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EFFECTS OF THE EUDRAGIT AND DRUG COAT ON THE RELEASE BEHAVIOUR OF POORLY SOLUBLE DRUG BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Solid dispersions traditionally have been used as effective methods to improve the dissolution properties and bioavailability of poorly water-soluble drugs. Furosemide a loop diuretic belonging to Biopharmaceutical Classification System (BCS) Class IV, has very poor water solubility. The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug, furosemide, by solid dispersion technique as well as to evaluate the potential of Eudragit RL-100, RS-100 and Drug coat L -100, S -100 (methacrylic acid polymers) as carriers for solid dispersions. Solid dispersions were prepared by solvent evaporation technique. The solid dispersions were characterized for particle size, particle size distribution, solubility studies and interaction studies such as FTIR spectroscopy. Solid state characterizations i.e., X-Ray diffraction study; Differential Scanning Calorimetry and Scanning Electron Microscopy were also carried out for the best formulation. In contrast to the very slow dissolution rate of pure furosemide, the dispersion of the drug in the polymer considerably enhanced solubility. The aqueous solubility of furosemide was favoured by formulating it into a solid dispersion. Also it was concluded that Eudragit RL-100 proved to be the best carrier.

INTRODUCTION: Solid dispersions (SDs) are resulted by dispersion of drug in biologically inert matrix. They can be used to increase the solubility of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound surface, as well as increasing the interfacial area available for drug dissolution. Although the latter can be easily accomplished by, for example, decreasing the particle size of the drug powder but micronized powders may result in further complications as they occasionally tend to agglomerate. A more preferable solution would be to introduce the drug in the form of a molecular dispersion. The formulation of poorly soluble compounds for oral delivery now presents one of the greatest and most frequent challenges to formulation scientists in the pharmaceutical industry [1, 2, 3, 4].

The therapeutic efficacy of a drug product intended to be administered by the oral route depends first of all on its absorption by the gastro-intestinal tract. The relationship between dissolution rate and absorption is particularly distinct when considering drugs of low aqueous solubility. Poorly soluble drugs have shown to pocess unpredictable absorption pattern and are slowly absorbed as compared with drugs with higher solubility. Several methods have been employed to improve the solubility of poorly water soluble drugs [5].

The mechanisms of enhancement of dissolution rate of SDs have been proposed by several investigators. A molecular dispersion of the drug in polymeric carriers may be lead to particle size reduction and surface area enhancement, which results in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process, and there is an improvement in drug solubility and wettability due to surrounding hydrophilic carriers. The method of preparation and type of the carrier used are important influences on the properties of solid dispersion. The method used to prepare the SDs include the melting or fusion method, solvent evaporation method, kneading method, spray-dried method and supercritical fluid process [6, 7, 8, 9, 10]. Among the carriers used in the formulation of SDs, polyethylene glycol and polyvinylpyrrolidone are the most commonly used. Both polymers show excellent water solubility [11].

Others carriers are also used to prepare the solid dispersions like Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Poly (2-hydroxyethylmethacrylate) etc.

Furosemide 5- (aminosulfonyl)-4-chloro-2-[(furanylmethyl) amino] benzoic acid is a diuretic and antihypertensive drug, practically insoluble in water and belongs to BCS Class IV. The rate of absorption and the extent of bioavailability for such an insoluble hydrophobic drug are controlled by the rate of dissolution in the gastrointestinal fluids. Improvement of aqueous solubility in such a case is a valuable aim to improve therapeutic efficacy [12].

The purpose of the present work was to improve the aqueous solubility and dissolution rate of furosemide by preparing the solid dispersion with different carriers. Also the study focussed on evaluating the property of Eudragit RL-100, RS-100 and Drug coat L-100, S-100 (methacrylic acid polymer) as possible carriers in the preparation of solid dispersions.

MATERIALS AND METHODS: Furosemide was received as gift sample from Micro labs, Bangalore, India. Eudragit RL 100, RS 100 were obtained from Evonik Degussa India Pvt. Ltd, Mumbai. Drug coat L-100 and S-100 (methacrylic acid polymer) were received as a gift sample from Vikram Thermo

(India) Ltd. Gujarat. These polymers Drug coat L-100 and S-100 are indigenous and the technological properties of these polymers were not yet reported. All other chemicals and solvents used were of analytical grade.

