IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Solubility And Bioavailability Enhancement Of BCS Class-IV Drug: Furosemide"

1YOGASMITA DEY, 2PINAKI SHANKAR PRADHAN, 3MANTHAN DANDPAT

1Associate Professor , 2B.pharm , 3B.pharm

1Kalinga institute of pharmaceutical sciences ,

2Kalinga institute of pharmaceutical sciences ,

3Kalinga institute of pharmaceutical sciences

➢ ABSTRACT

Biopharmaceutical classification system (BCS) class IV drugs (low-solubility low-permeability) are generally poor drug candidates, yet, ~5% of oral drugs on the market belong to this class. While solubility is often predictable, intestinal permeability is rather complicated and highly dependent on many biochemical/physiological parameters. In this work, we investigated the solubility/permeability of BCS class IV drug, furosemide, considering the complexity of the entire small intestine (SI). Furosemide solubility, physicochemical properties, and intestinal permeability were thoroughly investigated in-vitro and in-vivo throughout the SI. In addition, advanced Size reduction process (Top down and bottom up process) were used to elucidate furosemide regional-dependent absorption pattern. Furosemide was found to be a low-solubility compound. By preparing Nanosuspension in context of reducing particle size. Nanosuspension technologies use top-down (size reduction) or bottom-up (particle assembly) approaches, often combined, to create drug nanoparticles for enhanced delivery, with top-down methods like milling/homogenization breaking down larger particles, and bottom-up methods like anti-solvent precipitation building up from molecules.

➢ INTRODUCTION

"TITLE : Solubility and Bioavailability Enhancement of BCS class-IV drug: Furosemide"

Nanosuspension

A nanosuspension is a cutting-edge pharmaceutical formulation that transforms poorly soluble drugs into a colloidal dispersion of pure drug nanoparticles (typically 10-1000 nm in size) suspended in an aqueous vehicle, stabilized by surfactants or polymers. This technology is particularly valuable for Biopharmaceutics Classification System (BCS) Class IV drugs (low solubility, low permeability) as it drastically improves their therapeutic efficacy.

Biopharmaceutical Classification System

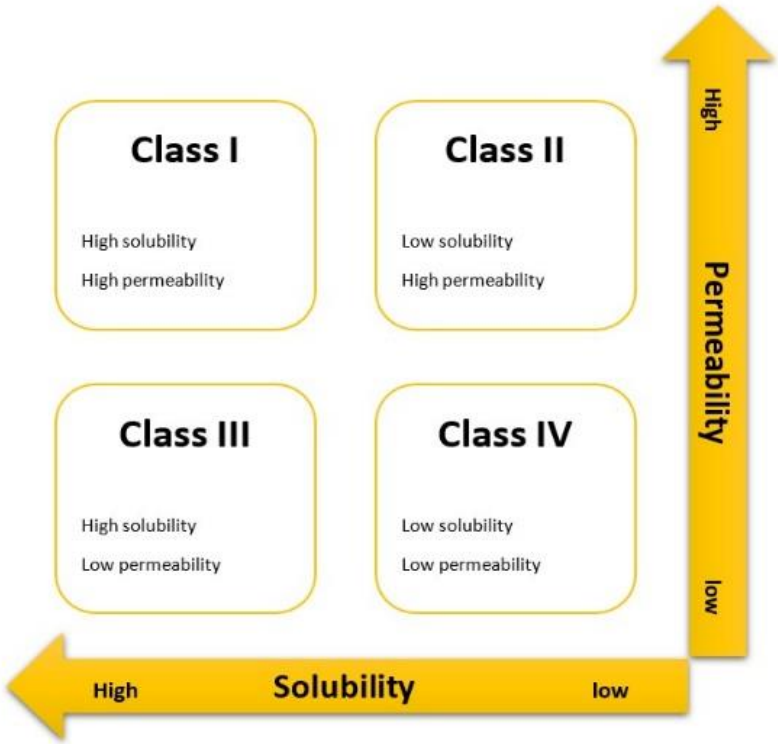
The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies i.e., it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:

Class I: high solubility, high permeability

Class II: low solubility, high permeability

Class III: high solubility, low permeability

Class IV: low solubility, low permeability



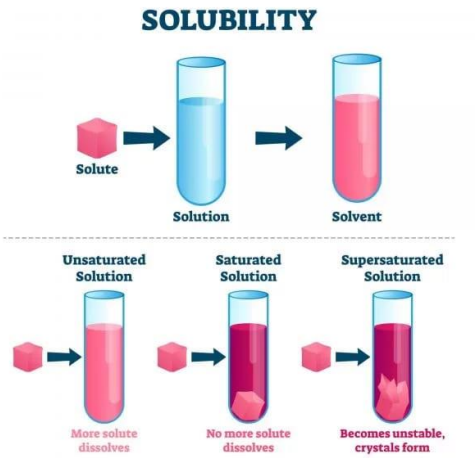
(Biopharmaceutical Classification Systems)

- **Furosemide Drug**

Furosemide is a potent loop diuretic that primarily works by inhibiting the sodium-potassium-chloride (Na+/K+/2Cl-) cotransporter (NKCC2) in the thick ascending limb of the loop of Henle in the kidneys. This action significantly increases the excretion of water, sodium, and other electrolytes in the urine.

