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Pharmaceutical Sciences **RESEARCH ARTICLE ……!!!**

SOLID LIPID MICROPARTICLES (SLMS): AN EFFECTIVE LIPID BASED TECHNOLOGY FOR DELIVERY OF HYDROPHOBIC DRUGS

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KEYWORDS:

Nitrofurantoin Solid lipid Microparticles, Drug Delivery, Lipid-based, Loading Capacity, Drug Entrapment , Scannning Electron Microscopy.

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ABSTRACT

The objectives of the work were to develop a lipid based delivery system for Nitrofurantoin. Nitrofurantoin loaded solid lipid microparticles (SLMs) were formulated by solvent evaporation method and analysed for their encapsulation efficiency (EE%), *in vitro* release, particle size, micrometric properties, percentage yield, drug loading, scanning electron microscopy, fourier transform infrared radiations. In micrometric properties we evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. The flow properties were good. The mean particle size of the microparticles for all the formulations was found between 10-150 µm which indicated that with the increase in polymer concentration, the particle size of microspheres increased. The percentage yield of different formulations F1 to F4 were calculated and the yield was found to be in the range of 66.66 – 78.33%. The percentage entrapment efficiency of Nitrofurantoin microparticles for formulation F1 to F4 was found to be in the range of 69.13±0.14 – 80.02±0.47 %. The scanning electron microscopy was used to determine the shape and surface morphology of microparticls. In SEM microparticles was uniform and spherical in shape. The drug release was found to be 61.01±0.03 – 73.06±0.04in phosphate buffer 6.8. Nitrofurantoin loaded SLMs exhibited good properties and could be used orally twice daily for the treatment of urinary tract infections.

1. SOLID LIPID MICROPARTICLES (SLMs)

Microparticles or microspheres, as they are interchangeably called, are fine spheres usually less than 1000µm in diameter. Microparticles can be prepared by well-established manufacturing processes. An incorporated drug can be distributed homogenously throughout the polymer matrix (microparticles), or it can be encapsulated into a polymer surrounding to form a drug reservoir (microcapsules).[1] They can also facilitate the administration, masking the organoleptic properties and protecting the drug solid.[3] Lipid Microparticles (SLMs) are defined as solid lipids, 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. In recent years, biocompatible lipid microparticles have been reported as potential drug carrier systems, and as alternative materials to polymer. They can be considered as physiologically compatible, physicochemical stable and allowing a large scale production at a relatively low production cost than liposome.[4] These micrometer-sized particles consist of a solid fat core based on naturally occurring lipids and stabilized by surfactant molecule.[1] Solid lipid preparations represent an alternative drug carrier systems to the traditional colloidal carriers (e.g.; emulsions, liposomes and polymeric nano-/micro–particles). Solid lipid nanoparticles (SLNs) and Solid lipid microparticles (SLMs) are equivalent in their composition, physicochemically stable, can be produced on a large–scale industrially and since they are prepared from natural lipids so physiologically compatible with low toxicity. The only difference between (SLNs) and (SLMs) is their size scale, which enables their administration to the body via different routes to the body via different routes.

2. MATERIALS

Nitrofurantoin was procured from Cipla Pharmaceuticals Baddi. Stearic acid was from Nice Chemicals Pvt.Ltd, Kerala. Di methyl sulfoxide, Tween 80, Di methyl formamide, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium chloride, Hydrochloric acid and Sodium hydroxide was from S.D Fine Chemicals lab, Mumbai.

3. PREPARATION OF SLMs BY SOLVENT EVAPORATION METHOD

3.1 Solvent emulsification/evaporation technique:

Microparticles were prepared by weighing drug and polymer (stearic acid) in varying ratios (1:1, 1:2, 1:3, 1:4). Add tween 80 (0.1ml), dimethyl formamide (2ml) and steric acid in a beaker on magnetic stirrer. SLMs were prepared by o/w melt preparation technique. Stearic acid was melted on a water bath with a temperature limit of 72°C. The drug particles grounded to the fine size were dispersed in molten mass of stearic acid. Aqueous phase was consisting of water and tween 80. At

72°C the molten phase was slowly added to the aqueous phase by steering with vigrous agitation at room temperature and then dimethylsulfoxide was added to it. The mixture was stirred on magnetic stirrer at 1000 rpm for 30 to 45 min and the solvent was allowed to evaporate completely. The microparticles were separated by filteration and dried at room temperature.[64] The composition of various formulations shown in table 1.

Table 1: Formulation Plan for the Microsparticles

Materials	F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:4)
Nitrofurantoin (mg)	100	100	100	100
Stearic acid (mg)	100	200	300	400
Dimethyl sulfoxide (ml)	2	2	2	2
Tween 80 (ml)	0.1	0.1	0.1	0.1
Distilled water (qs)	qs	qs	qs	qs

4. EVALUATION OF MICROPARTICLES

4.1 Micromeritic Properties: The microparticles were characterized by their micromeritic properties and after evaluation it was found that microparticles were good in flow and uniform.