Determination of solubility of Furosemide in water: Solubility studies were performed by placing single dose of the drug in 25 ml of screw-capped bottles containing 20 ml of water and placed in a water bath shaker. The bottle was capped tightly, thermostated at 37±0.2^{o}C and was shaken at 40 rpm. After 24 h, 2 ml of the solution were filtered (pore size 0.45 µm), suitably diluted and assayed for furosemide spectrophotometrically at 271nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan).

Preparation and Evaluation of the Physical Mixtures: Physical mixtures of drug with the selected carriers were prepared for both solubility and dissolution studies. Samples with the same actual composition of the solid dispersions were prepared by simply triturating the powdered drug and selected carriers Eudragit RL-100, RS-100 and Drug coat L-100, S-100 in a mortar and further analysed for solubility and dissolution studies. At specific time intervals the withdrawn samples were filtered, suitably diluted and assayed spectrophotometrically at 271 nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan).

Preparation of solid dispersions (Solvent evaporation method): Weighed amount of furosemide, Eudragit RL-100, RS-100 and Drug coat L-100, S-100 at different drug-to-polymer ratios were dissolved in 15ml of methanol as shown in **Table 1**. The solution was stirred at room temperature for 10 mins, and the solvent was then evaporated at room temperature. Solid residue was dried in a desiccator for 24 hrs. The product thus obtained was ground in a mortar and passed through a sieve # 85 and stored in amber coloured screw capped bottles.

TABLE 1: COMPOSITION OF FUROSEMIDE SOLID DISPERSION FORMULATIONS AT VARIOUS DRUGS: POLYMER RATIOS

Carrier	Ratio					
	1:0.5	1:1	1:1.5	1:2	1:2.5	1:3
Eudragit RL-100	F1	F2	F3	F4	F5	F6
Eudragit RS-100	F7	F8	F9	F10	F11	F12
Drug coat L-100	F13	F14	F15	F16	F17	F18
Drug coat S-100	F19	F20	F21	F22	F23	F24

Evaluation of Solid Dispersions:

Determination of Drug Content: The drug content of the solid dispersions was determined in triplicate. Solid dispersions equivalent to one dose (20 mg) of drug was taken and dissolved in 100 ml of 0.1M NaOH. The samples were filtered, suitably diluted and assayed spectrophotometrically at 271 nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan). The polymers did not interfere with the drug extraction and determination at the specified wavelength.

Determination of solubility of Solid Dispersions: Solubility studies were performed by placing the solid dispersion equivalent to one dose of the drug (20 mg) in 25 ml of water in different screw-capped solubility bottles and placed in water bath shaker. The bottles were capped tightly, thermostated at 37±0.2^{o}C. After specific time interval the samples were withdrawn filtered through membrane filters (whatman filter paper pore size 0.45µm) and assayed spectrophotometrically at 271nm.

Particle Size Analysis: Particle size of SDs of all formulations was determined using microscopic method (optical microscope) with glycerine as dispersion medium for sample. In optical microscopy method particle size of SDs was determined by using 10 X objective lens. A clean glass slide was taken and small drop of glycerine was added and spread over the slide. Small

quantities of SDs particles were then place over the slide and size of about 100 particles was determined.

Based on the drug content, Solubility studies and particle size analysis formulations F6, F12, F18 and F24 with Drug: polymer ratio 1:3 exhibited most satisfactory results. Hence, these formulations were selected and evaluated for drug release profile. The formulations were compared with marketed formulation during the study.

***In-vitro* drug release profile:** The dissolution studies were carried out in (TDT -06PL, Electrolab, Mumbai, India) Dissolution apparatus USP Type 2. The Temperature and paddle speed were maintained at 37.0±0.5^{o}C at 75 rpm for 2 hrs. The dissolution medium consisted of 500 ml of pH (1.2) simulated gastric medium. At predetermined time, 5 ml samples were withdrawn filtered through 0.45µm Whatman filter paper, diluted suitably and analyzed spectrophotometrically at 271nm (Model UV- 1700, UV- Visible spectrophotometer, Shimadzu, Kyoto, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added to maintain the sink conditions. The polymers did not interfere with the UV analysis of the drug. The mean of three determinations was calculated.

