



PREPARATION AND CHARACTERISATION OF ASPIRIN LOADED ETHYLCELLULOSE NANOPARTICLES BY SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Aim:-In the present study Aspirin loaded Ethyl cellulose nanoparticles were prepared by solvent evaporation method in the presence of Tween 20 as emulsifying agent and ethyl acetate as organic solvent. Three formulations were prepared by varying the concentration of polymer and the influence of process parameters such as solvent mixture, composition, concentration of the emulsifying agent and speed of stirring has been examined. All the three formulations are evaluated for drug content, product yield, particle size, entrapment efficiency and loading capacity. Entrapment efficiency and loading capacity were determined by ELTEK NP 400 Ultracentrifuge. The particle size and

stability of the formulations were determined by HORIBA SZ-100 series particle size analyzer. Entrapment efficiencies were found to be 93.4%, 96.2% and 98.6% and the loading capacities were found to be 32.22%, 34.6% and 35.77% respectively for F1, F2 and F3 formulations. Comparative study was performed to determine the best method for the preparation of Aspirin loaded ethyl cellulose nanoparticles. From the evaluation studies it was observed that F2 formulation was giving promising results. The average particle size of the best formulation, F2 was found to be 444.5nm and zeta potential was found to be 41.5mV. Invitro drug release studies were performed to determine the sustain release nature of the formulation and drug release was sustained up to 12hrs for nanoparticles prepared by F2 formulation.

Key words: Nanoparticles, Aspirin, Ethyl cellulose, Solvent evaporation, Drug release.

INTRODUCTION

The major goals in designing polymeric nanoparticles as a delivery system is to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm⁽¹⁾. Due to large surface to volume ratio, the nano-scale structures have unique properties and dissolution behaviors which are expected to avoid the unwanted side effects. Sustained release of the drug from the nanoparticles maintains the therapeutic concentration for long durations. Polymeric nanoparticles are prepared by various techniques like Amphiphilic cross linking, Polymerization methods and Solvent precipitation methods. The choice of a particular approach depends mainly on the physicochemical properties of the polymer (i.e., solubility and molecular weight) and the nature of incorporated active pharmaceutical ingredient (i.e. hydrophobicity/ hydrophilicity of the drug and its sensitivity to the solvent). With regard to the formulation of polymeric nanoparticles, the solvent extraction/evaporation method is one of the most widely employed techniques and poly (vinyl alcohol) (PVA) is the most commonly used emulsifier in the process.

The solvent evaporation method has been used to prepare biocompatible and biodegradable/non biodegradable polymer nano particles like PLGA, PLA, ethyl cellulose, acrylate polymers and acrylate co polymers^(2,3,4). In O/W single emulsion solvent evaporation method, the polymers are dissolved in a suitable water miscible organic solvent, and active pharmaceutical ingredient is dissolved in this polymeric solution. This is emulsified in aqueous continuous phase containing surfactant/stabilizing/emulsifying agent. The most common stabilizers are hydrophilic molecules such as poly (vinyl alcohol), polysorbates (TWEEN[®]), poly (acrylic acid), poloxamers (or Pluronic[®]) and sodium dodecyl sulfate⁽⁵⁾. The various parameters that govern the formation of nanoparticles includes drug solubility, types of solvent, rate of diffusion of the solvent, temperature, polymer composition, the nature of the polymers, viscosity and pH of the external phase⁽⁶⁾. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs⁽⁷⁾.

In the present work, Aspirin loaded ethyl cellulose nanoparticles are prepared by O/W single emulsion solvent evaporation technique.