4.2 Determination of Particle Size: The particle size of the microparticles was determined by using an optical microscope using a pre-calibrated ocular micrometer. About 100 particles of each formulations were observed and counted.[2]

4.3 Determination of Percentage Yield: The percentage yield (w/w) was determined by using formula:[3]

Percentage Yield = (Total amount of dried microspheres)/Total amount of drug and polymer × 100

4.4 Drug Loading: Accurately weighed 50 mg microparticles were crushed in mortar with pestle and dissolved in 100 ml of phosphate buffer ph 6.8 . The solution was filtered through whatman filter paper. From the filterate, appropriate dilutions were made and samples were analysed spectrophotometrically at 280.5 nm and the amount of drug encapsulated in the microspheres were calculated.[4]

Drug Loading = (Weight of drug in microparticles)/Weight of micrparticles

4.5 Entrapment Efficiency: Accurately weighed 50 mg microparticles were crushed and dissolved in 100 ml of phosphate buffer ph 6.8 . The mixture was filtered with whatman filter paper. From the filterate dilutions were made and samples were analysed spectrophotometrically at 280.5 nm.[5]

Entrapment Efficiency = (Weight of drug in microparticles)/Weight of drug added×100

4.6 Scanning Electron Microscopy (SEM): Scanning electron microscopy was done to characterize the shape and surface topography of the microparticles.

4.7 Fourier Transform Infrared Radiations (FTIR): The FTIR spectra of drug – loaded microspheres was done. Samples were prepared in KBr disks (2 mg sample in 200 mg KBr) and scanned between 400 – 4000 cm^{-1} at resolution 2 cm^{-1}.[6]

4.8 *In-vitro* Drug Release Study: Accurately weighed microparticles equivalent to 15 mg of drug were filled into the hard gelatine capsule bodies by hand filling. Then body and cap joined and sealed. Drug release studies were carried out at 37±5º C in 900 ml phosphate buffer pH 6.8 in a USP type II (paddle type) dissolution apparatus at 50 rpm. At predetermined time intervals of 1 hr, 5 ml of sample was withdrawn and replaced by an equal volume of fresh dissolution medium. The withdrawn samples were filtered and analysed spectrophotometrically at 267 nm. Each test was carried out in triplicate.[7] The percentage drug release was calculated and plotted against time verses cumulative percentage drug released as shown in figure 5.9.

5. DRUG RELEASE KINETIC MODELS

The release rates were analysed by zero order kinetic model, first order kinetic model, Higuchi model and Korsmeyer peppas model, which have been suggested to describe drug release kinetics from microparticles.

5.1 Zero Order Kinetic Model: Zero order describes the systems where the release rate of drug is independent of its concentration. The drug release kinetics from zero order can be expressed by the equation:[7,10]

$$C = C_o - K_{ot}$$

Where, C = Amount of drug release

C_o = Initial amount of drug in solution

K_o = Zero order rate constant

t = time

For study of release kinetics, the graph plotted between cummulative amount of drug released verses time.

5.2 First Order Kinetic Model: This model is used to describe the absorption and elimination of some drugs. The drug release which follows the first order kinetic can be expressed by the equation:

$$\text{Log } C = \text{Log } C_o - Kt/2.303$$

Where, C_o = Initial concentration of drug

K = First order constant

T = time

The data obtained were plotted between log cummulative percentage drug remaining verses time.

5.3 Higuchi Model: It describes the drug release from matrix system. This model is often applicable to the different geometric and porous system. The equation of Higuchi model is:[7,9]

$$F_t = Q = K_H \times t^{1/2}$$

Where, K_H = Higuchi dissolution constant.

Data obtained were plotted between cummulative percentage of drug release verses square root of time.

5.4 Korsemeyer Peppas Model: Korsemeyer et al (1983) derived a simple relationship which describes the release of drug from a polymeric system. To illustrate the mechanism of drug release, 60% of drug release data was fitted in krosmeyer peppas model.[7,10]

$$C_t/C\infty = kt^n$$

Where, Ct/C∞ = Fraction of drug release at time t

K = rate constant

N = release exponent

To study the release kinetics, data obtained from *in – vitro* drug release studies were plotted between log cummulative percentage drug released verses log time.

6. RESULTS AND DISCUSSION

7 IDENTIFICATION OF DRUG

The drug was identified by different methods including organoleptic properties, melting range, λmax, partition coefficient FTIR spectroscopy and SEM. All the parameters were found within limit and complies requirements of official's compendia.