Kinetic Modeling of Drug Release: To find out the mechanism of drug release from solid dispersion, the dissolution data of SDs of each batch was treated with kinetics release equation. Higuchi's square root at time: $Q = K_H t½$. Where Q is the amount of drug released at time t, K_H is Higuchi's square root of time kinetics drug release constant.

Based on the above results the most satisfactory formulation F6 was selected. This was further subjected for FTIR, DSC, XRD and SEM analysis.

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu FTIR-8700 spectrophotometer. Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}.

Differential scanning calorimeter (DSC): DSC analysis was performed using Shimadzu-Thermal Analyzer DT 40 (Kyoto, Japan) on 2- to 8-mg samples (Sartorius BP 210 S electronic microbalance, Goettingen, Germany). Samples were heated in an open aluminum pans at a rate of 10^{o}C per min^{-1} in a 30 to 300^{o}C temperature range under a nitrogen flow of 40 mL/min.

Scanning electron microscopy (SEM): Scanning electron microscopy (SEM) was used to visualise the surface morphology. SDs were coated with platinum sputter coater 208 HR (Cressington Sci-entific Instruments Ltd., Watford, UK) to assure conductivity. Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

Powder X-ray diffraction (PXRD): X-ray powder diffraction patterns were recorded on a Jeol JDX 8030 x-ray diffractometer (Tokyo, Japan) using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a 25-mA current. The scanning rate employed was 1^{0} min^{-1} over the 10 to 30^{0} diffraction angle (2θ) range.

Accelerated stability studies: Stability studies were carried out for the formulation F6 as per ICH guidelines for six months under the storage conditions of 40±2^{o}C/ 75 % ± 5% RH and various physicochemical parameter (appearance, percentage drug content and release profile) were monitored periodically for six months.

RESULTS AND DISCUSSION: The present investigation was aimed to prepare solid dispersions of furosemide by solvent evaporation method using Eudragit RL-100, RS-100 and Drug coat L-100, S-100. Eudragit RS-100 has a lower content of quaternary ammonium groups and is considered as less permeable to water as compared to more permeable Eudragit RL-100. Whereas drug coat L- 100 and S-100 are practically insoluble in water. Methanol was employed as a common solvent to dissolve the polymers as well as drug. The preliminary trials conducted revealed that solid dispersions with low polymer ratio resulted in poor drug release whereas those prepared with high polymer ratio exhibited quicker drug release.

Solubility of furosemide, physical mixture and solid dispersion in water: The solubility of pure furosemide, physical mixtures and solid dispersions were carried out in water. It showed that the solubility of pure furosemide is 0.019 mg/ml and 0.143 mg/ml from physical mixture (**Fig. 1**) whereas it was 0.768 mg/ml from the SDs formulation F6 in (**Fig. 2**).