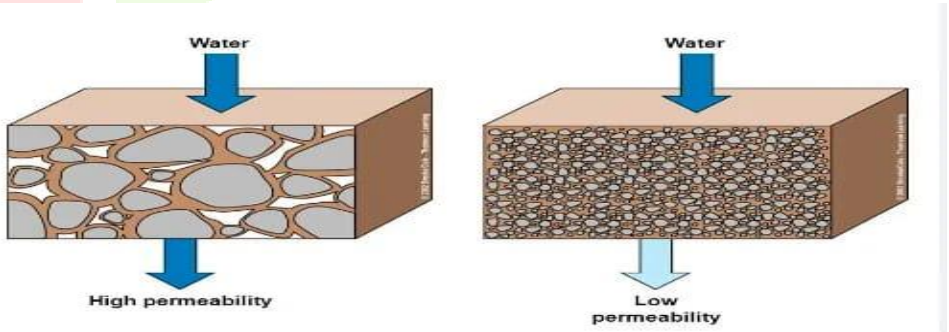
- **Solubility**

Particle-size reduction is one of the most commonly used processes in the formulation development. Due to the size reduction, the surface area of the particles increases, allowing a greater interaction with the solvent and improving the dissolution. There are two major types of size reduction based on the dimension of the size of the particle: micronization (particles between 1–1000 μm) and nanonization (particles in the submicron range, <1 μm). Micronization is a widely used method to enhance the bioavailability of an API. It is usually performed by milling (jet/ball milling) or high-pressure homogenization. Equilibrium solubility is not affected by micronization, but the dissolution rate will improve . In contrast, nanonization can affect both the solubility and the dissolution rate.



- **Permeability**

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced prior to absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged drug in feces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.



- **Bioavailability**

The Portion of drug or other substance which enters the systemic circulation when introduced into the body and so is able to have an active effect. As nanosupension increases the solubility of drugs by reducing particle size, thus it helps to enhance also bioavailability.

➢ LITERATURE REVIEW

1. **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Ida Ghlichloo; Valerie Gerriets. National Library of medicines.**

Conventional drug delivery systems like tablets and capsules have poor bioavailability and inconsistent drug levels. **Novel drug delivery systems (NDDS)** were developed to address these issues and maintain therapeutic drug concentrations over extended periods. Nanosuspensions are considered a type of novel drug delivery system (NDDS) specifically designed to improve the solubility and bioavailability of poorly soluble drugs. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics (the study of kinetics of **Absorption**, **Distribution**, **Metabolism** and **Excretion** of **Drugs**) and thus improves drug safety and efficacy.

2. **Diclofenac, Robert A. Alfaro; Donald D. Davis. National Library of medicines**

By Conventional Dosage Form like onset of action for Diclofenac Sodium Tablets may take longer up to 2-4 hours to reach peak effect.

3. **Media milling process optimization for manufacture of drug nanoparticles using design of experiments (DOE)**

A stirred media mill uses a magnetic stirrer (or a similar rotating device) to induce collisions between grinding media (like beads or balls) and the material being milled. This process reduces the particle size of the material by mechanical abrasion and impact.

4. **Overview of milling techniques for improving the solubility of poorly water-soluble drugs Author links open overlay panel, Zhi Hui Loh aAsim Kumar Samanta b Paul Wan Sia Heng.**

Media milling is a technique used to enhance drug solubility, particularly for poorly water-soluble drugs, by reducing particle size to the nanoscale, often creating nanosuspensions. This method utilizes a liquid medium and milling beads to break down drug particles, increasing their surface area and thus improving dissolution rate and bioavailability**.**

5. **Review on Furosemide Santosh B. Dighe, Sonawane Shubham Ramesh, Thete Bhati Sharad, Tarkase Sahil Bhausaheb Department Pharmacology, PRCOP Loni.**

   Furosemide is a potent loop diuretic used to treat hypertension and edematous conditions associated with heart, renal, and hepatic failure. Its mode of action involves inhibiting chloride reabsorption in the ascending limb of the loop of Henle.

