension) week,*

*the dose is usually increased to 5 mg once daily.*

**2.2.3.1. Mechanism of Action**

The mechanism of action of the above **‘drug’** shall be described individually as under :

**2.2.3.1. Quinethazone**

The **‘drug’** is a quinazoline derivative having 6-thiazide-like effect. Based on the available clinical

evidence one may suggest that its site, mechanism of action, electrolyte excretion pattern and above all

the therapeutic activities are very much similar to those of **CTZ.**

**2.2.3.2. Chlorthalidone**

The biochemical studies carried out with the **‘drug’** suggest that the prolonged duration of action

is solely on account of the slow gastrointestinal absorption, enterohepatic recirculation and above all the

critical binding to RBCs in the body. It has been observed that nearly 30–60% of the **‘drug’** gets excreted

almost unchanged by the kidney.

**SAR of Chlorthalidone.** The *enol-*form (*i.e.,* the acid form) of chlorthalidone is the **‘active**

**drug’** as depicted below :

It is not strictly speaking a thiazide.

**2.2.3.3. Metolazone**

The **‘drug’** exerts its inhibition of Na+ (and Cl–) reabsorption in early *distal tubule* and the

*ascending limb of loop of Henle.* It is also demonstrated to show its action primarily to inhibit Na+

reabsorption both at the *cortical diluting site* and in the *proximal convoluted tubule.* Its long duration of

action ranging between 12 to 24 hours is appreciably attributed to protein binding as well as enterohepatic

recycling.

However, it may be more effective in comparison to the thiazide like diuretics in the usual treatment

of edema in subjects having compromised renal function. About 95% of the plasma drug gets bound to

plasma proteins in normal controls ; whereas, about 90% is bound in patients with severe renal failure.

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**2.2.3.4. Indapamide**

The **‘drug’** is taken up preferentially and reversibly by the erythrocytes in the peripheral blood.

It has been observed that the whole blood/plasma ratio is about 6 : 1 at the time of peak concentration

and reduces to 3.5 : 1 after a lapse of 8 hr. It has been found that 71 to 79% of the drug gets bound to

plasma proteins. It gets metabolized extensively *in vivo* ; and only 7% of the unchanged form of the drug

is excreted by the kidneys.

**SAR of Indapamide.** It apparently differs from the **thiazides** structurally. However, it may be

viewed chemically as comprising of a **polar sulphamoylchlorobenzamide** and a highly **lipoidal**

**methylindolyl** functional moiety.

**2.2.4. ‘Loop’ and ‘High-Ceiling’ Diuretics**

These are a group of diuretics which essentially contain carboxylic acid moietics. They usually

produce an intense diuresis of relatively short duration (4-6 hrs) with rapid onset (30 min). They have

been found to act mainly on the ascending limb of the loop of Henle (hence often referred to as **loop**

**diuretics**), besides exerting some effect on both the proximal and distal tubules. They seem to act by

inhibiting th reabsorption of Cl– (and therefore of NaCl). They cause loss of Cl–, Na+ and K+ ions to a

considerable extent.

The **‘loop diuretics’** usually possess a much greater diuretic profile in comparison to the **‘thiazides’ ;**

and are observed to be even more potent and effective in a situation having electrolyte as well as acidbase

disturbances concurrently. Besides, the time of onset and duration of action of the **‘high-ceiling**

**diuretics’** are emuch shorter than those with the *thiazides.*

Interestingly, there exists a little controversy with regard to the *relative superiority* of the **‘loop**

**diuretics’** in a specific situation of hypertension intimately associated with renal insufficiency than the

*thiazides.* Furthermore, the former tend to *enhance* renal blood flow, whereas the latter tend to *minimise*

renal blood flow, and thereby lead to further compromise to renal function.

As a point of caution it may, be added that a very **‘close monitoring is absolutely warranted’** to

avoid severe ensuing electrolyte imbalances in patients being treated with the *‘loop diuretics’* by virtue

of the fact that they normally possess much greater potency in comparison to the *thiazides.*

**Examples : Bumetanide ; Furosemide ; Etacrynic acid.**

**A. Burmetanide INN, BAN, USAN,**

3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid ; Benzoic acid, 3-(amino-sulphonyl)-5-

(butylamino)-4-phenoxy- ; Bumex(R) (Hoffman-La Roche) ;

Burinex(R) (Leo, U.K.)