7.1 Evaluation of microparticles

7.1.1 Micromeritic Properties: The results of all four formulations are shown in table 5.1 which were evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. The Carr's compressibility index for formulation F1 was found in the range of 10.41±0.12 which indicated the excellent flow properties, the formulations F2 and F3 was found in the range of 14.81±0.11 and 14.28±0.16 which indicated the good flow properties and F4 formulation was found in the range of 18.96±0.22 which indicated fair to passable flow properties.T he value of Hausner's ratio for all the formulations was 1.11±0.09, 1.17±0.02, 1.16±0.06 and 1.23±0.08 which indicated the better flo.w properties.

7.1.2 Particle Size Determination: The mean particle size of the microspheres for all the formulations was found between 10-50 µm which indicated that with the increase in polymer concentration, the particle size of microspheres increased. This may be because of viscosity of the

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polymer solution which increases as the polymer concentration increases which in turn decreased the stirring efficiency. As the stirring rate is kept constant for all batches, it was found to be insufficient to break the particles into smaller size at higher polymer concentration. The mean particle size for formulations F1 to F4 was 10.62±1.21 to 38.91±1.91.The microscopic view of microspheres for all the formulations are shown in figure 2 and 3.

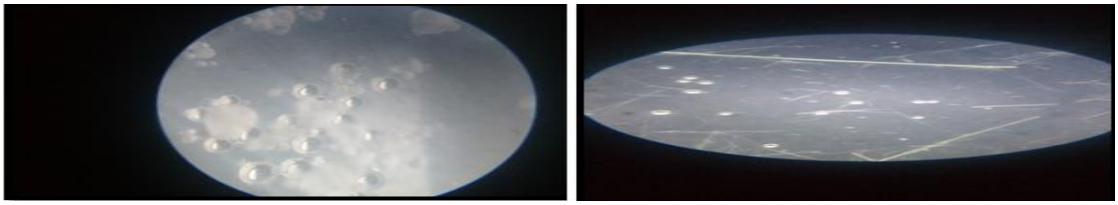

Figure 2: Microscopic View of Formulation (F1) (F2) containing Microparticles

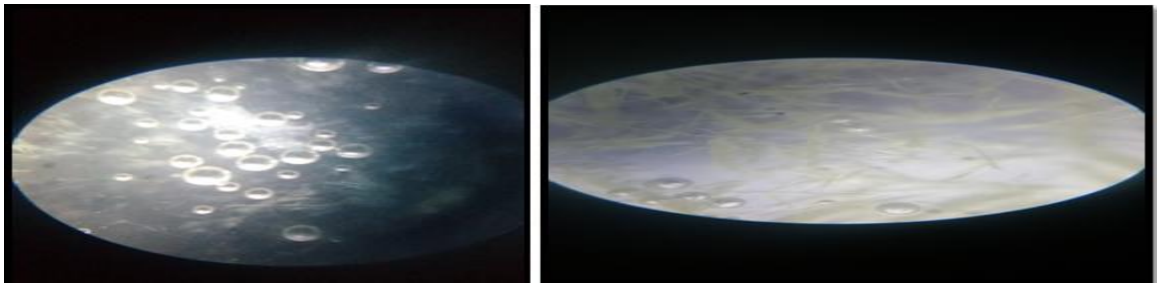

Fig 3: Microscopic View of Formulation (F3) (F4) containing Microparticles

7.1.3 Percentage Yield: The percentage yield of different formulations F1 to F4 were calculated and the yield was found to be in the range of 66.66 – 78.33%. The loss of material during preparation of microspheres can be attributed to the process parameters as well as during filteration of microspheres. Percentage yield of all batches is shown in table 5.3.

7.1.4 Estimation of Drug Loading and Encapsulation Efficiency: The drug loading was found to be in the range of 10.37±0.02 - 14.01±0.41 mg for formulations F1 to F4. The formulation F3 showed highest drug content i.e 14.01±0.41 mg, while the formulation F1 showed lowest drug content i.e 10.37±0.02 mg. The percentage entrapment efficiency of Nitrofurantoin microparticles for formulation F1 to F4 was found to be in the range of 69.13±0.14 – 80.02±0.47 %. The entrapment efficiency of the drug depended on the solubility of the drug in the solvent and continuous phase. An increased in the concentration of polymer in a fixed volume of organic solvent resulted in increased in entrapment efficiency. The percentage drug loading and percentage entrapment efficiency is shown in table 4.

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Table 4: Drug Content and Entrapment Efficiency

Formulation	Drug Loading (mg)	% Practical yield	Entrapment Efficiency (%w/w)
F1	10.37±0.02	66.66	69.13±0.14
F2	12.03±0.26	71.11	75.08±0.31
F3	14.01±0.41	78.33	80.02±0.47
F4	11.92±0.65	74.66	76.16±0.15

7.1.5 Scanning Electron Microscopy: The scanning electron microscopy was used to determine the shape and surface morphology of microparticles. F3 formulation was the best formulation. SEM images of the formulation F3 as shown in figure 4 and 5 revealed that the microspheres were spherical in shape.