In the present study, Ethyl cellulose (EC) was chosen as the material for the particle matrix. Ethyl cellulose is a non-ionic, inert hydrophobic, non-biodegradable and biocompatible

polymer with minimum toxicity. It is one of the extensively studied encapsulating materials for the controlled release of pharmaceuticals (^[8]). Aspirin is used as model active ingredient in which it has been incorporated into the particle matrix for the formation of EC Nanoparticles. Aspirin or Acetyl Salicylic Acid is a Non steroidal anti-inflammatory drug, which acts by inhibition of prostaglandin synthesis by blocking cyclo-oxygenase enzyme (COX-1) in the body to reduce pain and swelling (^[9,10]). It is used to prevent chronic deformity, which occurs due to inflammation, synovial proliferation and erosion of bone and hence useful in the treatment of arthritis at initial stages. For treatment of inflammatory diseases such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, the recommended dosage interval is 6 to 8 hours with maximum dose of 3 grams per day in divided doses.

In view of all the above, the present study was taken up with an objective of preparing Aspirin loaded ethyl cellulose nanoparticles by O/W single emulsion solvent evaporation technique.

MATERIALS AND METHODOLOGY

Materials

Aspirin was commercially obtained from HIMEDIA, Mumbai. Ethyl acetate was supplied from Sigma Aldrich, Mumbai.

Preparation of Nanoparticles

Emulsion-solvent-evaporation technique was used to prepare ethyl cellulose nanoparticles containing aspirin. Aspirin and ethyl cellulose were dissolved in ethyl acetate at various drug-polymer ratios (1:1, 1:1.5, 1:2) as tabulated below. Then this organic dispersion was emulsified by mixing at 1100rpm, with a REMI LAB overhead stirrer provided with a three bladed paddle rotor, into an aqueous external phase containing tween-20(0.25%) at room temperature. The organic phase was added drop wise to the aqueous phase at a constant rate. Stirring of the O/W emulsion was continued until the ethyl acetate has evaporated. The resultant dispersion were collected by filtration and kept for drying for further studies.

Formulations	Drug(Aspirin)mg	Polymer(Ethyl cellulose)mg	Amt of solvent (Ethyl acetate)consumed(ml)
F1= 1:1	500	500	6
F2=1:1.5	500	750	9
F3= 1:2	500	1000	15

Characterisation Of Nanoparticles

The obtained formulations of Aspirin loaded Ethyl cellulose nanoparticles are characterized for following parameters.

Determination of drug content

Free drug of the formulations was first determined in the supernatant by choosing a solvent in which only the free drug gets dissolved and not the other ingredients. To determine the drug content, 50mg drug equivalent to formulation was weighed accurately and transferred into three necked RBF containing 50ml of methanol. The solution was stirred at 700rpm for 3hrs by using magnetic stirrer. The resultant solution was filtered and the amount of the drug in the filtrate was estimated after suitable dilution by ultraviolet (UV) spectrophotometer at 276 nm.

Entrapment efficiency

Entrapment efficiency indicates the amount of drug encapsulated in the formulation. The method of choice for drug content determination is separation of free drug by ultra centrifugation, followed by quantitative analysis of the drug from the formulation. The samples were centrifuged by using ultracentrifuge at 17640 rpm for 40min.

Percentage entrapment efficiency may be calculated from the following formula:

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug encapsulated in the formulation}}{\text{Total amount of drug in the formulation}} \times 100$$

Loading Capacity

The loading capacity (L.C) refers to the percentage amount of drug entrapped in nanoparticles:

$$\text{L.C.} = \frac{\text{Total amount of drug} - \text{amount of unbound drug}}{\text{Nanoparticles weight}} \times 100$$

Invitro drug release kinetics

Invitro drug release studies were conducted by means of orbitary shaker. 50mg of each accurately weighed formulation was transferred into 250ml conical flask containing 50ml pH7.4 phosphate buffer. They were kept in an orbitary shaker at 100 rpm maintained at 37°C. Aliquots of 5ml buffer were withdrawn at predefined time intervals and the medium was replaced with same volume of buffer. The withdrawn samples are centrifuged at 3000rpm for

15min. The supernatant sample was collected. This study was carried out for 12hrs, and the concentration of drug release was estimated by determining the absorbance at 276 nm using Elico UV spectrophotometer model no: 164.