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**Bumetanide** *is used in the treatment of renal insufficiency and, in conditions which warrant*

*forced diuresis regimens for the control and management of acute drug poisoning e.g., barbiturate*

*poisoning in attempted suicide cases. It is also employed in the treatment of oedema.*

**Dose :** *For oedema, usual, oral 1mg once in the morning followed by another similar dose after*

*6–8 hours if necessary.*

**B. Furosemide INN, USAN Frusemide BAN,**

4-Chloro-N-furfuryl-5-sulphamoylanthranilic acid ; Benzoic acid, 5-(amino-sulphonyl)-4-chloro-

2-[(2-furanylmethyl) amino]- ; Frusemide (BP ; Eur. P.,) ; Furosemide (USP.) ;

Lasix(R) (Hoechst) ; SK-Furosemide(R) (SK & F)

**Synthesis**

2, 4-Dichloro-5-sulphamoyl benzoic acid may be prepared by reacting 2, 4-dichlorobenzoic acid

with chlorosulphonic acid at an elevated temperature and then carrying out the amidation. This on

treatment with furfuryl amine in the presence of sodium bicarbonate, affords nucleophilic aromatic

displacement of the highly activated chlorine at C-2, thereby yielding furosemide. However, the protection

of the chlorine atom at C-4 may be achieved by regulating the temperature of the furfurylamination.

**Furosemide** possesses relatively high efficacy, rapid onset of action, short duration of action,

and 1:10 ratio between the minimum and maximum diuretic dose. It is used for the *treatment of oedema*

*associated with renal disease, nephrotic syndrome, cirrhosis of the liver and congestive heart failure. It*

*has an edge over other commonly used diuretic agents specifically when a greater diuretic potential is*

*required. It may also be employed towards the management of hypertension.*

**Dose :** *Oral, 40 to 600 mg per day ; usual, 40 to 80 mg per day ; i.m. or i.v., 20 to 40 mg.*

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**C. Etacrynic Acid INN, Ethacrynic Acid BAN, USAN,**

[2, 3-Dichloro-4-(2-methylenebutyryl) phenoxy] acetic acid ; Acetic acid, [2, 3-dichloro-4-(2-

methylene-1-oxobutyl) phenoxyl]- ; Ethacrynic acid (BP., USP.) ; Etacrynic Acid (Eur. P.) ;

Edecrin(R) (Merck Sharp & Dohme)

**Synthesis**

2, 3-Dichloro-phenoxy acetic acid undergoes **Friedal-Craft’s reaction** with 4-butyryl chloride

to yield the corresponding 4-butyryl analogue. This is subsequently subjected to **Mannich reaction**

with formaldehyde and dimethylamino thereby introducing the methylene group caused by thermal

decomposition, yields the official compound.

**Ethacrynic acid** is normally used in the *treatment of fluid retensive conditions due to congestive*

*heart failure, cirrhosis of the liver, renal disease, and the nephrotic syndrome. It is invariably employed*

*for the control and management of ascites due to lymphoedema, idiopathic oedema and malignancy. It*

*is also recommended through i.v. in an emergency situation of acute pulmonary oedema.*

**Dose :** *50 to 200 mg per day ; 50 mg 2 times daily or 2 times every alternate day ; i.v. 100 mg per*

*day in divided doses.*

**2.2.4.1. Mechanism of Action**

The mechanism of action of the various **‘loop diuretics’** discussed in the previous section shall

be dealt with in the sections that follows :

**2.2.4.1.1. Bumetanide**

The **‘drug’** is found to inhibit both chloride and sodium reabsorption in the ascending limb of the

loop of Henle. Besides, it is somewhat little more *chloruretic* than *natriuretic*. It markedly affords dilation

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of renal vasculature and enhances the renal blood flow. It gets bound to protein to an extent of 95%, and

the volume of distribution ranges between 12–35 L. Nearly 45% of an oral dose gets excreted almost

unchanged. The biological half-life varies between 1–1.5 hr. and is usually prolonged in patients having

renal failure.