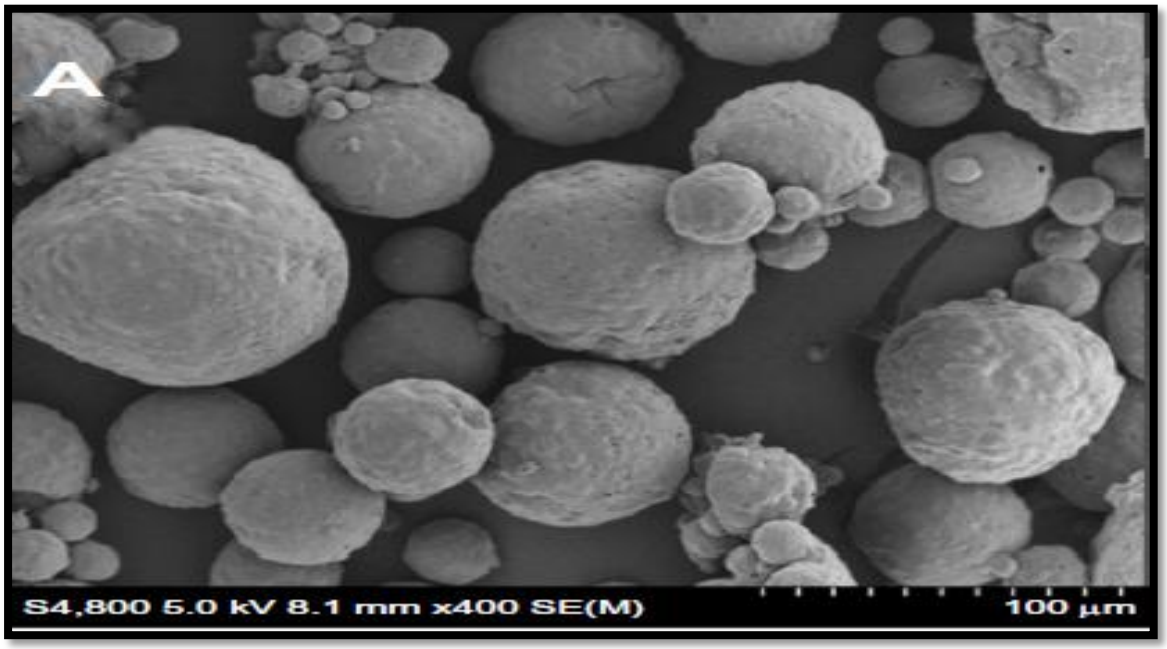

Fig 4: Scanning Electron Microscopy of Formulation (F3)

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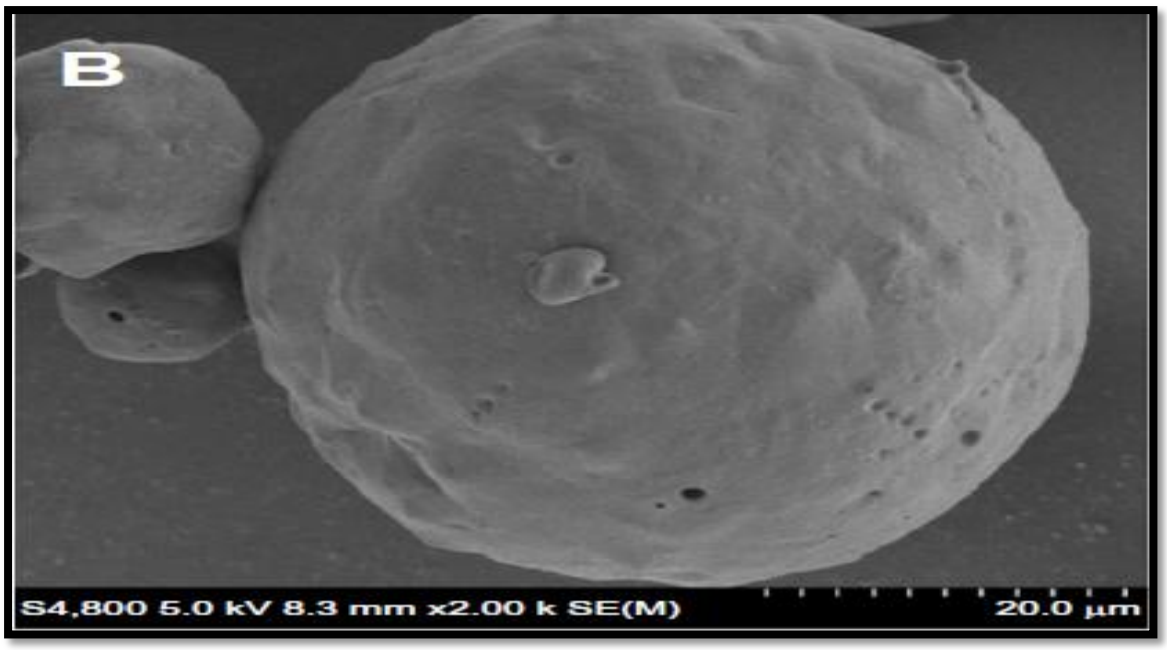

