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A RESEARCH ARTICLE ON
DESIGN, DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERES OF FUROSEMIDE BY MIXED SOLVENCY CONCEPT

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ABSTRACT
The development of controlled oral drug delivery systems is crucial for enhancing patient compliance, improving bioavailability, and extending the duration of drug action. This study focuses on the design, development, and evaluation of floating microspheres of Furosemide using the mixed solvency concept. Furosemide is a high-ceiling diuretic used for oedema, hypertension, and chronic renal insufficiency, acting by inhibiting the Na-K-2Cl symport in the Loop of Henle. Microspheres, defined as solid, approximately spherical particles ranging from 1 to 1000 µm , are a type of drug delivery system that can be classified as microcapsules or micromatrices. The floating drug delivery system aims to prolong gastric residence time and is classified into effervescent and non-effervescent types. Floating microspheres were prepared using various porogens like Hexane and heptane. The physicochemical properties of the drug were confirmed; Furosemide's melting point was found to be 206–208°C , and its solubility was determined in various solvents and across different pH levels, showing a significant increase in solubility with increasing pH. The research involved spectroscopic analysis (FTIR, UV) , particle size determination by optical microscopy, encapsulation efficiency calculation, and in vitro drug release studies. The final drug release profiles suggest the successful formulation of controlled-release floating microspheres, with different batches exhibiting varied release rates over time, indicating the potential for prolonged drug delivery.
KEY WORDS: *Furosemide; Microspheres; Floating Microspheres; Controlled Drug Delivery; Oral Drug Delivery.*

1. INTRODUCTION
Oral drug delivery is the most desirable and preferred method of administering therapeutic agents and is generally considered the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process [1].

1.1. ORAL CONTROLLED DRUG DELIVERY
In the mid- to late 1960s, the term "controlled drug delivery" came into being to describe new concepts of dosage-form design. These concepts usually involved controlling drug dissolution, but also had additional objectives. The primary objectives of a controlled-release system have been to enhance safety and extend the duration of action. Today, we also have controlled-release systems designed to produce more reliable absorption and to improve bioavailability and efficiency of delivery [2,3].

TYPES OF CONTROLLED DRUG DELIVERY SYSTEMS [4]
- Dissolution-controlled release
- Osmotically controlled release
- Diffusion-controlled release
- Chemically controlled release
- Miscellaneous forms of controlled release

1.2. Floating drug delivery systems are classified depending on the use of two formulation variables: effervescent and non-effervescent systems [5,6].
- Effervescent Floating Dosage Forms
- Non-effervescent Floating Dosage Forms

1.3. MICROSPHERES AS DRUG DELIVERY SYSTEM
Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin; the synthetic polymers include polylactic acid and polyglycolic acid. Microspheres are small and have large surface-to-volume ratios. At the lower end of their size range, they have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity [7,8].

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TYPES OF MICROSPHERES [9]

Microcapsules: The entrapped substance is surrounded by a distinct capsule wall.
Micromatrices: The entrapped substance is dispersed throughout the microsphere's matrix.

2. DRUG PROFILE

Furosemide is benzoic-sulphonamide-furan. It is a diuretic with a fast onset and short duration that is used for oedema, hypertension and chronic renal insufficiency [10,11].

Figure 1: 4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid

MECHANISM OF ACTION

Furosemide is a high-ceiling diuretic. It acts by inhibiting Na-K-2Cl symport in the thick ascending limb of the Loop of Henle. It is an inhibitor of carbonic anhydrase [12].

Furosemide increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium and bicarbonate. It causes renal vasodilatation and transiently increases glomerular filtration rate [13].

3. MATERIALS AND METHODOLOGY

Materials Aceves et al. prepared and characterised physical mixtures and solid dispersions of Furosemide with Eudragit RS and Eudragit RL. To prepare floating microspheres, various Porogens such as Hexane and heptane have been used.