**SAR of Bumetanide.** The presence of a 3-aminobenzoic acid along with the sulphonamido

moiety at C-5 renders the drug significantly potent (1 mg ≡40 mg Furosemide). Furthermore, the presence

of the phenoxy functional group at C-4 may substantially account for this portion through markedly

enhanced lipophilicity. Interestingly, a rather newer structural analogue **azosemide,** is of great therapeutic

advantage because of its logical as well as successful replacement of the COOH moiety with the

corresponding isosteric tetrazolyl moiety.

**2.2.4.1.2. Furosemide**

The **‘drug’** is found to be slightly more potent than the organomercurial agents (see section

13.2.1.), is orally effective ; and its diuretic action is independent of possible changes taking place in

body acid-base balance. It has been demonstrated that it acts predominantly not only on the proximal

and distal tubules but also on the ascending limb of the loop of Henle.

Furthermore, the renal excretion was observed to be the major channel of elimination and invariably

averaged 92% of the administered dose levels, having a mean renal clearance of 149 mL. min– 1. Because,

this quantum appreciably exceeds the prevailing glomerular filtrate rate, it is believed that the tubular

secretion of this drug takes place, even though 95% of it gets bound to plasma protein.

**2.2.4.1.3. Ethacrynic Acid**

The **‘drug’** happens to be powerful loop diuretic whose exact molecular mechanism of action is

not yet fully understood. Interestingly, it has been observed that it does possess marked pharmacodynamic

similarities of the mercurial diuretics like *‘mersalyl’,* which being a phenoxyacetic structural analogue.

Besides, it exhibits both *in vivo* and *in vivo* compatibility in its reaction with SH moieties. Moreover, it

logically competes with them for the same receptors.

**Ethacrynic acid** is an aryloxyacetic acid derivative which acts as a potent short-acting diuretic.

It actually gives rise to the excretion of virtually an isoosmotic urine by altogether stopping Na+

reabsorption from the loop of Henle ; however, the excretion of Cl– is even greater than Na+. It has been

observed that nearly 95% of the **‘drug’** gets bound to the plasma proteins. Plasma half-life stands at

about 1 hr.

The maximum water as well as sodium diuresis is very much identical to that with **furosemide ;**

but largely exceeds that with the thiazides.

**SARs of Aryloylphenoxyacetic acids.** The comparative study of nine aryloylphenoxyacetic

acids revealed that the very presence of an activated double bond susceptible to a nucleophilic attack is

almost imperative to cause an effective diuresis. Furthermore, the plausible reduction of the double

bond, thereby making 1, 4-addition of an SH moiety practically impossible, ultimately lowered appreciably

but failed to eliminate **saluretic activity.** It may be suggested that there exists no definite evidence to

demonstrate the sulphhydryl binding in the mechanism of diuretic action of **ethacrynic-type drugs.**

H C C C 5 2— — —– H C C C 5 2— — —–

O H O

CH2

En z –SH

Enz S CH 2 – – —

— OCH COOH 2 — OCH COOH 2

C l C l C l C l

Ethac rynic acid

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**2.2.5. Aldosterone Inhibitors**

**Aldosterone** is one of the most important members amongst the corticosteroids secreted by the

adrenal cortex. It promotes the retention of Na+, Cl– and water *via* distal tubular reabsorption.

**Aldosterone inhibitors (antihormone diuretics)** are agents which particularly compete with

aldosterone at the specific receptor site located in the distal tubule, thereby reversing the electrolyte

actions of this naturally occurring hormone, and causing diuresis. The following are the two members of

this class of compounds, namely ; **spironolactone** and **metyrapone.**

**A. Spironolactone INN, BAN, USAN,**

17-Hydroxy-7-mercapto-3-oxo-17-pregn-4-ene-21-carboxylic acid, -lactone acetate ; Pregn-

4-ene-21-carboxylic acid, 7-(acetylthio)-17-hydroxy-3-oxo--lactone, (7, 17)- ; 7-Acetylthio-

3-oxo-17-pregn-4-ene-21, 17-carbolactone acid -lactone ; Spirolactone ; BP ; USP ;

Aldactone(R) (Searle)