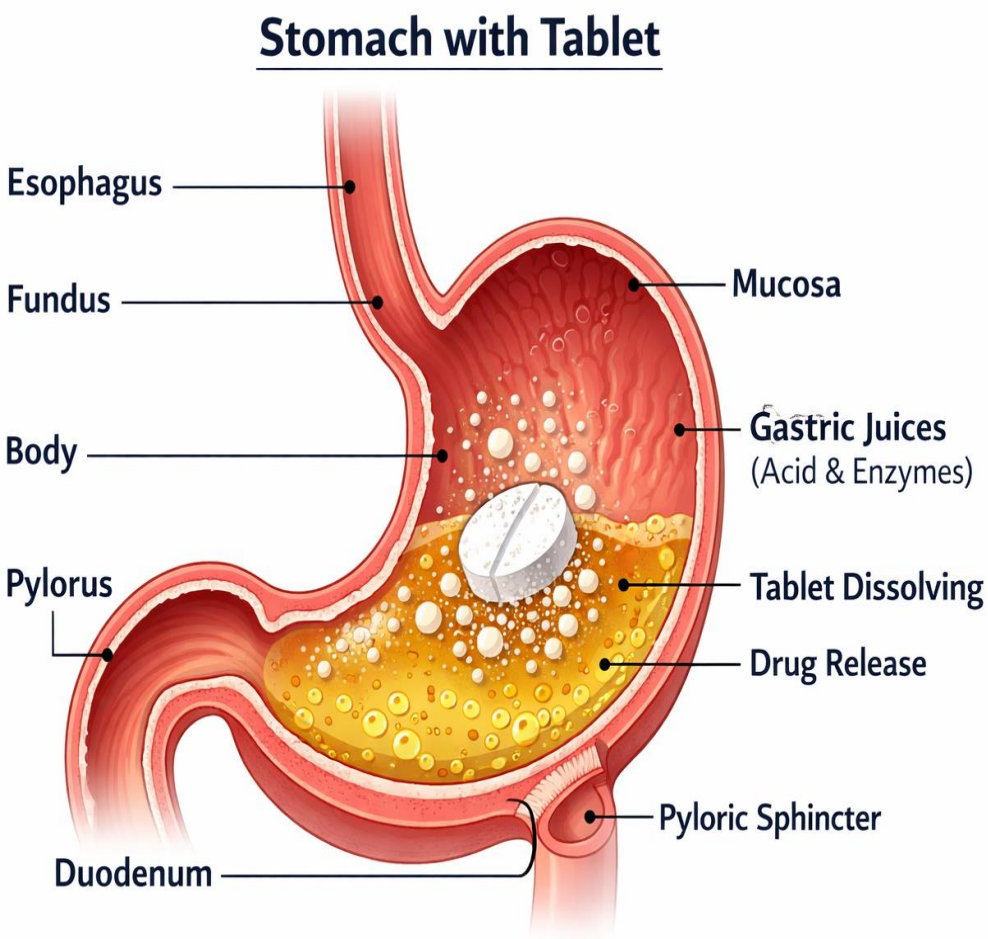
6. Nanosuspension: An approach to enhance solubility of drugs Vishal R Patel 1, Y K Agrawal

One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Formulation as nanosuspension is an attractive and promising alternative to solve these problems. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. This review article describes the preparation methods, characterization, and applications of the nanosuspension.

