CHAPTER 3

MODEL DRUG - FRUSEMIDE
A PROFILE

THE MODEL DRUG ------- FRUSEMIDE (Furosemide)

3.1 Introduction

Furosemide (INN) or **frusemide** (former BAN) is a **loop diuretic** used in the treatment of congestive heart failure and edema. It is most commonly marketed by **Sanofi-Aventis** under the brand name **Lasix**. It has also been used to prevent thoroughbred race horses from bleeding through the nose during races. Along with some other diuretics, furosemide is also included on the World Anti-Doping Agency's **banned drug list** due to its alleged use as a masking agent for other drugs. Chemically, it is an **anthranilic acid** derivative.

3.2 Pharmacological Category[1]

Loop Diuretics (Founded around 1964)

3.3 Chemical Name and Molecular Formula [2,4,5]

Systematic (IUPAC) name --

5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino] benzoic acid

Chemical name, Molecular formula and Molecular weight—

4-chloro-N-furfuryl-5-sulphamoyl anthranilic acid

$C_{12}H_{11}ClN_2O_5S$ **Mol.Wt. -- 330.74**

3.4 Definition[2]

Frusemide contains not less than 98.5 percent and not more than 101.0 percent of **$C_{12}H_{11}ClN_2O_5S$** calculated with reference to dried substance.

3.5 Structural Formula [2,4,5]

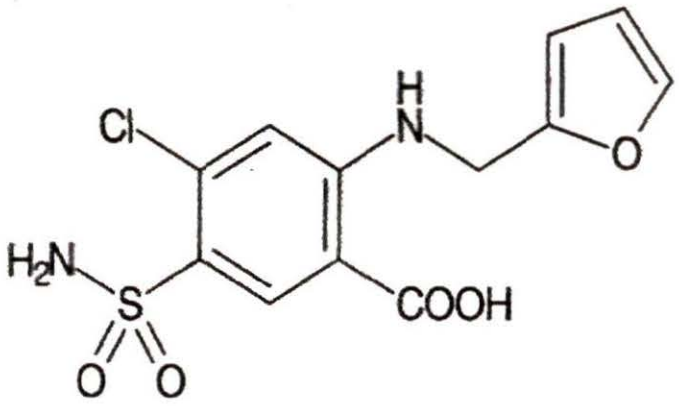

Figure 3.1 Two - Dimensional structure of Frusemide molecule

Figure 3.2 Three - Dimensional structure of Frusemide molecule

3.6 Generic Name [2,4] Frusemide (IP) Furosemide (BP, USP, EuroP)

3.7 Brand Names [5]

Some of the brand names under which furosemide is marketed across the world include: Aisemide®, Beronald®, Desdemin®, Discoid®, Diural®, Diurapid®, Dryptal®, Durafurid®, Errolon®, Eutensin®, Frusetic®, Frusid®, Fulsix®, Fuluvamide®, Furesis®, Furo-Puren®, Furosedon®, Hydro-rapid®, Impugan®, Katlex®, Lasilix®, Lasix®, Lodix®, Lowpston®, Macasirool®, Mirfat®, Nicorol®, Odemase®, Oedemex®, Profemin®, Rosemide®, Rusyde®, Salix®, Trofurit®, Urex®

3.8 Physicochemical information[2,4,5]

1. **Description** --- A white or almost white, odorless, tasteless, crystalline powder.
2. **Solubility** --- a) Practically insoluble in Water and Chloroform.
   b) Sparingly soluble in Ethanol (95%).
   c) Slightly soluble in Ether.
   d) Freely soluble in Methanol, Acetone and Dimethyl formamide.
   e) Dissolves in dilute aqueous solution of alkali hydroxide.
3. **Melting Point** --- About 210 °C with decomposition
4. **pH** --- 8.9 – 9.3
5. **pKa** --- 3.9
6. **Assay of Frusemide** [2]

The supplied drug Frusemide, courtesy Aventis Pharmaceuticals, Ankleshwar, was assayed as per Indian Pharmacopoeia, 1996, Appendix 5.5.