It acts both as a diuretic and as an antihypertensive drug. It is mostly employed in the *treatment of*

*refractory oedema associated with congestive heart failure, nephrotic syndrome or cirrhosis of the liver*

*in which secretion of aldosterone plays a part. It has also been used successfully in the treatment of*

*primary hyperaldosteronism.*

**Dose :** *Usual, initial, 100 mg per day in divided doses ; in hyperaldosteronism 400 mg per day.*

**B. Metyrapone INN, BAN, USAN,**

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2-Methyl-1, 2-di-3-pyridyl-1-propanone ; 1-Propanone, 2-methyl-1, 2-di-3-pyridinyl- ; BP ; USP ;

Metopirone(R) (Ciba-Geigy).

**Metyrapone** inhibits the synthesis of aldosterone which has been used in the treatment of some

cases of resistant oedema. It is necessary to administer a glucocorticoid (cortisone) along with metyrapone

because the latter also exerts an inhibitory effect on the former.

**Dose :** *2.5 to 4.5 mg per day in divided doses.*

**2.2.5.1. Mechanism of Action**

The mechanism of action of the two compounds discussed in the previous section shall be treated

as under :

**2.2.5.1.1. Spironolactone**

It is a purely synthetic steroid which essentially exerts its action as a **‘competitive antagonist’** of

the potent, endogeneous **mineral-corticosteroid, aldosterone.** Its *natriuretic* action seems to be slightly

more particularly in the long-term therapy. In other words, it reverses these electrolyte changes by

blocking the renal tubular action of the hormone. Importantly, by critically inhibiting Na+ reabsorption

**spironolactone** produces diuresis and simultaneously minimises the K+ excretion.

It has been duly observed that this **‘drug’** blocks the sodium-retaining effects of aldosterone on

the distal convoluted tubule, in doing so it particularly corrects one of the most cardinal mechanisms

solely responsible for causing edema ; however, **spironolactone** is effective only in the presence of

**aldosterone.**

It is metabolized rapidly after the oral administration. It is found that metabolites are excreted

mostly in the urine, but also in bile. The primary metabolite is, *canrenone,* which attains the peak

plasma levels within a span of 2–4 hr after oral administration of the drug.

The half-life of canrenone, following multiple doses of the drug is 13 to 24 hour. It has been

observed that both **spironolactone** and **carnenone** are usually get bound to the plasma proteins even

more than 90%.

**Note : The *‘drug’* is particularly ineffective in such clinical situations that are known to have**

**high circulating aldosterone levels (*e.g*., cirrhosis with ascites).**

**2.2.5.1.2. Metyrapone**

The **‘drug’** is a purely synthetic compound which possesses a distinct unique characteristic

feature of inhibiting 11--hydroxylation in the biosynthesis of cortisol, corticosterone and aldosterone.

Therefore, it is invariably employed to test for *hypothalamic-pituitary* function. However, in the normal

individual, the drug essentially blocks the specific enzymatic step that ultimately leads to the synthesis

of **cortisol** and **corticosterone** (*in vivo*), causing an absolute intense stimulation of **adrenocorticotropic**

**hormone (ACTH)** secretion and inducing thereby a marked and pronounced enhancement in the urinary

excretion of 17-hydroxy-corticosteroids.

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**2.2.6. Purine or Xanthine Diuretics**

These are the structural analogues of the parent compounds of unsubstituted **purine** (7-imidazo

[4, 5-*d*] pyrimidine) and **xanthine.**

(7-Imidazo [4, 5-*d*] pyrimidine) (3, 7-Dihydro-1H-purine-2, 6-dione)

**Caffeine :** 1, 3, 7-Trimethyl xanthine ;

**Theophylline :** 1, 3-Dimethyl xanthine ;

**Theobromine :** 3, 7-Dimethyl xanthine ;

**Caffeine, theophylline** and **theobromine** are the three important members of the xanthine

diuretics, which are commonly found in the common beverages *viz.,* **coffee** (*Coffee arabica*), **coca-cola**

(*Cola acuminata*) and **cocoa** (*Theobroma cacao*) contain **caffeine ; tea** (*Thea sinensis*) contains **caffeine**

and **theophylline ;** and **cocoa** (*Theobroma cacao*) contains **theobromine.**

**1. Caffeine BAN, USAN,**

1, 3, 7-Trimethylxanthine ; 1H-Purine-2, 6-dione, 3, 7-dihydro-1, 3, 7-trimethyl- ; Guranine ;

Methyl-theobromine ; Caffeine (BP ; USP ;) ;

Coffeinum (Eur. P.).