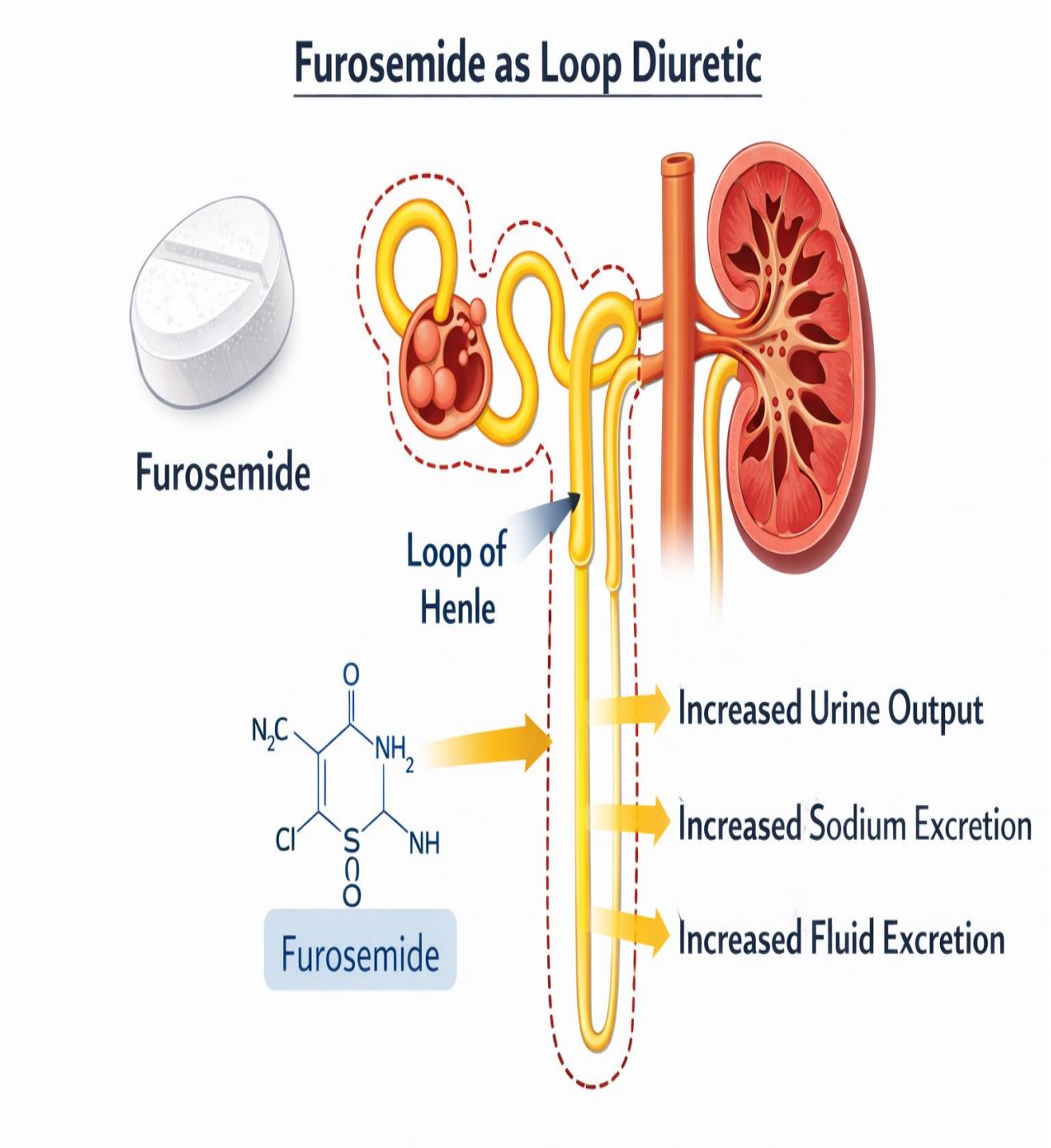
➢ AIM & OBJECTIVES

- Preparation of **Nanosuspension** is simple and applicable to all drugs which are water insoluble.
- Nanosuspensions have garnered recent attention as a promising strategy for mitigating the bioavailability challenges of **hydrophobic drugs**, particularly those characterized by **poor solubility** in water.
- Based on the Bio pharmaceutics Classification System, drugs are classified into four categories depending on their solubility and permeability properties like **CLASS I** compounds are the ones **having higher solubility and permeability; CLASS II** representing **Lower Solubility But Higher Permeability**; **CLASS III** showing **higher solubility but less permeability**; and lastly **CLASS IV** compounds **with very less count of solubility and permeability index.**
- The problem is even more complex for drugs like **Furosemide** which are poorly soluble in aqueous media, belonging to **BCS class IV** as classified by **Biopharmaceutical Classification System.**
- One of the major problems associated with **Furosemide** is very low **Bioavailability.**
- Addressing solubility issues associated with **Furosemide** has largely resolved the need to enhance **drug Solubility and bioavailability.**

- There are different Oral Conventional Dosage Forms of **Furosemide** like Furosemide tablet in strengths of 20 mg, 40mg & 80 mg.
- **Furosemide** is a potent loop diuretic.
- **Conventional drug delivery systems** like tablets and capsules have poor bioavailability and inconsistent drug levels. **Novel drug delivery systems (NDDS)** were developed to address these issues and maintain therapeutic drug concentrations over extended periods.
- Nanosuspensions are considered a type of novel drug delivery system (NDDS) specifically designed to improve the solubility and bioavailability of poorly soluble drugs.
- A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics (the study of kinetics of **Absorption**, **Distribution**, **Metabolism** and **Excretion** of **Drugs**) and thus improves drug safety and efficacy.
- The reduction in particle size achieved through nanosuspension technology leads to an improved drug **Dissolution Rate.**
- In nanosuspensions the drug is in contact with the **Gastrointestinal Mucosa** for a longer period, stimulating **Better Absorption.**
- Nanosuspensions offer versatility in drug delivery and various routes can be used to administer them, including **Parenteral, Oral, Dermal, Pulmonary** and **Ocular** routes, providing treatment options that are flexible.
- **Poorly Water-Soluble BCS Class- IV drugs** to achieve minimal drug doses, sustained drug release, a reduction in systemic toxicity.
- **Furosemide Nanosuspension** preapared by the use of **Media Milling Techniques.**
- In this Media Milling Techniques, we use the **Magnetic Stirrer machine** to reduce Particle size of **Furosemide.**
- In media milling, a magnetic stirrer is used to generate a rotating magnetic field that drives a stir bar within a liquid medium.
- By Collision between magnetic bead, Particles of **Furosemide** and wall of container in the presence of **Magnetic field**, the particle size of **Furosemide** reduced to **Nano Form**.
- This technique is employed to **disperse and suspend particles.**
- This technique also increases the Surface area of **Furosemide drug,** which will lead to enhance Solubility and Bioavailability of our drug by increasing **Dissolution rate of Furosemide.**



(Biopharmaceutical Classification System –IV drugs in Stomach)



(Conventional Dosage form of Furosemide tablet after 6 to 8 hours)

