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Research Article

# Solubility Enhancement of Furosemide Drug using Self EmulsifyingDrug Delivery System

**Suraj T Landge, Dr A V Chandewar**

[1]*Research Scholar, P. Wadhwani College of Pharmacy, Yavatmal (Maharashtra), India.
[2] Principal, P. Wadhwani College of Pharmacy, Yavatmal (Maharashtra), India

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**Corresponding author:** Suraj T Landge

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**Abstract:**

Present experimental work was aimed, to prepare optimized, stable Solid self-emulsifyingdrug delivery system containing Furosemide drug.

The combination of the various solubilizer and hydrophilic surfactants like Poloxamer 188, polysorbate 80 and Medium chain triglycrides were used in the present study. PEG-40 Hydrogenated Castor Oil was used as solvent cum co surfactant on the basis of solubility of Furosemide. The formulations were so designed that they form nano dispersion on contact with water or GI fluids which increases the permeability through GI membrane.

All the prototype formulation tested for in vitro dissolution formed nano emulsion in 15 min. In case of the optimized formulation where the drug dissolution enhances with time indicating good thermodynamic stability of nanoemulsion produced on contact with aqueous fluids.

**Keywords:** Furosemide, PEG-40, Self Emulsifying Drug Delivery system.

## Introduction

The most commonly encountered solid oral dosage forms on the market are tablets and capsules. All these oral dosage forms either follow an immediate or a modified drug release profile.

Immediate drug delivery systems are dosage forms that allow the drug to dissolve in the gastrointestinal content with no intention of delaying or prolonging the drug dissolution or absorption. Specifications regarding dissolution characteristics of immediate release dosage forms indicate that at least 85% of the drug should be dissolved in a 60 minute span. Biopharmaceutic Classification System (BCS)

A Biopharmaceutics Classification System (BCS) was introduced by Amidon et al. in 1995 as a basis for predicting the likelihood of *in vitro-in vivo* correlations for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption.[1]

The BCS classification scheme is subdivided into four groups with respect to aqueous solubility and intestinal permeability, as shown in table 1.

**Table 1: The Bio pharmaceutics Classification System for Drugs**

| Class | Solubility | Permeability | AbsorptionPattern | Rate-LimitingStep in Absorption | Drug Examples |
|---|---|---|---|---|---|
| I | High | High | Well absorbed | Gastric emptying | Diltiazem |
| II | Low | High | Variable | Dissolution | Nifedipine |
| III | High | Low | Variable | Permeability | Insulin |
| IV | Low | Low | Poorly absorbed | Case by case | Furosemide |

The FDA has set specifications regarding the solubility and permeability class boundaries used for this BCS classification.

Solubility: a drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

Permeability: in the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study). The permeability class of a drug may also be determined using in vivo intestinal perfusion approaches (human or appropriate animal models) or in vitro permeation studies (excised human or animal intestinal tissues or monolayers of cultured intestinal cells).[2,3]

**Materials and Methods**:

Materials- Gift sample of Furosemide Mfg. Jun. 2012 and retest period May 2014) was provided by M/s Themis Laboratories Pvt. Ltd., Thane. Excipients like polaxomer 188,PEG 40,spray dried lactose,crosspovidone,Magnesium stearate etc. were provided by sun pharma,badoda for preparation of furosemide tablet.

**Methods:**

- Preparation of Furosemide granules and Tablets-
- The various steps involved in the formulation of Furosemide tablets were as under
- Preparation molten mixture of solubalizer, surfactant and drug and their particle size reduction using zirconium beads under stirring
- Hot melt granulation of lactose and Magnesium aluminometasilicate using above molten mass
- Sieving the milled granules through 40 ASTM mesh.
- Blending the sieved granules with disintegrant followed by lubricant.
- Compression into tablets.

The qualitative and quantitative composition of different prototype formulation was as under.

**1. Prototype Formulation A:** These prototypes contained combination of PEG-40 Hydrogenated Castor Oil as solubalizer and Medium chain triglyceride as surfactant, spray dried lactose and Magnesium aluminometasilicate as the diluents and crospovidone as disintegrant.

**2. Prototype Formulation B:** These prototypes contained combination of PEG-40Hydrogenated Castor Oil as solubalizer and Poloxamer 188 as surfactant. , spray dried lactose and Magnesium aluminometasilicate as the diluents and crospovidone as disintegrant.

**Prototype Formulation C:** These prototypes contained combination of PEG-40 Hydrogenated Castor Oil as solubalizer and Polysorbate 80 as surfactant, spray dried lactose and Magnesium aluminometasilicate as the diluents and crospovidone as disintegrant.