RESULTS

The obtained formulations were evaluated for the above mentioned parameters and the results are discussed as follows:

Estimation of Drug content

The drug content was evaluated for all the formulations and it was observed that the nanoparticles prepared by F1 formulation showed a higher drug content value i.e., 93.4% when compared to F2 and F3 formulations. i.e. 89.1% and 73.6% respectively.

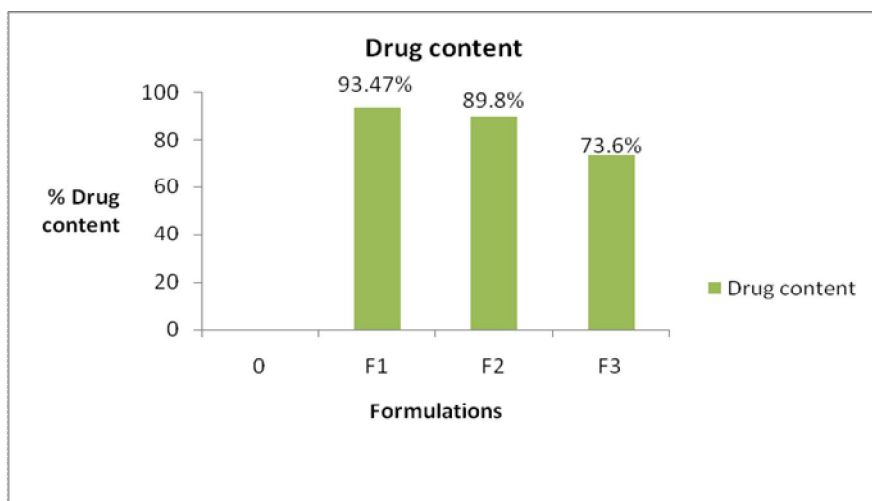


Fig.1 Estimation of drug content of all the formulations

Entrapment Efficiency of the formulations: Entrapment efficiency and loading capacity were found to be slightly better for F3 formulation on comparison to that of F1 and F2 formulation.