For Frusemide powders:

About 0.5 g of powder was accurately weighed, dissolved in 40 ml of dimethylformamide and titrated with 0.1 M sodium hydroxide using bromothymol blue solution as indicator. A blank determination was performed and necessary correction were made. Each ml of 0.2M sodium hydroxide is equivalent to 0.03307 g of $C_{12}H_{11}ClN_2O_5S$.

For Frusemide tablets:

Tablets 20 in number were weighed and powdered. A quantity of the powder equivalent to about 0.1 g of Frusemide was accurately weighed and shaken with 150 ml of 0.1M sodium hydroxide for 10 minutes. Sufficient amount of 0.1M sodium hydroxide solution was added to produce 250.0 ml and filtered. From this solution 5.0 ml was diluted to 200.0 ml with 0.1M sodium hydroxide solution and the absorbance of the resulting solution was measured at the maximum at about 271 nm. The content of $C_{12}H_{11}ClN_2O_5S$ was calculated taking 580 as the value of A (1%, 1 cm) at the maximum at about 271 nm.

3.9 Pharmacokinetic information[5,6,7,8,9]

1. Biological Half- Life: After I.V. administration
    a) 30 min for normal persons
    b) About 2 hours for patients with renal failure
2. Bioavailability: 43-69%, orally.
3. Excretion: Renal – 66%, Biliary – 33%
4. Metabolism: Hepatic and renal glucoronidation

3.10 Pharmacokinetic profile[5,6,7,8,9]

It is rapidly absorbed from the gastro intestinal tract (GIT). The absorption is variable and erratic. Bioavailability has been reported to be about 60 to 70%. About 99% of the drug remains bound to plasma albumin. It is mainly excreted in the urine unchanged. Non-renal elimination is considerably increased in renal failure. Frusemide crosses the placental barrier and is secreted in the milk. The clearance of the drug is not influenced by haemodialysis. The duration of diuretic effect is approximately for 2 – 3 hours. The peak diuresis occurs within the first and second hour. The onset starts very rapidly after I.V. administration and within 1 hour of oral administration. The duration of action is 6-8 hours. The diuretic inhibits primarily the absorption of sodium and chloride ion in both the proximal and distal tubules and in the loop of Henle.

Table 3.1 Pharmacokinetic data of Frusemide

Oral Bioavailability (%)	Urinary* Excretion (%)	Bound in Plasma (%)	Clearance (ml/min/kg)	V_d (l/kg)	Half life (min)	Toxic plasma conc. (mcg/ml)
61± 17	66± 7	98.8± 0.2	2.0± 0.4	0.11± 0.02	92± 7	25

* Effective plasma concentration is better correlated with concentration of drug in urine[8]

3.11 Pharmacology [9]

The drug Frusemide (also known as furosemide), which is a type of medicine called a loop diuretic. Loop diuretics act in the kidney to remove excess water from the blood, by causing an increase in the removal of salts such as potassium and sodium. This removal of salts causes water to be drawn out of the blood and into the kidneys, where it is then excreted in the urine. Removing water from the blood causes a decrease in the volume of fluid circulating through the blood vessels. This drop in fluid volume decreases the effort required by the heart to pump blood around the body. There are many conditions which may lead to an accumulation of fluid in the body (edema). Frusemide is commonly used in conditions such as heart failure, where the pumping mechanism of the heart is less effective. It is used to relieve the symptoms of heart failure, such as the shortness of breath seen with fluid on the lungs. At higher doses the amount of water drawn from the blood into the urine is much greater; therefore frusemide is also used when there is reduced production of urine in patients with kidney failure. Frusemide is also used to remove excess fluid associated with liver failure, hypertension, and poor circulation in the periphery (i.e. arms and legs).

3.12 Mode of Action[9]

Frusemide inhibits the reabsorption of electrolytes primarily in the ascending limb of the loop of Henle. It also increases renal blood flow and causes redistribution of blood flow within the renal cortex. Excretion of sodium, potassium, magnesium, calcium and chloride ions is increased and water excretion enhanced. It also decreases left ventricular filling pressure.

3.13 Clinical Information:[9]

3.13.1. Indications

- Treatment of edema associated with congestive cardiac failure, renal diseases (nephritic syndrome) and hepatic disorders.
- Management of oliguria in acute or chronic renal failure.
- Cerebral edema.
- In hypertension or as an adjunct to other antihypertensive agents.
- Forced alkaline diuresis in barbiturate poisoning.