Fig 5: Scanning Electron Microscopy of Formulation (F3)

7.1.6 *In - vitro* Drug Release Study: Dissolution study for all the formulations (F1 – F4) of microsparticles were carried out using USP type II (paddle type) dissolution apparatus at 50 rpm in phosphate buffer pH 6.8. Cummulative % drug released data was plotted between time (hrs) and cummulative % drug released as shown in figure 6. The drug release was found to be 61.01±0.03 – 73.06±0.04.

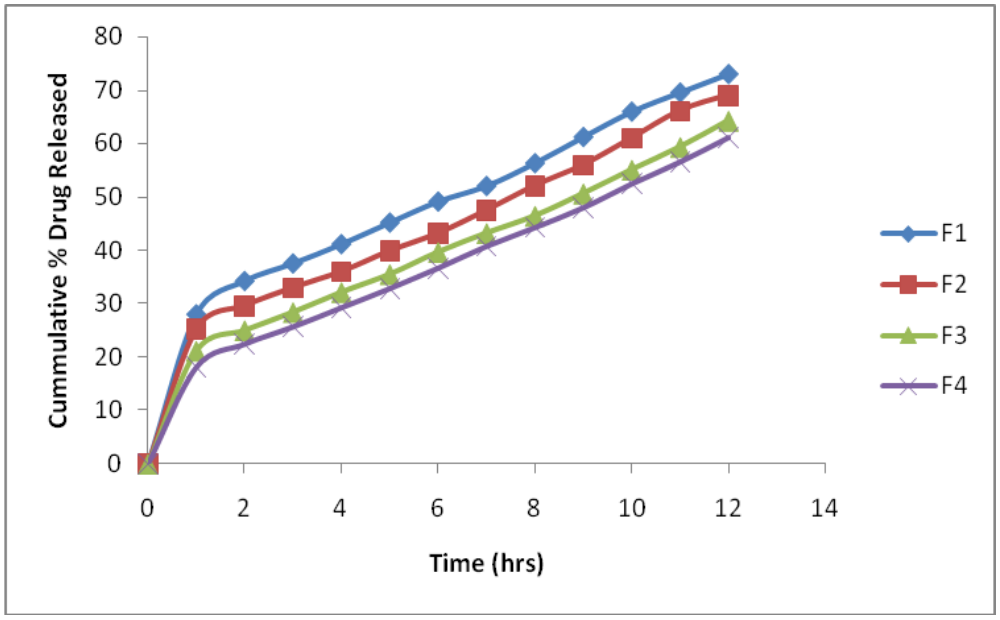

Fig 6: Cummulative % Drug Released from Microparticle Formulations

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7.1.7 Release Kinetics of the Selected Formulation (F3): The formulation F3 was selected for drug release kinetic models. *In-vitro* release studies of formulation F3 were plotted in different kinetic models.Zero order release model (cummulative amount of drug released and time). First order release model (log cummulative percentage drug remaining and time)Higuchi Model (cummulative percentage of drug release and square root of time) Krosmeyer Pappas Model (log cummulative percentage drug release and log time) shown in table 6 and graphs were shown in fig 7-10.