**General Method of Extraction**

The crude milled natural product is usually moistened with an aqueous alkali, for instance Na2CO3,

NaHCO3 or line so as to release the alkaloids from their respective salt and subsequently percolated

with benzene, ether, or some other appropriate water-immiscible solvent. The solvent layer is extracted

with dilute mineral acid to convert the alkaloids into their corresponding salts and also to push them into

the aqueous phase. The free alkaloids may be precipitated by the addition of alkali and finally separated

by suitable means.

The diuretic effects of **caffeine** are less than those of **theobromine** and **theophylline. Caffeine**

may enhance renal blood flow and glomerular filtration rate, but its main action may be attributed to the

reduction of the normal tubular reabsorption.

**Dose :** *100 to 300 mg.*

**2. Theophylline BAN, USAN,**

1, 3-Dimethylxanthine ; 3, 7-Dihydro-1, 3-dimethylpurine-2, 6 (1H)-dione ; BP ; USP ; Eur. P.,

Int. P., Ind. P. ;

Constant-T(R) (Ciba-Geigy) ; Duraphyl(R) (McNeil) ; Elixicon(R) (Berlex) ;

It may be extracted from the leaves of tea by the general method described under caffeine.

**Dose :** *Oral, 60 to 200 mg.*

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**3. Theobromine BAN, USAN,**

3, 7-Dimethylxanthine ; 3, 7-Dihydro-3, 7-dimethylpurine-2, 6 (1H)-dione ; Santheose ;

It is extracted from cocoa by adopting the general method discussed under caffeine.

It possesses a weaker diuretic activity than **theophylline.**

**Dose :** *300 to 600 mg.*

**2.2.6.1. Mechanism of Action**

The mechanism of action of the three well-known **‘purine diuertics’** shall be discussed as under :

**2.2.6.1.1. Caffeine**

It is a well-recognized **CNS-drug** which action is solely attributed on account of its inhibition of

the enzyme phosphodiesterase in the brain and the ultimate accumulation and actions of cyclic 3′, 5′-

adenosine monophosphate (C-AMP).

**Caffeine** stimulates the voluntary skeletal muscle, thereby enhancing the requisite force of

contraction and minimising the ensuing muscular fatigue. Besides, it is found to stimulate parietal cells,

increasing gastric juice (acid) secretion ; it also induces a mild diuretic action by aggravating renal

blood flow and glomerular filtration rate and lowering proximal tubular reabsorption of Na+ and H2O

significantly.

**2.2.6.1.2. Theophylline**

The **‘drug’** produces **CNS stimulation** and **skeletal muscles** but to a much lesser extent as

compared to caffeine ; however, it exhibits a greater effect on the coronary dilatation, smooth muscle

relaxation, diuresis and cardiac stimulation than caffeine.

In general, it possesses relatively more pharmacologic activity practically in all categories than

**‘theobromine’.**

**2.2.7. Pyrimidine Diuretics**

The display of diuretic properties by the methylated xanthines, stimulated enough interest in

research to establish and ascertain the fact whether or not the pyrimidine analogues, which incidentally

are closely related biochemically to the purine derivatives *in vivo,* also possess diuretic activity, This

paved the way towards the synthesis of two uracil analogues, namely : **aminometradine**-having 6-

amino group and **amisometradine-**having 1, 3-diaklyl substituents.

**A. Aminometradine INN, BAN, USAN,**

1-Allyl-6-amino-3-ethyluracil ; 1-Allyl-6-amino-3-ethyl-pyrimidine-2, 4 (1H, 3H)-dione ;

Aminometramide ; BPC (1959) ;

Minacard(R) (Searle)

It is a relatively weak diuretic which has been employed in the control of oedema in subjects

having mild congestive heart failure. It is rarely used now.