3.13.2. Dosage And Administration

a) Edema- # **Adults:** 40 mg o.d. may be increased to 80mg o.d.
Children: 3mg/ kg body weight daily

b) Hypertension - # **Adults:** 40 –80 mg (max.) – twice daily (b.d.)
Children: 2 mg/kg body wt. – twice daily (b.d.)

1. Tablets and Oral Solution

*** Edema**

Adults: The usual initial dose of furosemide is 20 to 80 mg given as a single dose. Ordinarily a prompt diuresis ensues. If needed, the same dose can be administered 6 to 8 hours later or the dose may be increased. The dose may be raised by 20 or 40 mg and given not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8 am and 2 pm). The dose of furosemide may be carefully titrated up to 600 mg/day in patients with clinically severe edematous states. Edema may be most efficiently and safely mobilized by giving furosemide on 2 to 4 consecutive days each week. When doses exceeding 80 mg/day are given for prolonged periods, careful clinical observation and laboratory monitoring are particularly advisable.

Pediatric Patients: The usual initial dose of oral furosemide in pediatric patients is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after

the initial dose, dosage may be increased by 1 or 2 mg/kg no sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended. For maintenance therapy in pediatric patients, the dose should be adjusted to the minimum effective level.

*** Hypertension**

Adults: The usual initial dose of furosemide for hypertension is 80 mg, usually divided into 40 mg twice a day. Dosage should then be adjusted according to response. If response is not satisfactory, add other antihypertensive agents. Changes in blood pressure must be carefully monitored when furosemide is used with other antihypertensive drugs, especially during initial therapy. To prevent excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50 percent when furosemide is added to the regimen. As the blood pressure falls under the potentiating effect of furosemide, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

2. Injection

*** Edema**

Adults: The usual initial dose of furosemide is 20 to 40 mg given as a single dose, injected intramuscularly or intravenously. The intravenous dose should be given slowly (1 to 2 minutes). Ordinarily a prompt diuresis ensues. If needed, another dose may be administered in the same manner 2 hours later or the dose may be increased. The dose may be raised by 20 mg and given not sooner than 2 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. If the physician elects to use high dose parenteral therapy, add the furosemide to either sodium chloride injection, lactated ringer's injection, or dextrose (5%) injection after pH has been adjusted to above 5.5, and administer as a controlled intravenous infusion at a rate not greater than 4 mg/min. Furosemide Injection is a buffered alkaline solution with a pH of about 9 and the drug may precipitate at pH values below 7. Care must be taken to ensure that the pH of the prepared infusion solution is in the weakly alkaline to neutral range. Acid solutions, including other parenteral medications (e.g., labetalol, ciprofloxacin, amrinone, and milrinone) must not be administered concurrently in the same infusion because they may cause precipitation of the furosemide. In addition, furosemide injection should not be added to a running intravenous line containing any of these acidic products.

*** Acute Pulmonary Edema**

The usual initial dose of furosemide is 40 mg injected slowly intravenously (over 1 to 2 minutes). If a satisfactory response does not occur within 1 hour, the dose may be increased to 80 mg injected slowly intravenously (over 1 to 2 minutes). If necessary, additional therapy (e.g., digitalis, oxygen) may be administered concomitantly.

 # Pediatric Patients: Parenteral therapy should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical. The usual initial dose of furosemide Injection (intravenously or intramuscularly) in pediatric patients is 1 mg/kg body weight and should be given slowly under close medical supervision. If the diuretic response to the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. Doses greater than 6 mg/kg body weight are not recommended. Furosemide Injection should be inspected visually for particulate matter and discoloration before administration. Do not use if solution is discolored. To insure patient safety, this needle should be handled with care and should be destroyed and discarded if damaged in any manner. If cannula is bent, no attempt should be made to straighten. To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand.

3.13.3 Route of Administration Oral, Intramuscular (I.M.), Intravenous (I.V.)

3.13.4 Contraindications

- States of electrolyte depletion.
- Severe hepatic dysfunction.
- Severe renal failure with complete anuria.