**A) Evaluation of Finished product**

**1.** The Furosemide tablets were evaluated for physical parameters such average weight,

content uniformity mechanical strength i.e.hardness, disintegration time and friability test ,Estimation of furesamide drug was done by HPLC Method.[4,5]

**2.** Dissolution tests on the prepared Furosemide tablets were performed using USP dissolution apparatus 2 (paddle) and 5.8 pH phosphate buffer as dissolution media.

**Results:**

Present experimental work was aimed, to prepare optimized, stable Solid self-emulsifying drug delivery system containing Furosemide. An attempt was to design and optimize and evaluate Self emulsifying drug delivery of the Furosemide tablets with the prime objective of enhancing the solubility of Furosemide. The combination of the various solubilizer and hydrophilic surfactants like Poloxamer 188, polysorbate 80 and Medium chain triglycrides were used in the present study.

**Table 2: Physical Characteristics of Furosemide Prototype Tablets**

| Parameter of Tablet | Unit | A1 | A2 | A3 | B1 | B2 | B3 | C1 | C2 | C3 |
|---|---|---|---|---|---|---|---|---|---|---|
| Average Wt. | mg | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Hardness | Kp | 7-10 | 7-9 | 7-11 | 7-10 | 7-9 | 6-9 | 7-9 | 7-10 | 7-9 |
| Friability (100 RPM) | % | 0.18 | 0.14 | Nil | 0.2 | 0.21 | 0.12 | 0.03 | 0.12 | 0.06 |
| Disintegration Time | Min. | 2-4 | 2-4 | 2-5 | 2-5 | 2-6 | 2-5 | 2-4 | 2-4 | 2-5 |

**In Vitro Dissolution of Prototype Furosemide Tablets**

Table illustrates the *in vitro* dissolution profile of Furosemide prototype A, B and C formulations respectively. [6,7]

**Table 3: Solubility Profile of Prototype A, B & C Formulations**

| **Samplinginterval (min)** | **% Dissolution Prototype** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A1 | A2 | A3 | B1 | B2 | B3 | C1 | C2 | C3 |
| 10 | 38 | 39 | 41 | 38 | 37 | 38 | 51 | 52 | 77 |
| 15 | 39 | 41 | 42 | 55 | 52 | 51 | 58 | 54 | 84 |
| 30 | 40 | 42 | 46 | 56 | 62 | 63 | 70 | 71 | 97 |
| 45 | 42 | 42 | 47 | 58 | 63 | 64 | 81 | 79 | 98 |
| 60 | 43 | 46 | 50 | 59 | 65 | 65 | 82 | 84 | 102 |

* Results are mean of 6 readings

All the prototype formulation tested for in vitro dissolution formed nano emulsion in 15minutes. Trend of drug dissolution of prototype A and B remain constant or increase margingally as the time increases, dissolution rate of drug remains constant or increases marginally until 60 minutes in case of prototypes A and B. This indicates that upon contact with dissolution media, formulations A1 to A3 and B1 to B3 form emulsions which have poor thermodynamic stability and eventually drug particle size in dispersion increases. This was not observed in the case of the prototype C3 formulation where the drug dissolution enhances with time indicating good thermodynamic stability of nanemulsion produced on contact with aqueous fluids.

Thus Prototype C3 in- process sample qualify all bench mark for SEDDS.

**Table 4: Stability Data of Furosemide Tablets Prototype C3**

| Time | Appearance | Assay | % Drug release in minutes | | | | |
|---|---|---|---|---|---|---|---|
| | | | 10 | 15 | 30 | 45 | 60 |
| Initial | White to off-white colour capsule shape tablet | 99.89 | 77 | 84 | 97 | 98 | 102 |
| 1M,40°C/75%RH | No change | 99.80 | 76 | 85 | 96 | 97 | 98 |
| 3M,40°C/75%RH | No change | 98.71 | 75 | 84 | 94 | 98 | 101 |