➢ METHODOLOGY

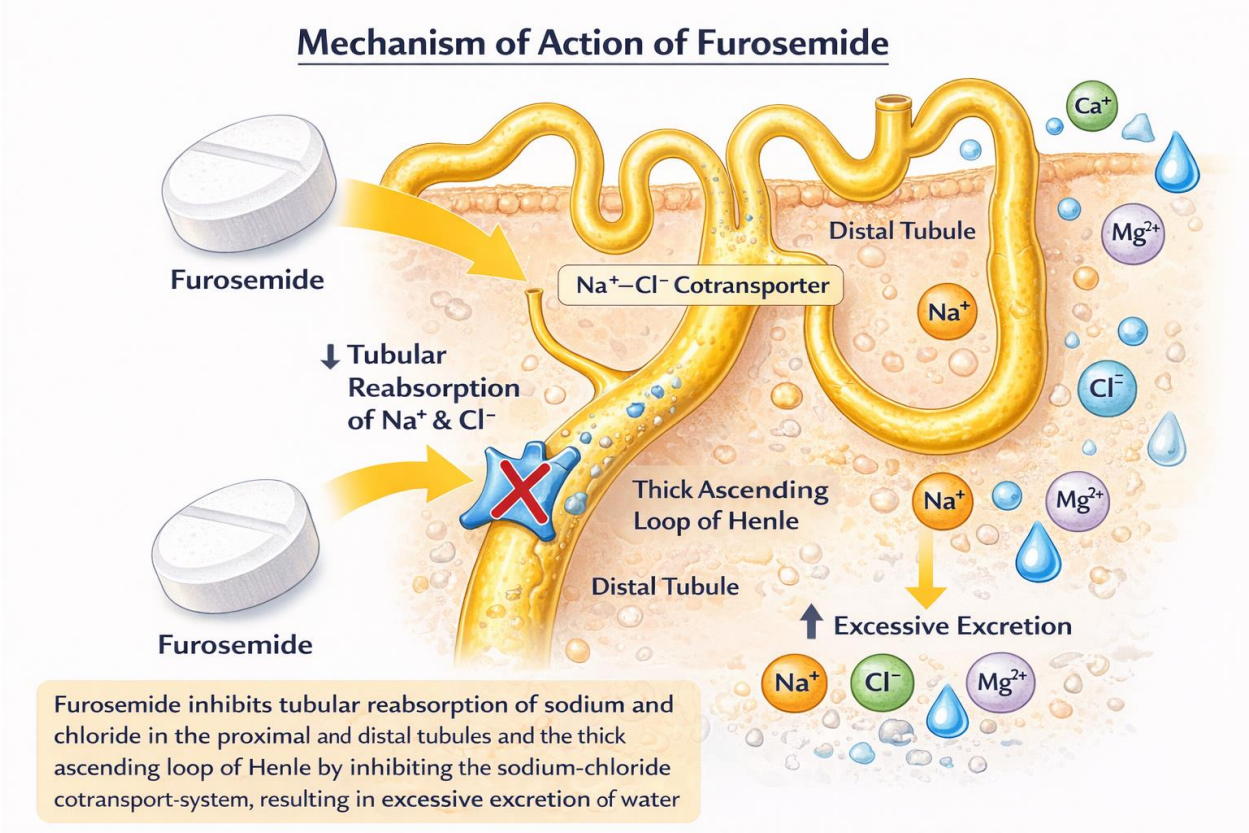
DRUG PROFILE OF FUROSEMIDE

Parameter	Details
Drug Name	Furosemide
Drug Class	Loop diuretic
BCS Class	Class-IV
Particle Size	3 to 10 µm
Mechanism of Action	Inhibits Na^+–K^+–$2Cl^-$ symporter in the thick ascending limb of the Loop of Henle leading to increased excretion of sodium, chloride, and water
Primary Uses / Indications	Edema (heart failure, cirrhosis, renal disease); Hypertension; Acute pulmonary edema; Hypercalcemia (adjunct)
Dosage Forms	Oral tablet, oral solution, IV injection
Typical Adult Dose	Edema: 20–80 mg PO once daily (may titrate); Hypertension: 40 mg PO twice daily; IV acute edema: 20–40 mg (may increase)
Duration of Action	Oral: 6–8 hours
Bioavailability	Approximately 50% (variable)
Protein Binding	Approximately 95%
Metabolism	Minor hepatic metabolism
Elimination	Renal excretion
Half-Life	1–2 hours (longer in renal impairment/elderly)
Common Side Effects	Dizziness, dehydration, polyuria, hypotension, electrolyte disturbances (low potassium/sodium), increased uric acid
Serious Adverse Effects	Severe hypokalemia, ototoxicity (especially rapid IV), Stevens–Johnson syndrome, renal impairment

Contraindications	Anuria, severe electrolyte depletion, hypersensitivity to furosemide or sulfonamides
Precautions	Use caution in renal/hepatic disease, diabetes, elderly, dehydration
Pregnancy Category	Category C (use only if benefit outweighs risk)
Lactation	May suppress lactation; caution advised
Drug Interactions	Corticosteroids and amphotericin B increase risk of hypokalemia; Aminoglycosides increase ototoxicity; NSAIDs reduce effect; Increases lithium levels; Potentiates antihypertensives
Monitoring Parameters	Serum electrolytes, renal function, blood pressure, weight, fluid balance, hearing with high-dose IV
Patient Counseling Points	Take in the morning, maintain hydration, potassium supplements may be required, report dizziness, cramps, ringing ears, rash
Storage	Store at room temperature, protected from light and moisture

MECHANISM OF ACTION OF FUROSEMIDE DRUG

- Furosemide inhibits tubular reabsorption of sodium and chloride in the proximal and distal tubules and the thick ascending loop of Henle by inhibiting the sodium-chloride cotransport system resulting in excessive excretion of water along with sodium, chloride, magnesium, and calcium.