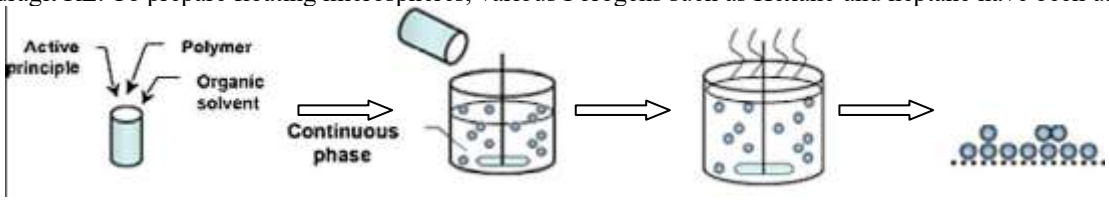

Figure 2: Diagrammatic representation of methodology

4. RESULT AND DISCUSSION

4.1. MELTING POINT DETERMINATION

The melting point range of the furosemide drug sample was found to be 206-208°C

4.2. INFRARED STUDY OF FUROSEMIDE

The infrared spectroscopic analysis of the furosemide drug sample was performed, and the spectrum obtained is shown in Figure 5.1.

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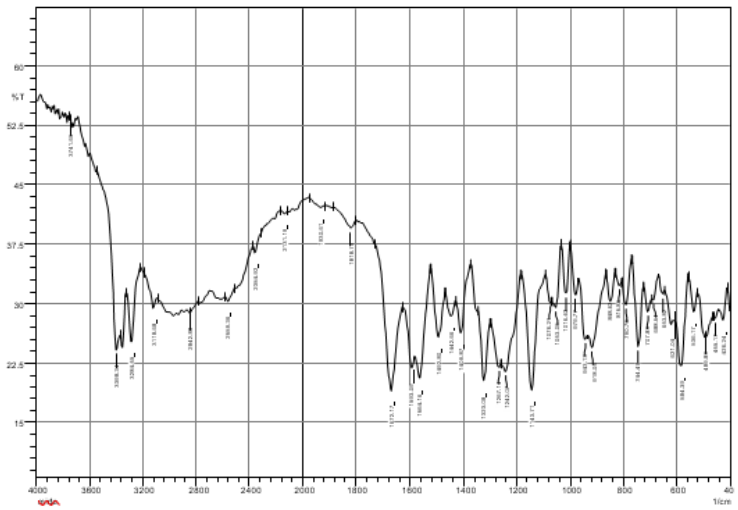

Figure 3: **FTIR Spectrum of Furosemide**

4.3. UV SPECTRA OF FUROSEMIDE

All the samples were scanned on a double beam UV-Visible spectrophotometer (Shimadzu® UV-1700) from 200-400 nm to determine the wavelength of maximum absorbance of furosemide.

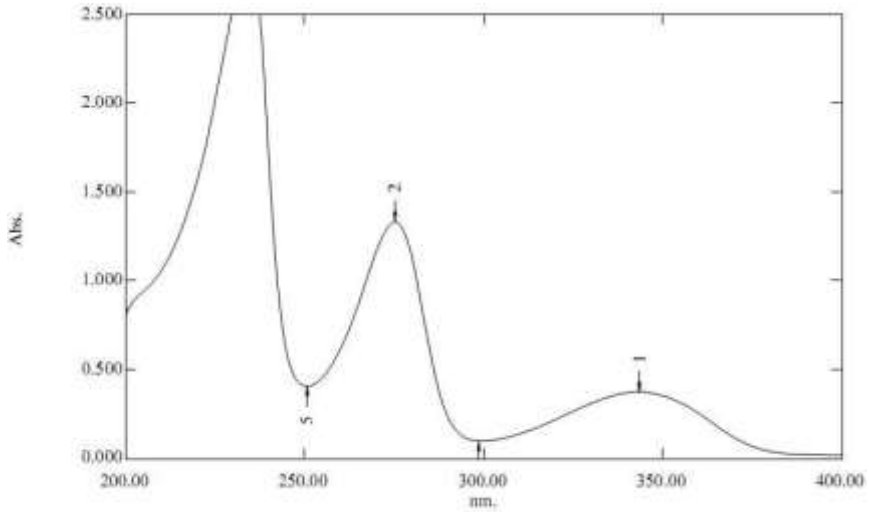

Figure 4: UV spectrum of furosemide in dissolution medium

Out of the three major peaks, the peak at 344.7 nm was selected for further analysis.