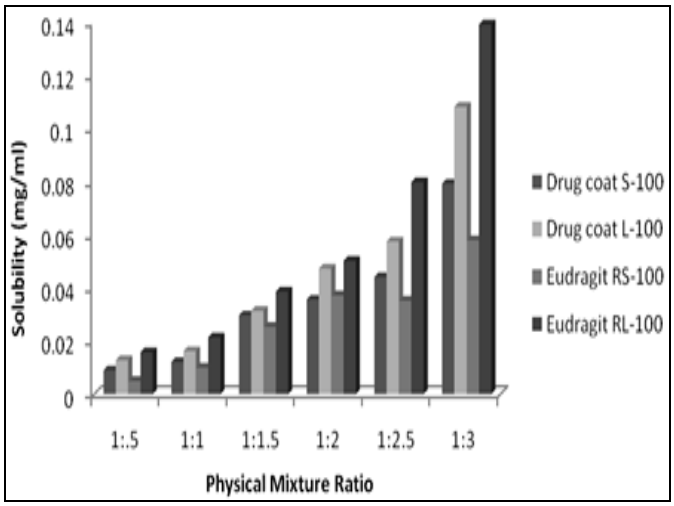

FIG. 1: COMPARATIVE SOLUBILITY PROFILE OF THE PHYSICAL MIXTURES

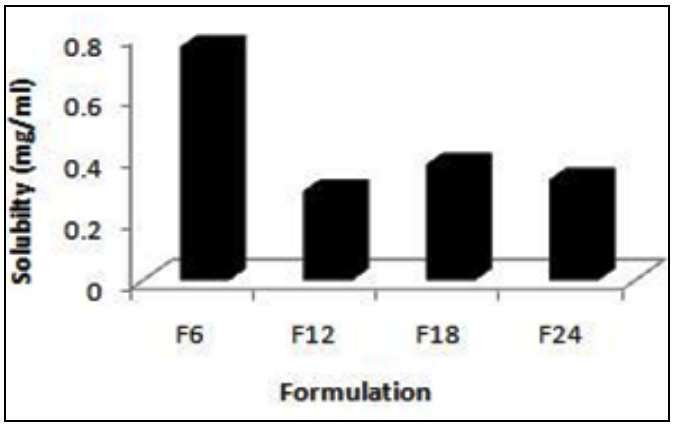

FIG. 2: COMPARATIVE SOLUBILITY PROFILE BETWEEN SELECTED FORMULATIONS

Formulations F12, F18 and F24 illustrated little increase in solubility profile as depicted in (Fig. 2). The aqueous solubility of furosemide from the 1:3 furosemide- Eudragit RL-100 SDs increased about 38-folds compared to that of pure furosemide. Drug release from solid dispersion prepared with Eudragit RS-100 and Drug coat L-100, S-100 alone was inherently sustained. The solubility of furosemide was found to be increasing constantly on increasing the concentration of the carrier Eudragit RL-100.

Drug content and Particle size: The content of the drug in the SDs formulations was determined as depicted in **Table 2**, which was ranging from 95.20 % to 98.43 %. The Particle size of SDs was determined for selected formulations and showed uniformity in particle size, with a size range of 100 to 135µm **Table 2**.

TABLE 2: DRUG CONTENT, PARTICLE SIZE RANGE AND HIGUCHI MODEL OF SELECTED FORMULATIONS

Formulation	Drug content (%)	Particle size range (µm)	Higuchi Model (R^2)
F6	99.74±0.142	105 ± 14	0.998
F12	96.12±0.307	146 ± 29	0.992
F18	97.73±0.153	123 ± 19	0.981
F24	94.52±0.403	134 ± 23	0.986

Dissolution studies: Release of furosemide from solid dispersions of selected formulations in acidic medium showed that the release rates of furosemide from solid dispersions were faster as compared with pure drug as well as from marketed formulation as shown in **(Fig. 3)**. The significant drug particle size reduction achieved in S.D contributes to this improved dissolution rate. Dissolution profiles of solid dispersion formulation F6 with Eudragit RL-100 showed an increase in dissolution rate when compared to formulations F12, F18 and F24. This phenomenon could be attributed to the high permeability characteristic of Eudragit RL-100 in water. About 60% of furosemide was released at pH 1.2 for 2 hrs as compared to pure drug and marketed formulation, probably due to the favourable solubility of the drug in the gastric juice.

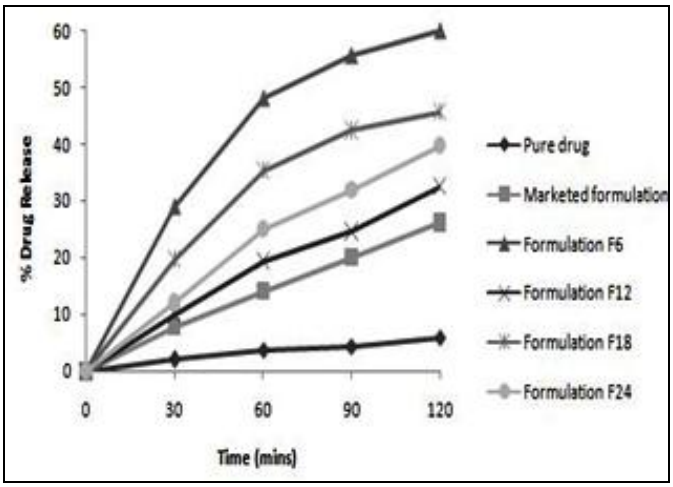

FIG. 3: COMPARATIVE DISSOLUTION PROFILE BETWEEN PURE DRUG, MARKETED AND SOLID DISPERSION FORMULATIONS F6, F12, F18, AND F24