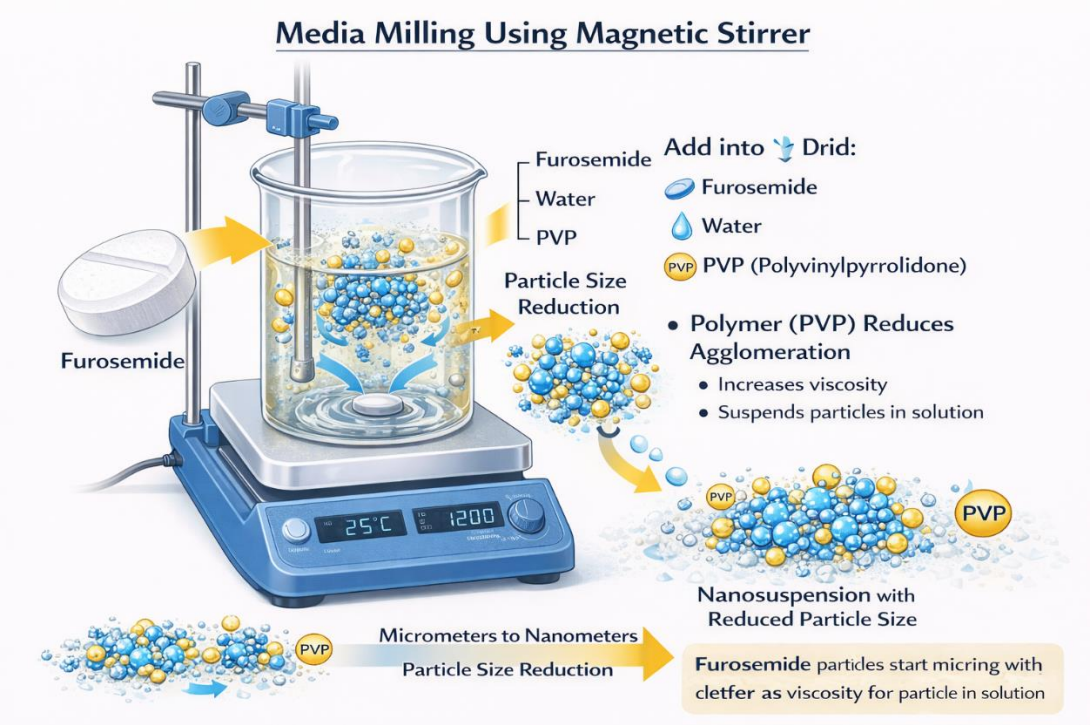
FORMULATION METHOD

- Particle size of Furosemide is 3 to 10 micrometer and one of the problems associated include low aqueous solubility, poor permeability, erratic and poor absorption, inter and intra subject variability and significant positive food effect which leads to low and variable bioavailability.
- By reducing Particle size of the drugs from micrometer to nanometer. The surface area of Furosemide increases.

- That particle size reduction done on the basis of two technology.
  - Top- Down Technology (Media milling Technique)
  - Bottom- up Technology (Precipitation)

❖ TOP- DOWN TECHNOLOGY (MEDIA MILLING TECHNIQUE)