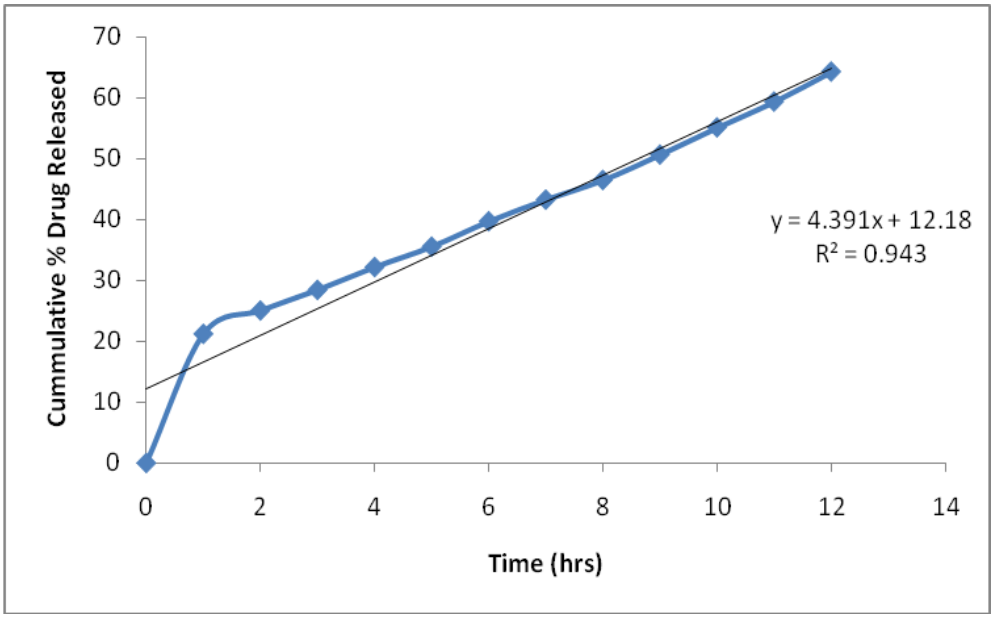

Figure 7: Zero Order Release of Formulation (F3)

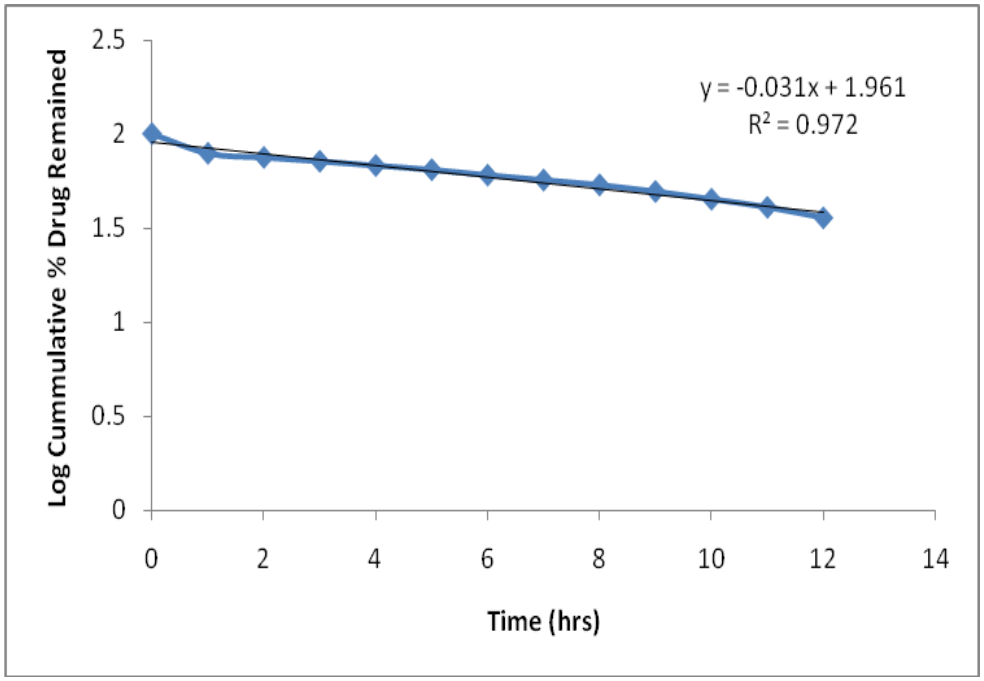

Figure 8: First Order Release of Formulation (F3)

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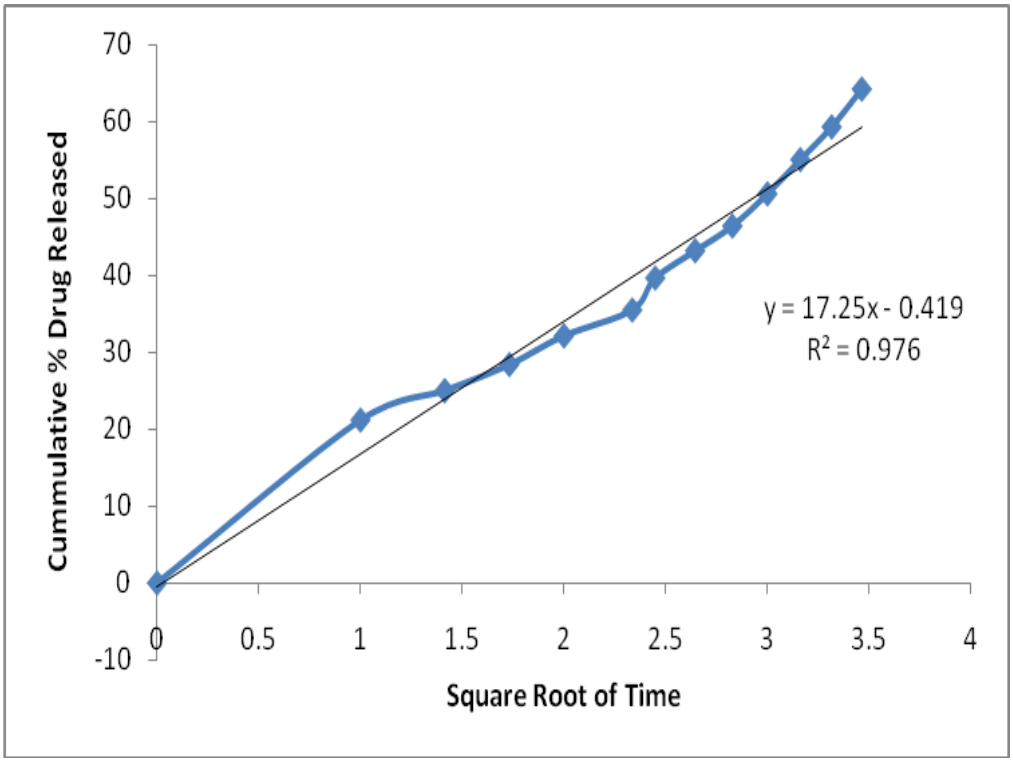