4.4. UV SPECTRA OF FUROSEMIDE IN ETHYL ACETATE

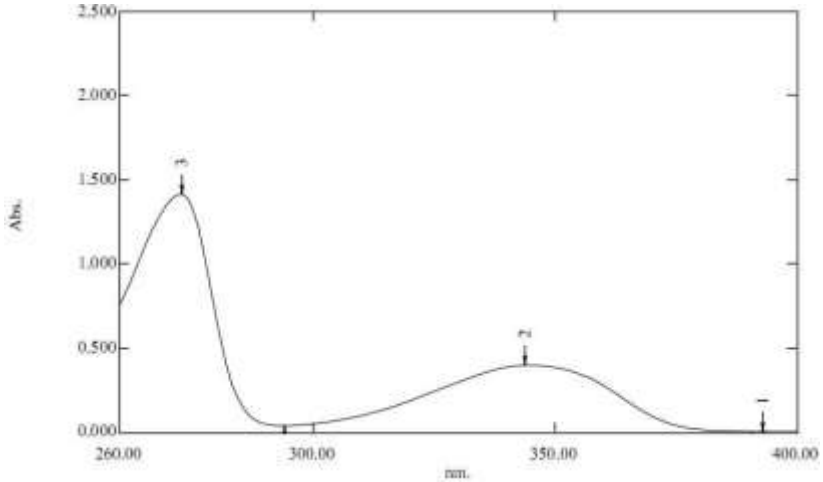

Fig 5: UV spectrum of furosemide in ethyl acetate

Out of the three major peaks, the peak at 344.6 nm was selected for further analysis.

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4.5. CALIBRATION CURVE OF FUROSEMIDE IN DEMINERALIZED WATER

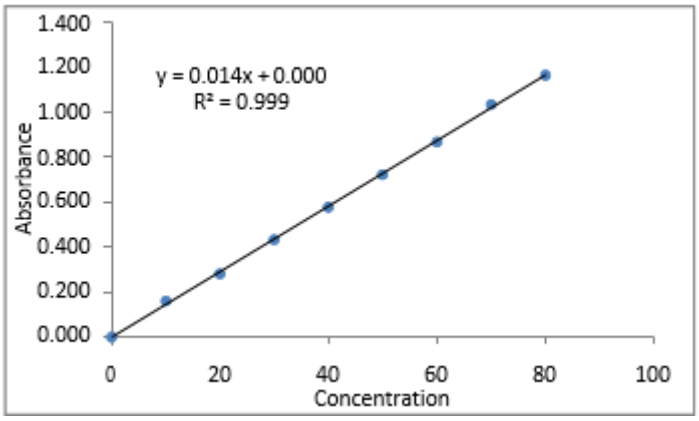

Figure 6: Calibration curve of furosemide in D.M. water

4.6. DETERMINATION OF SOLUBILITY

S. No.	Solvent	Solubility of furosemide (µg/ml)
1.	D.M. water	77
2.	0.1 N HCl	18
3.	Ethyl acetate	14890

Table 1: Determination of solubility

4.7. pH SOLUBILITY PROFILE OFFUROSEMIDE

pH	Solubility of furosemide (mg/ml)	pH	Solubility of furosemide (mg/ml)
1.2	0.020	6	1.829
2	0.016	7	8.344
2.8	0.056	8	10.854
4	0.054	9	10.778
5	0.417	10	10.826

Table 2: Solubility profile of furosemide

4.8. ENCAPSULATION EFFICIENCY

Fifteen mg of drug-loaded microspheres were accurately weighed and dissolved in 10 ml of methanol, sonicated for 15 min and then diluted five times with methanol. It was analysed at 341 nm on a double beam UV/Visible spectrophotometer (Shimadzu 160A). The percentage encapsulation efficiency was calculated as:

%Encapsulation Efficiency = (Actual drug loading/Theoretical drug loading) X 100

4.9. PARTICLE SIZE

Particle size was determined by optical microscopy using a light microscope. An ocular eyepiece calibrated with a stage micrometre was used. Microspheres were dispersed in 0.5% Tween 80 and spread on a microscopic slide. Using a 10X objective, 75 microspheres were observed, and the average size was determined.