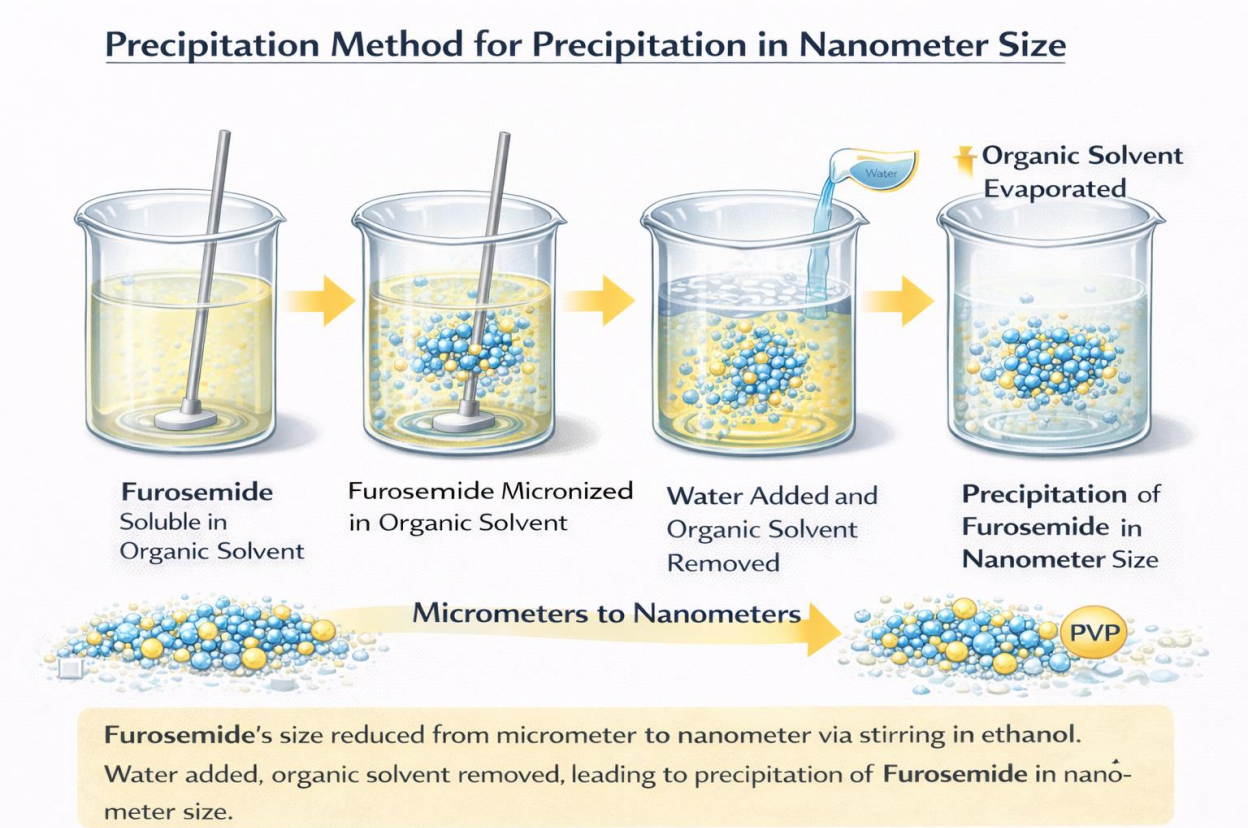
- Normally for Media milling technique both magnetic stirrer and mechanical stirrer used for size reduction process
- In Magnetic Stirrer method, We take required amount of Furosemide drug, water and PVP as polymer in a beaker.
- After adding all the above given material by the use of magnetic bead we start stirring our solution with a specific temperature and rotation speed.
- Due to collision between wall and magnetic bead the particle size of Furosemide reduced from micrometer to nanometer and PVP (Poly Vinyl Pyrrolidone) polymer used to reduce agglomeration.
- PVP helps to reduce agglomeration by increasing viscosity of Nanosuspension by enhancing the particle in suspending form.



- In Mechanical Stirrer Method. We take required amount of Furosemide drug, water and PVP as polymer in a beaker.
- After that by the help of mechanical stirrer the attrition mechanism the particles of Furosemide drugs reduced to Nanometer and convert into Nanosuspension.

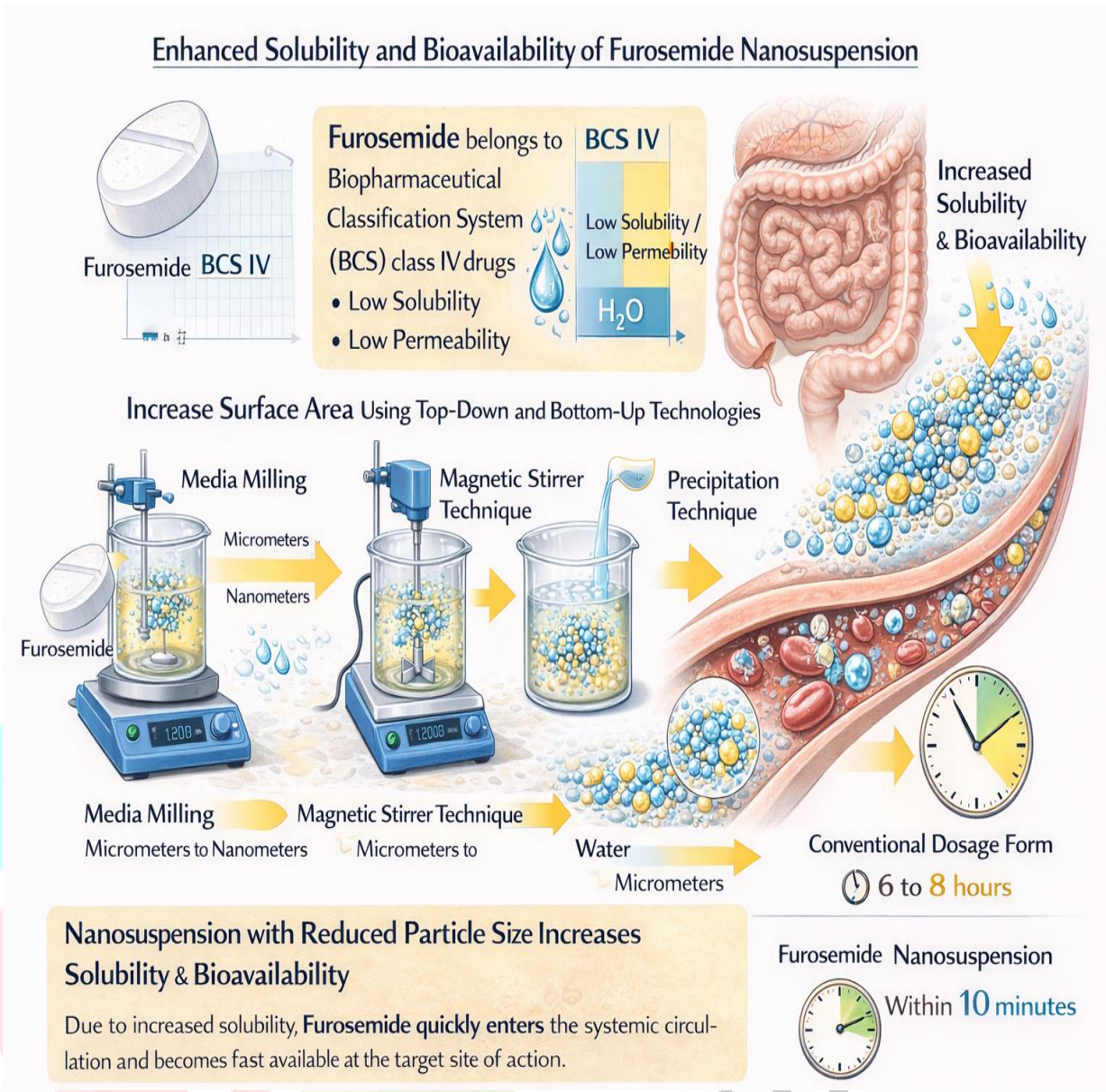
❖ BOTTOM-UP TECHNOLOGY (PRECIPITATION TECHNIQUE)