Figure 9: Higuchi Model of Formulation (F3)

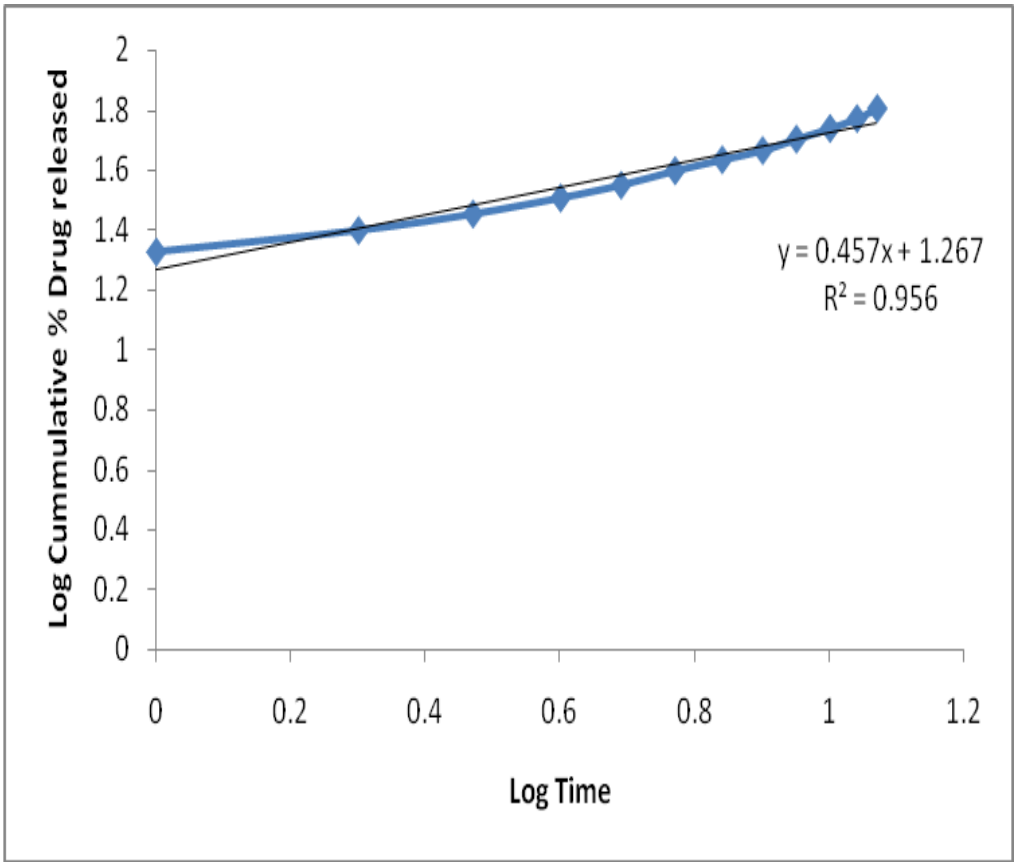

Figure 10: Korsemeyer peppas Model of Formulation

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8. FTIR SPECTRA

FTIR spectra was done with polymer and drug and there was no interactions were shown there.