**Dose :** *200 to 800 mg per day in divided doses on 3 days a week, or on alternate days.*

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**2.2.7.1. Mechanism of Action**

The **‘drug’** essentially has a pyrimidine nucleus that possesses an almost similar activity as those

of the purine derivatives, such as : **caffeine, theophylline** etc. Besides, aminometradine happens to be

intimately related biochemically to the xanthine analogues.

**2.2.8. Osmotic Diuretics**

The functional capacity and reabsorption capability of the renal tubule towards various electrolytes

and nonelectrolytes are restricted to a limited extent only, and this vary with respect to each ionic species.

A large intake of any of these substances by an individual, may enhance its concentration in the body

fluids and will ultimately affect the glomerular filtration rate and the reabsorption capacity of the tubule.

The substance will finally appear in the urine with an increased volume of water. Such a substance

which increases the output of urine in this fashion is called **osmotic diuretics.**

**Osmotic diuretics** may be classified into *two* sub-groups, *viz.,*

(*a*) **Osmotic electrolytes,** *e.g.,* potassium and sodium salts, and

(*b*) **Osmotic nonelectrolytes,** *e.g.,* urea, sucrose, mannitol, trometamol.

**A. Sodium Acid Phosphate BAN,**

NaH2PO4 . H2O

Sodium acid phosphate (BP ; Int. P ; Ind. P ;) ; Sodiumbiphosphate USP *;*

*It is used quite often as a urinary acidifier, for instance, during therapy with methenamine.*

**Dose :** *500 mg to 1 g to 6 times daily ; usual, 600 mg 4 times per day.*

**B. Potassium Acetate BAN, USAN,**

CH3COOK

Acetic acid, potassium salt ; BP ; USP ; Ind. P ;

It has been used as a diuretic.

**C. Urea BAN, USAN,**

H2NCONH2

Carbamide ; BP ; USP ; Ind. P. ;

Ureaphil(R) (Abbott) ; Elaqua XX(R) (Elder)

It is an osmotic diuretic with a low renal threshold. It is also *administered to maintain the output*

*of urine during surgical procedures. It is also recommended to decrease intra-ocular pressure in acute*

*glaucoma.*

**Dose :** *Oral, up to 20 g from 2 to 5 times per day ; as a 40% solution in water or carbonated*

*beverages, has been given as maintenance therapy after i.v. application for the relief of cerebral oedema.*

**D. Mannitol BAN, USAN,**

D-Mannitol ; BP ; USP ;

Osmitrol(R) (Travenol, U.K.)

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**Preparation**

On commercial scale it is produced by the catalytic or electrolytic reduction of certain

monosaccharides, for instance, glucose and mannose.

*It is a diuretic and a diagnostic agent for the kidney function test. The osmotic and diuretic is*

*usually initiated by the administration of a hypertonic solution of mannitol. It is also employed to lower*

*the intraocular pressure and cerebrospinal fluid pressure, before, during the after surgical procedures.*

*Mannitol is considered to be superior to dextrose because of the fact that it is both metabolized in vivo*

*and reabsorbed by the renal tubule to a negligible extent.*

**Dose :** *Usual, i.v. infusion, 50 to 200 g per day ; as diuretic, 50 to 100 g, administered as a 5 to*

*20% solution.*

**E. Trometamol INN, BAN, Tromethamine USAN,**

2-Amino-2-(hydroxymethyl)-1, 3-propanediol ; 1, 3-Propanediol, 2-amino-2-(hydroxymethyl)- ;

Trihydroxymethylaminomethane ; *Tris*-(hydroxymethyl) aminomethane ; 2-Amino-2-

(hydroxymethyl) propane-1, 3-diol ; Tromethamine USP. ;

THAM(R) (Abbott)

It is an organic amine base that reacts with cations of fixed or metabolic acids and also combines

with H+ ions from H2CO3 to yield bicarbonate as well as a cationic buffer. *An intravenous infusion*

*usually affords an osmotic diuresis.*

**Dose :** *Usual, 300 mg/kg body weight administered i.v. as a 0.3 M solution stretched over a*

*period of not less than 60 minutes.*

**2.2.8.1. Mechanism of Action**

The mechanism of action of a few **osmotic diuretics** are enumerated in the sections that follow :

**2.2.8.1.1. Sodium Acid Phosphate**

The inorganic salt when employed in large doses usually cause short-term diuresis besides affording

acidification.