3.13.5 Precautions

- Excessive diuresis may cause dehydration, decreased blood volume and circulatory collapse; correct hypovolemia before administration.
- Electrolytes to be checked periodically.
- Hypokalemia can occur especially in patients on salt restriction, cirrhosis and in the elderly. In digitalized patients this can precipitate cardio toxicity. Hence concurrent potassium supplements to be used.
- It contains a sulphonamide moiety. So it is to be avoided in patients who are allergic to sulphonamides.
- It causes hyperglycemia and aggravates or unmasks diabetes mellitus.
- It is not effective in patients with a creatinine clearance of less than 30 ml.
- Hyponatremia can occur in patients with severe CCF when on salt restriction.
- Can exacerbate or activate systemic lupus erythematosus in susceptible patients.
- Administration Instructions:
  - Give I.V. injections very slowly – rate not more than 4 mg/minutes.
  - For infusion, diluents to be used are normal saline or 5 % dextrose.
  - Administer tablets with food.

3.13.6 Drug Interactions

 # Potentially fatal

- Salicylate toxicity is increased due to decreased excretion.
- Risk of major bleeding episodes due to increased effects of anticoagulants.
- Lithium carbonate – by decreasing its excretion, may precipitate toxicity.
- Increase toxicity of digoxin, amiodarone, disopyramide, astemizole, terfenadine, flecanamide and quinidine and antagonizes effects of lignocaine by causing hypokalemia.

 # Non fatal

- With amino glycosides – risk of ototoxicity is increased.
- Indomethacin and ketorolac reduces effects of frusemide.

- With sulphonyl ureas - loss of control of diabetes due to antagonism of its effects may occur.
- Enhances hypotensive effects of antihypertensives agents.
- Steroids antagonises diuretic effects of frusemide.

3.13.7 Adverse Effects

 # Common Effects:-

- Orthostatic hypotension and dizziness.
- Fluid and electrolyte imbalance including hypokalemia, hyponatraemia and hypochloraemic alkalosis.
- Hyperuricaemia can precipitate attacks of gout.
- Otto–toxicity– tinnitus and hearing loss, especially if given along with amino glycosides.

 # Rare effects:

- Hypersensitivity reaction – skin rashes, photosensitivity reaction, eosinophilia etc.
- Pancreatitis and cholestatic jaundice.
- Dizziness, headache and paraesthesias.
- Hyperglycemia, increase in plasma cholesterol and TGL levels.

3.13.8 Drug Toxicity

At dose of more than 700 mg/kg – dehydration, blood volume depletion, hypotension, circulatory collapse, electrolyte imbalances – hypokalemia, metabolic alkalosis.

3.13.9 Treatment of Toxicity

Supportive and symptomatic treatment – management of electrolyte and fluid imbalance. I.V. fluids and trendelenburg's position to combat hypotension.

3.13.10 Storage ---------- Well closed light resistant container.

3.13.11 Shelf Life ---------- 3 years.

3.13.12 Market Availability[9]

Tablets

To be dispensed in well-closed, light-resistant containers. Exposure to light might cause a slight discoloration. Discolored tablets should not be dispensed.

20 mg Tablets: Lasix tablets 20 mg are supplied as white, oval, monogrammed tablets. They are imprinted with "Lasix" on one side and "Hoechst" on the other.

40 mg Tablets: Lasix tablets 40 mg are supplied as white, round, monogrammed, scored tablets. They are imprinted with "Lasix" on one side and the Hoechst logo on the other.

80 mg Tablets: Lasix tablets 80 mg are supplied as white, round, monogrammed, facetted edge tablets. They are imprinted with "Lasix 80" on one side and the Hoechst logo on the other.

Oral Solution

It is to be stored at controlled room temperature (59°-86° F) and to be dispensed in light-resistant containers. Opened bottle should be discarded after 60 days.

Injection

Storage: It is to be stored at controlled room temperature (59°-86° F).

Discolored solution should not be used. Syringes should be protected from light. Syringe should not be removed from individual package until time of use.