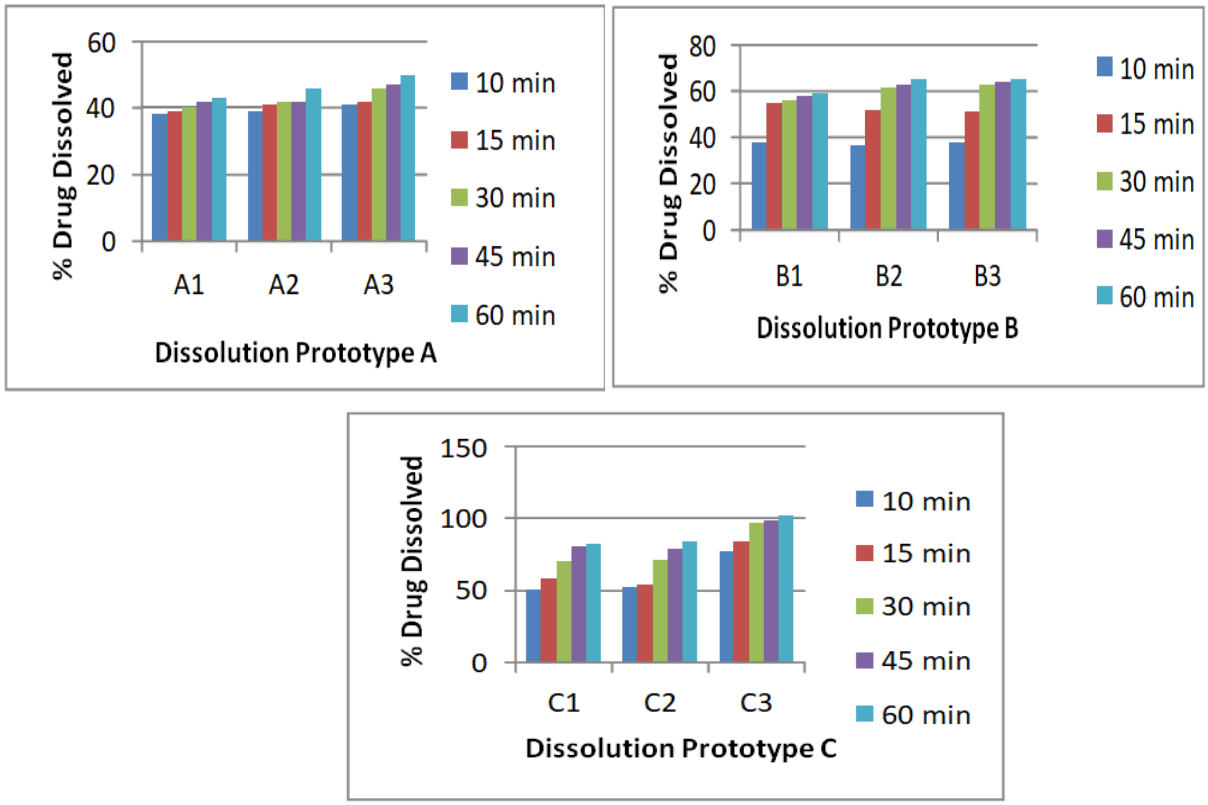


**Figure 1: Graph showing % drug dissolved for Prototype A , Prototype B & Prototype C**

## Conclusion

The combination of the solubilizer polysorbat 80 and PEG-40 Hydrogenated Castor Oil used in the present study to prepare Furosemide particles by hot milling with lipidic excipients objective of producing drug-excipient particles having improved dissolution rate in aqueous milieu.

Combinations of PEG-40 Hydrogenated Castor Oil and different surfactant were evaluated, as the major solubility enhancing excipients which also facilitate the lymphatic absorption and avoid first-pass hepatic metabolism. The formulation were so designed that they form stable colloidal emulsion (nanosized) on contact with water or GI fluids which increases drug solubility facilitates permeability through GI membrane.

However, the major deciding factor in the selection of optimum formulation was size distribution of particles produced on dilution with aqueous fluids and their stability (preferably nanosized) and the *in vitro* drug dissolution rate. It can be concluded that

formulation containing the combination of drug, PEG-40 Hydrogenated Castor Oil and polysorbate 80 having ratio about (1:4:0.4)

Drug have highest solubility in Polysorbate 80 as compared to other surfactant. In molten state drug solubalize in oil and surfactant and milling give additional benefit to entrapped drug in vicinity of the lipidic excipients which are used as granulating fluid. Polysorbate 80 is relatively more hydrophilic and less viscous as compared to other surfactant which might have favoured better rate of drug dissolution of the product and hence prototype C3 was considered the best of all formulations designed.

Thus, the optimized composition of tablet formulation C3 was designed in the present study to arrive at a formulation.

Accelerated stability study on the optimized composition in Alu- alu bliser packaging further demonstrated no adverse changes occur in the formulation when evaluated for parameters such as disintegration time, drug content and in vitro dissolution. [8,9,10]

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