**2.2.8.1.2. Urea**

Simply by employing large amounts (*e.g.,* 15 g or an adult) for the water-soluble and also

nonmetabolizable compounds to afford a hypertonic condition *i.e.,* high osmolarity, water content is

eventually withdrawn from tissues for instance, the eye-ball, thereby lowering pressure in it appreciably

(*i.e.,* intraocular pressure). It also helps in reducing the intracranial pressure using almost the same mechanism.

**2.2.8.1.3. Mannitol**

The IV administration of the hypertonic solutions of the **‘drug’**, which is a sugar alcohol, is

usually employed to promote an **osmotic diuresis.** It invariably exerts its action because of the glaring

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fact that the drug is not absorbed significantly from the GI-tract ; and if administered orally, it gives rise

to definite osmotic diarrhea.

It is found that when this *‘drug’* is administered parenterally it gets distributed adequately in the

extracellular space. Furthermore, only a small portion ranging between 7–10% usually gets metabolized

to glycogen ; and remaining quantity is excreted in the urine. Plasma half-life after single IV dose is only

15 minutes having normal renal function.

**2.2.8.1.4. Tromethamine (Trometamol)**

The **‘drug’** happens to be a weak amine base having pKa value of 7.8 at the normal body temperature

(98.4°F). Hence, it is almost very close to plasma pH (7.4) ; and, therefore, well-acceptable for

the preparation of a buffer mixture for controlling the extracellular pH.

It is, however, pertinent to state here that at pH 7.4 (plasma pH) it is almost 30% non ionized ;

and, therefore, it slowly penetrates the cells, where it would buffer the intracellular contents. Under the

prevailing circumstances it is able to react with any proton donor, and the usual notion that it reacts first

and foremost with carbonic acid (H2CO3) or CO2 is absolutely erroneous. In this manner protons are

removed from the H3O+ ions, whereby the ionization of H2CO3 is shifted so as to minimise *p*CO2 and

also to enhance the concentration of HCO3

–. Thus, the excess quantum of HCO3

– gets excreted slowly

through the kidney. This is, therefore, an extremely beneficial manner by which the level of high

*p*CO2 may be managed conveniently in various conditions, namely : **respiratory acidosis** (*e.g.,* drug

intoxication, asphyxia neonatorum, status asthmaticus etc.) wherein the pulmonary ventilation is quite

insufficient.

**2.2.9. Acidotic Diuretics**

The **acidotic diuretics** are essentially the inorganic compounds having a cation function. Examples

are-ammonium or calcium, combined with a fixed anion *viz.,* **chloride ion**, which causes two vital,

actions, namely ; **systemic hyperchloremic acidosis** and **weak diuretic effect**. These compounds (*e.g.,*

**ammonium chloride**, **calcium chloride**) invariably potentiate the diuretic action of mercurial diuretics

and hence may be administered at least 48–72 hours prior to the treatment of a mercurial compound so

as to facilitate hyperchloremic acidosis. Recently, insoluble **cation exchange resins** have been used to

act as diuretics by this mechanism.

**A. Ammonium Chloride BAN, USAN,**

NH4Cl

Sal ammoniac ; Muriate of ammonia ; BP ; USP ; Eur. P., Int. P ;

Expiger(R) (Pharmacia, Denm.)

**Ammonium chloride** causes diuresis by inducing mild acidosis. The acid-forming property is

due to the conversion of NH4

+ ion to urea, which leaves the Cl– ion free to combine with the available

cation, liberated from the elastic HCO3

– ion. This eventually upsets the BHCO3 : H2CO3 ratio thereby

causing acidosis, thus :

2NH4Cl + CO2 →H2NCONH2 + H2O + 2HCl

NaHCO3 + HCl →NaCl + H2CO3

The liberated acid may be buffered by the phosphates as follows :

Na2HPO4 + H2CO3 NaH2PO4 + NaHCO3

Disodium hydrogen Sodium acid

phosphate phosphate