3.14 Rationality of Selection of Frusemide as Model Drug[13]

1. It is the most popularly prescribed drug in the management of hypertension and all categories of edema.
2. Conventional dosage forms produce brief but intense diuresis provoking electrolytic imbalance, muscular cramps and overall discomfort. Clinical studies demonstrated that sustained release preparations can produce the similar diuretic effect without producing the major side effects of conventional tablets.
3. The fluctuations in the concentration of drug in the blood with conventional dosage forms generally leads to an inefficient therapy leading to excessive use of drug due to multiple dosing which can be avoided by controlling the release .
4. Biological half life of Frusemide is very short (2 hrs for patients with renal failure, 30 minute for normal human) which requires multiple dosing, so as to maintain the plasma concentration of the drug at effective therapeutic level. Formulating the drug in a controlled

release delivery system can decrease the frequency of dosing and increase patient acceptability.

5. Drugs with a single oral dose greater than 500 mg are poor candidates for oral controlled release product since the absorption mechanism will generate a substantially high volume of the product. Single oral dose of Frusemide is 40 mg which makes it a suitable candidate.

6. Diffusivity in the intestinal lumen during absorption of the drug is greatly influenced by its' molecular weight. Frusemide having a molecular weight[2] of 330.74 produce sufficient diffusivity.

7. The drug having low apparent volume of distribution (11.4% of body weight independent of dose) makes it ideal for controlled release formulation.

8. Drugs with greater aqueous solubility are difficult to incorporate in controlled release dosage form. Frusemide being practically insoluble in water makes it a suitable candidate.

9. The toxic concentration of the drug being 25mcg per kg body mass indicates sufficient safety range of the drug to be administered in a sustained release dosage form.

3.15 FTIR Spectra of Frusemide: [3] (Official Standard spectra)

Infrared absorption spectra is concordant with the spectrum obtained with Frusemide *RS*. Major peaks are at 1028,1143,1241,1323,1561,1591,1601 and 1669 cm^{-1}.

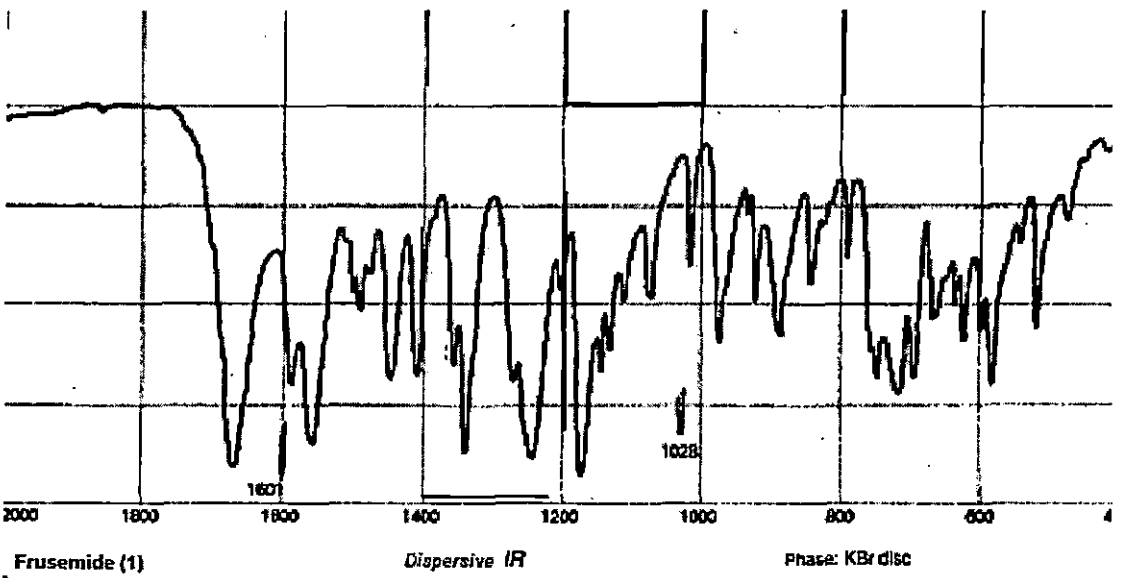

Figure 3.3 Infra Red (IR) spectra of standard frusemide powder

3.16 REFERENCES

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