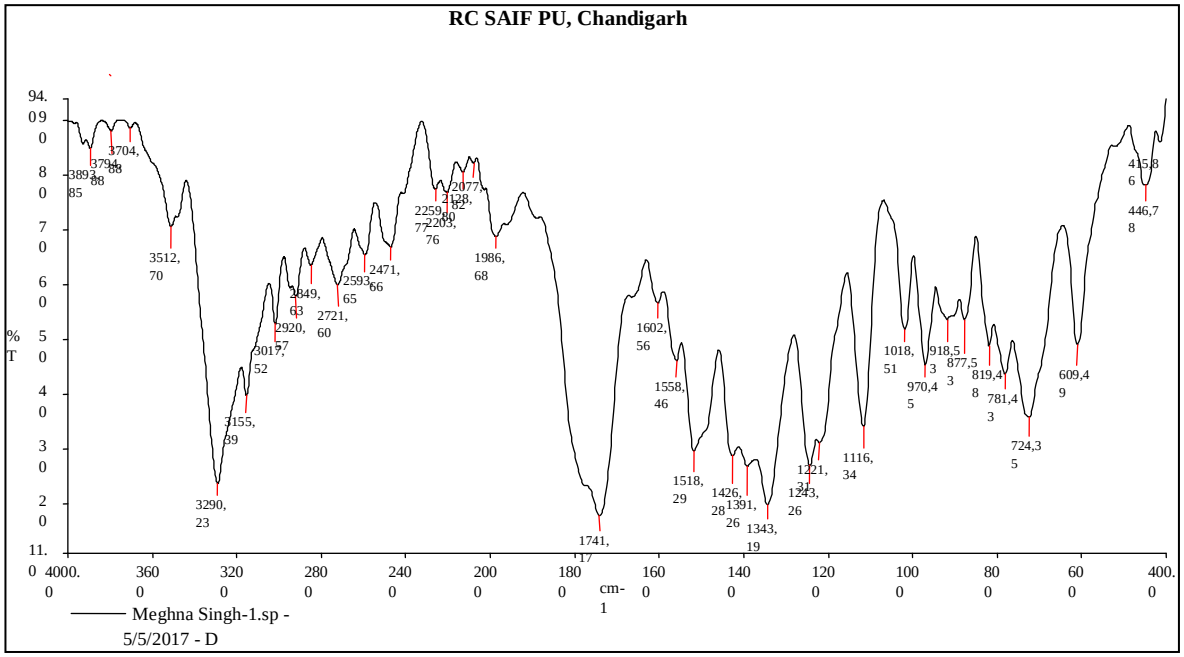

Figure 14: FTIR spectrum of Nitrofurantoin

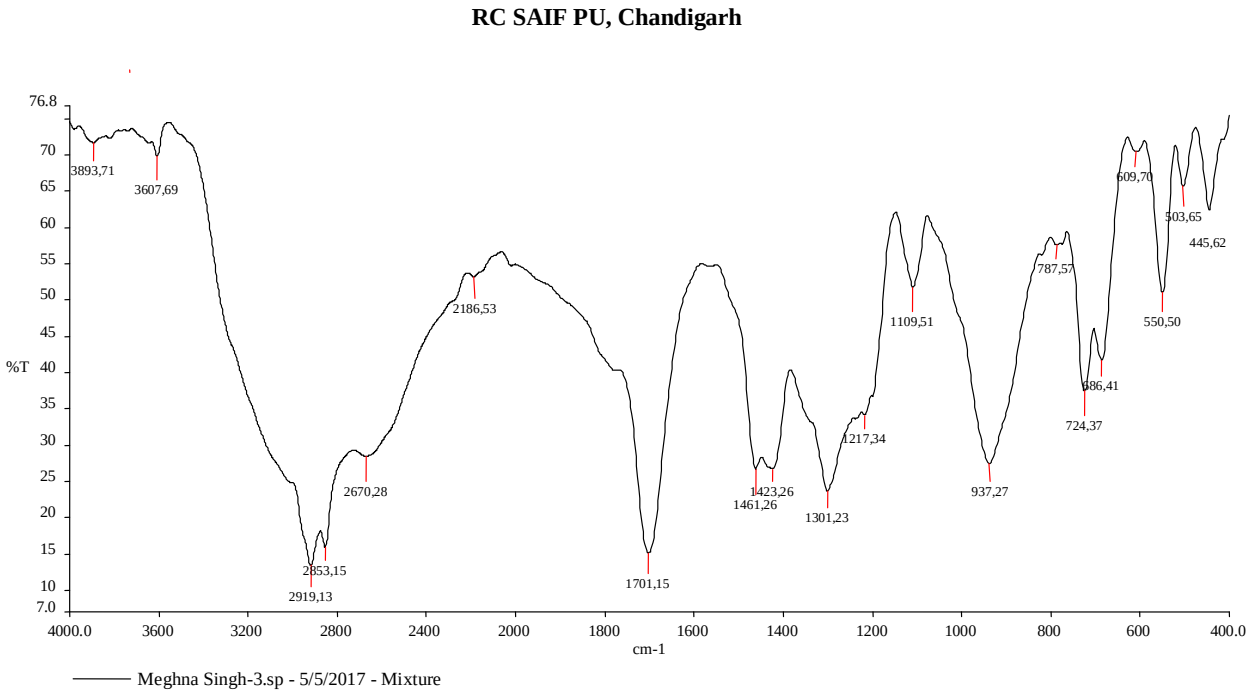

Figure 16: FTIR spectrum of nitrofurantoin and stearic acid

Stability Study: The stability studies of formulation (F3) at 40°C/75% RH showed no significant change in physical appearance drug content and lag time at the end of two months.

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