Although, the solid dispersions have significantly increased furosemide dissolution rate, each system behaves in a characteristic way depending on the carriers concentration used. When the carrier concentration increased the dissolution rate was higher. The dissolution profiles were analyzed by least square linear regression. Solid dispersion systems have a better fit than those of the physical mixtures Table 2.

Kinetic treatment of Dissolution Data: To interpret the release kinetics and mechanism of drug release from solid dispersions. The best fit with higher correlation ($r^2 > 0.98$) was found with the Higuchi's equation. Formulations F6, F12, F18 and F24 follows Higuchi model with R^2 values 0.998, 0.992, 0.981 and 0.986 respectively. The release kinetic analysis of selected formulations is as shown in Table 2.

FTIR Spectroscopy: IR spectra of furosemide and its physical mixture with Eudragit RL-100 are presented in **(Fig. 4)**. Pure furosemide and physical mixture spectra showed sharp characteristic peaks at 3400.27, 3122.54, 1665, and 1560 cm^{-1}. The above characteristic peaks appear in both the spectra have the same wave numbers indicating no interaction between the drug and the carrier. But in SDs there was little change in the spectrum as shown in (Fig. 4) when the concentration of carrier was increased, the disappearance of the amine group signal 3400 cm^{-1} was observed.

Differential Scanning Calorimetry (DSC): DSC thermogram of SD formulation F6 is presented in **(Fig. 5)** compared with pure drug and physical mixture. DSC results showed that Furosemide melted at 230°C; however, the acrylic resin Eudragit RL-100 does not present any thermal transition in physical mixture, as the melting point did not shift significantly.

We can conclude that no interaction exists between the drug and the polymer. S.D formulation F6 showed that drug peak intensity was reduced further, compared to physical mixture and shifted towards lower temperature. This indicated that furosemide crystallinity was reduced and the drug might have got converted into the amorphous form. It is also suggested that furosemide may be soluble in the liquid phase of Eudragit RL-100.