4.10. IN VITRO DRUG RELEASE

S.No.	Concentration of polysorbate 20 (% v/v)	Solubility of furosemide	Minimum volume required for 3 times the sink conditions (ml)
1	0	0.001778	13497.49
2	1	0.009783	2453.33
3	1.5	0.015955	1504.26
4	2	0.026913	891.76

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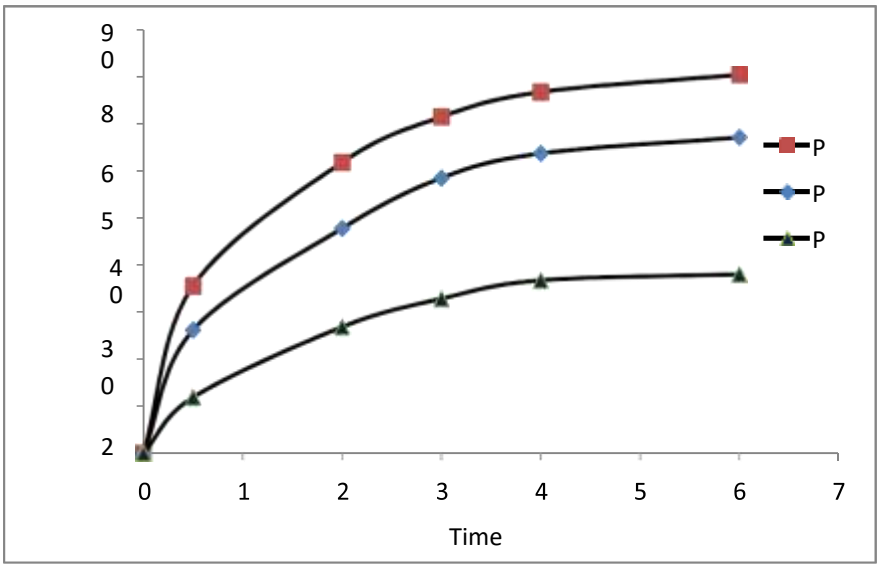

Figure 7: In vitro release profile of pre-optimisation batches

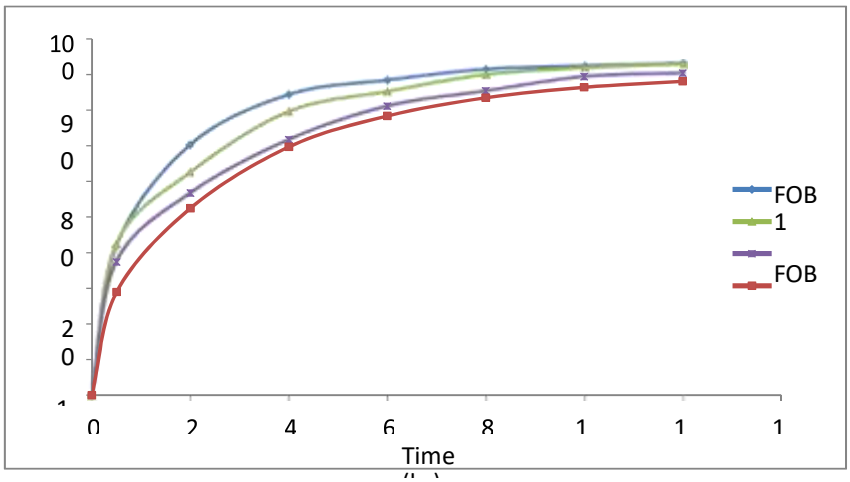

Figure 8: Cumulative % drug release v/s time plot of furosemide microspheres

CONCLUSION

Physicochemical characterization confirmed the identity and purity of the drug, with a melting point of 206–208°C and characteristic UV peaks at 344.7 nm in dissolution medium and 344.6 nm in ethyl acetate. Solubility profiling indicated that Furosemide's solubility significantly increases as the pH rises, which is an important consideration for a gastroretentive system. The methodology successfully yielded Furosemide-loaded microspheres, as confirmed by encapsulation efficiency and particle size analysis. Most critically, in vitro drug release profiles (Figures 7 and 8) clearly indicate a sustained release pattern over several hours (up to 7-14 hours), demonstrating that the formulated floating microspheres are capable of providing the desired controlled-release characteristics. This success meets the primary objectives of controlled-release systems, which include extending the duration of action and improving the efficiency of drug delivery. The floating microsphere formulation thus represents a promising approach for a better-controlled oral delivery of Furosemide.

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