- In this technology Furosemide drug is soluble in organic solvent like ethanol, as it is less soluble in water.
- By stirring size of Furosemide is reduced from micrometer to nanometer.
- Water added to above solution and then removal of Organic solvent done.
- Precipitation of Furosemide occur in nanometer size.



➢ CONCLUSION

- Due to Furosemide belongs to Biopharmaceutical Classification System (BCS) class IV drugs. It has low Solubility and Low Permeability characters.
- By reducing Particle size of Furosemide from micrometer to nanometer with the help of both Top-down and Bottom up technology. E.g. Media miling Technique, Magnetic Stirrer Technique & Precipitation Technique. We increase the surface area of the drugs.
- As surface area of Furosemide increase it leads to rise solubility of own in water.
- Our body contains 70% of water to provide onset of action at any local site drug Solubility should increase.
- Due to size reduction of our drug, when it reaches in GI tract it starts to absorb quickly from the blood vessel of stomach.
- Due to increased solubility Furosemide enters in the systemic circulation and becomes fast available at target site of action, which is also known as bioavailability.
- Thus in nanometer form Furosemide not only increases solubility but also increase bioavailability.
- Conventional Dosage form of Furosemide requires 6 to 8 hours to provide result whereas Furosemide Nan suspension gives result within 10 minutses.



➢ REFERENCES

1. Furosemide – StatPearls – NCBI Bookshelf. [Link] https://www.ncbi.nlm.nih.gov/books/NBK499921/
2. Rxlist Drug A – Z list. [Link] https://www.rxlist.com/furosemide-drug.htm.
3. Drugbank [Link] https://go.drugbank.com/drugs/DB00695.
4. FDA Approved Drug Products: Furosemide Injection, for intravenous or intramuscular use. [Link]https://www.accessdata.fda.gov/drugsatfda_docs/label /2016/018667s036lbl.pdf.
5. KD Tripathi Essential of medical pharmacology 8th edition. Pg. no. 625.
6. Karen Whalen, PharmD, BCPS, FAPhA, Carinda Field, PharmD, FCCM, Rajan Radhakrishnan, B.pharm, MSc, PhD. Lippincott Illustrated Reviews: Pharmacology Seventh Edition. Pg. No. 655.

7. Boles Ponto LL, Schoenwald RD: Furosemide (frusemide). A pharmacokinetic/Pharmacodynamic review (Part I). Clin Pharmacokinet. 1990 May; 18(5):381-408. Doi: 10.2165/00003088-199018050-00004.[Article]

8. mr. j. Mohamed Meeran, Development and Characterization of Furosemide Loaded Nanoparticles. (Research Article) pg no.51[Article]

9. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. Anaesthesia. 2010 Mar; 65(3): 283-93. Doi: 10.1111/j.1365-2044.2009.06228.x. Epub 2010 Jan 19. PMID: 20085566 [Article]

10. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther. 1995 Jun; 57(6): 601-9.
11. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. (2019) 394:1949–64. doi: 0.1016/S0140-6736(19)32563-2
12. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. (2015) 41:1411–23. doi: 10.1007/s00134-015-3934-7
13. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clin J Am Soc Nephro. (2013) 8:1661–9. doi: 10.2215/CJN.00270113
14. Kari JA, Alhasan KA, Shalaby MA, Khathlan N, Safdar OY, Al RS, et al. Outcome of pediatric acute kidney injury: a multicenter prospective cohort study. Pediatr Nephrol. (2018) 33:335–40. doi: 10.1007/s00467-017-3786-1
15. Alkandari O, Eddington KA, Hyder A, Gauvin F, Ducruet T, Gottesman R, et al. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study. Crit Care. (2011) 15:R146. doi: 10.1186/cc10269
16. Slater MB, Gruneir A, Rochon PA, Howard AW, Koren G, Parshuram CS. Risk factors of acute kidney injury in critically ill children. Pediatr Crit Care Med. (2016) 17:e391–8. doi: 10.1097/PCC.0000000000000859