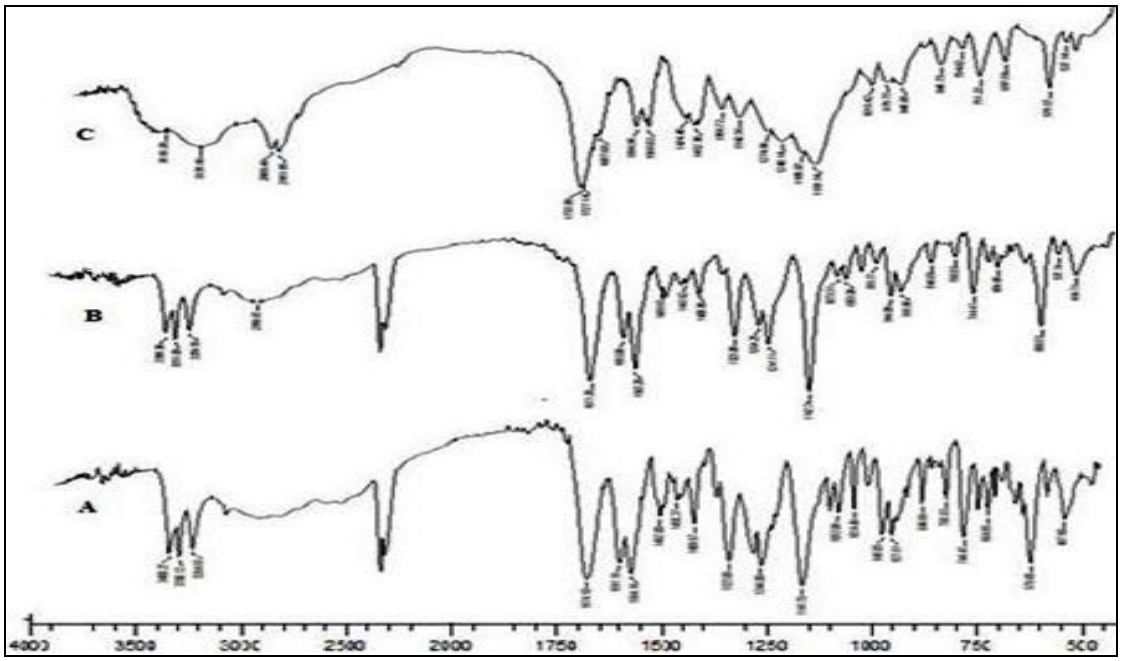

FIG. 4: IR SPECTRA OF A) PURE DRUG, B) PHYSICAL MIXTURE AND C) FORMULATION F6

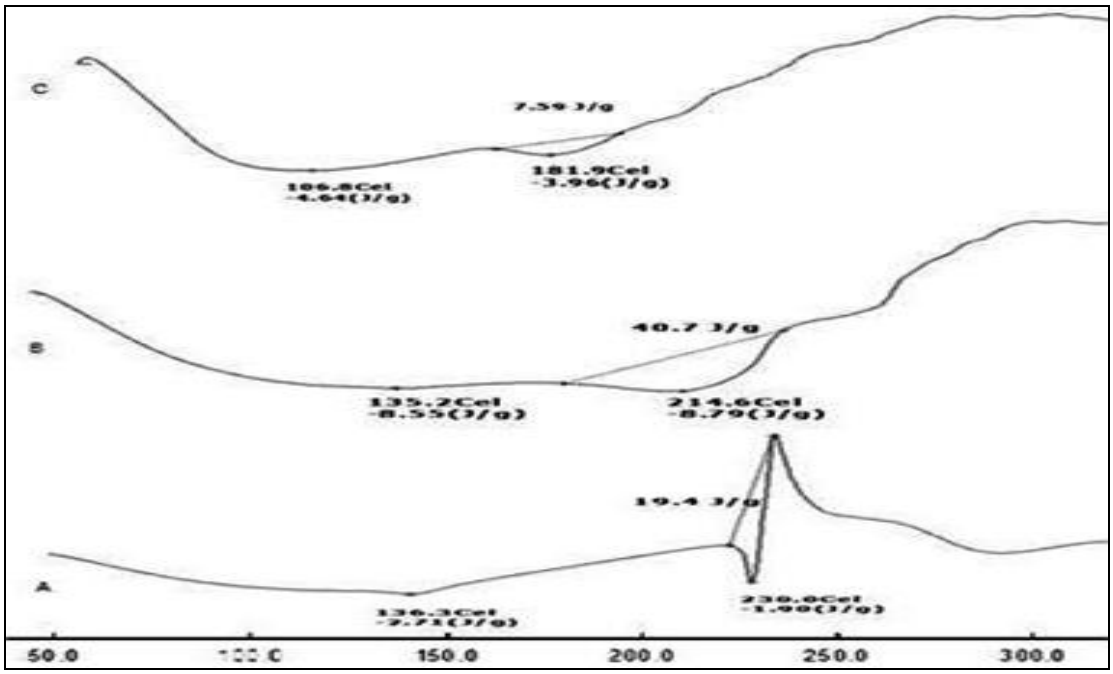

FIG. 5: DSC CURVES OF A) PURE DRUG, B) PHYSICAL MIXTURE AND C) FORMULATION F6

Scanning Electron Microscopy: SEM of pure drug, Eudragit RL-100 and SD formulation F6 confirmed the crystalline character of Furosemide and the amorphous character of the carrier Eudragit RL-100 (**Fig. 6**). Electronic microscopy micrographs showed that the furosemide crystalline habit changed to a new phase. At the lower concentration of Eudragit, furosemide needle crystals were still observed, however, at higher Eudragit concentration the Furosemide needle crystals were not present.

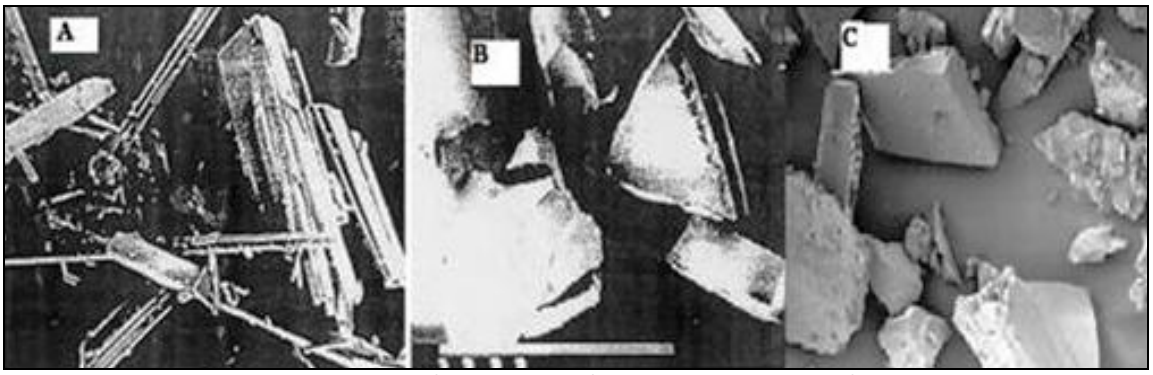

FIG. 6: SCANNING ELECTRONIC MICROGRAPH OF A) PURE DRUG, B) EUDRAGIT RL-100 AND C) SOLID DISPERSION FORMULATION F6

X-ray Diffraction: The XRD of pure furosemide shows the sharp peaks as shown in (**Fig. 7**). The Eudragit RL-100 shows an amorphous character as observed by the lack of defined peaks in the XRD. But in solid dispersion formulation F6 does not show any peak as compared to pure drug. In the range studied some furosemide peaks disappeared and new peaks were formed. Thus a new phase is possible, since the new peaks do not fit to the original peaks of furosemide or to the carrier. A decrease of peak intensity by increasing polymer content was detected.

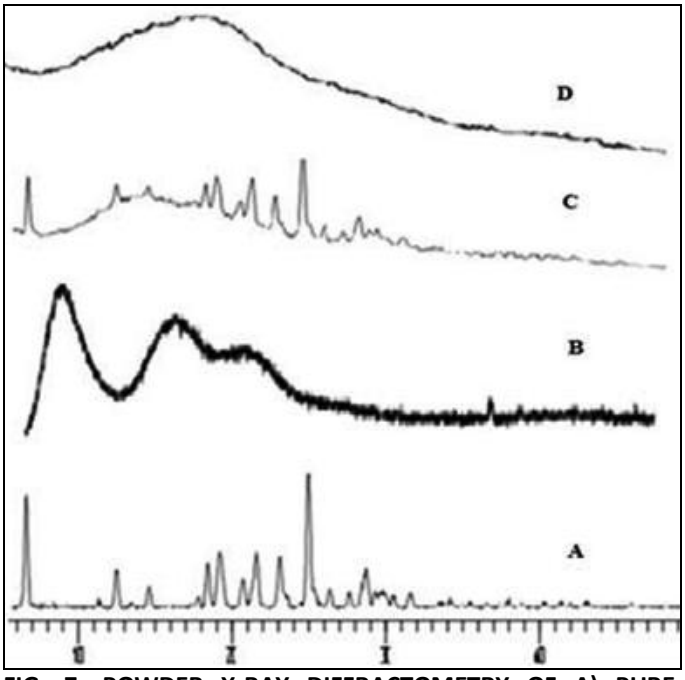

FIG. 7: POWDER X-RAY DIFFRACTOMETRY OF A) PURE DRUG, B) EUDRAGIT RL-100, C) PHYSICAL MIXTURE AND D) FORMULATION F6

Stability Studies: The best formulation was subjected to accelerated stability studies as per the ICH guidelines. There were no changes in appearances and percentage drug content of SDs stored at different temperature at 40±2^{o}C/ 75 % ± 5% RH. All the parameters were within the limit after six months.

CONCLUSIONS: It is concluded that stable solid dispersions of furosemide can be obtained by solvent evaporation technique with Eudragit RL-100 as the carrier. The S.D exhibits better dissolution profile than the marketed formulations.

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