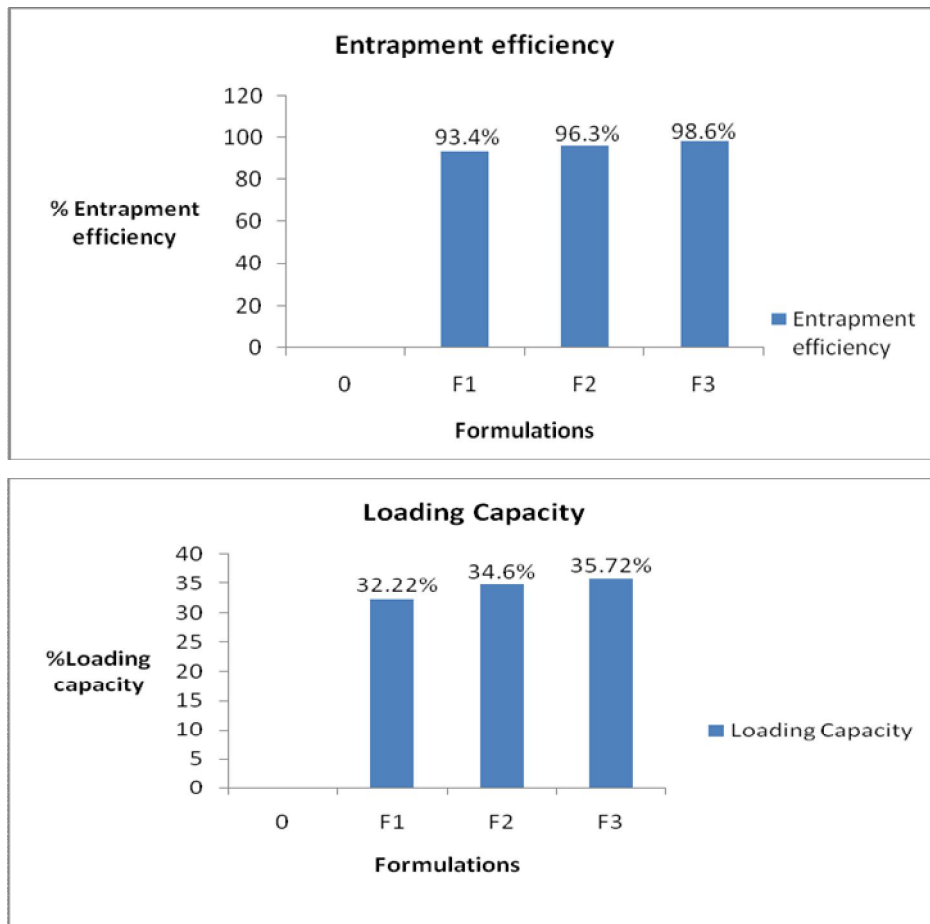
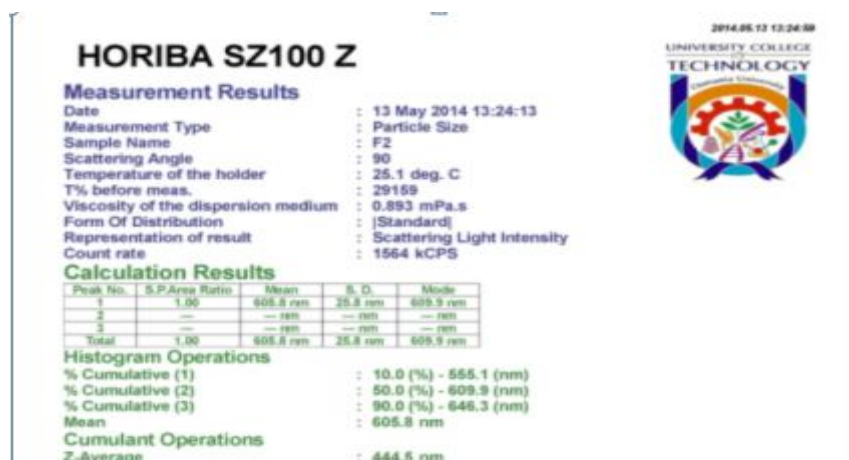


Fig.2- Entrapment efficiency and loading capacity of both the formulations

Particle size Determination

The mean particle diameter of the F2 formulation was determined by using Horiba SZ-100 series zeta Nanoparticle analyzer. The average particle size for F2 formulation was found to be 444.5nm and zeta potential was found to be 41.5mV.



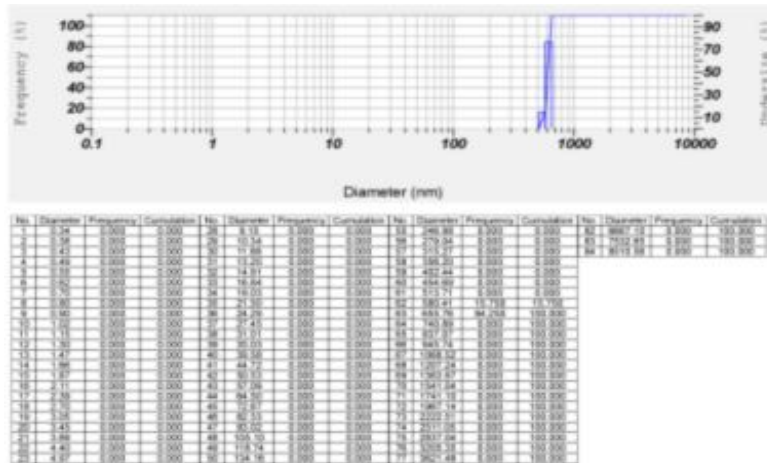


Fig.3- The average particle size of Aspirin loaded ethyl cellulose nanoparticles by solvent evaporation technique for F2 formulation.

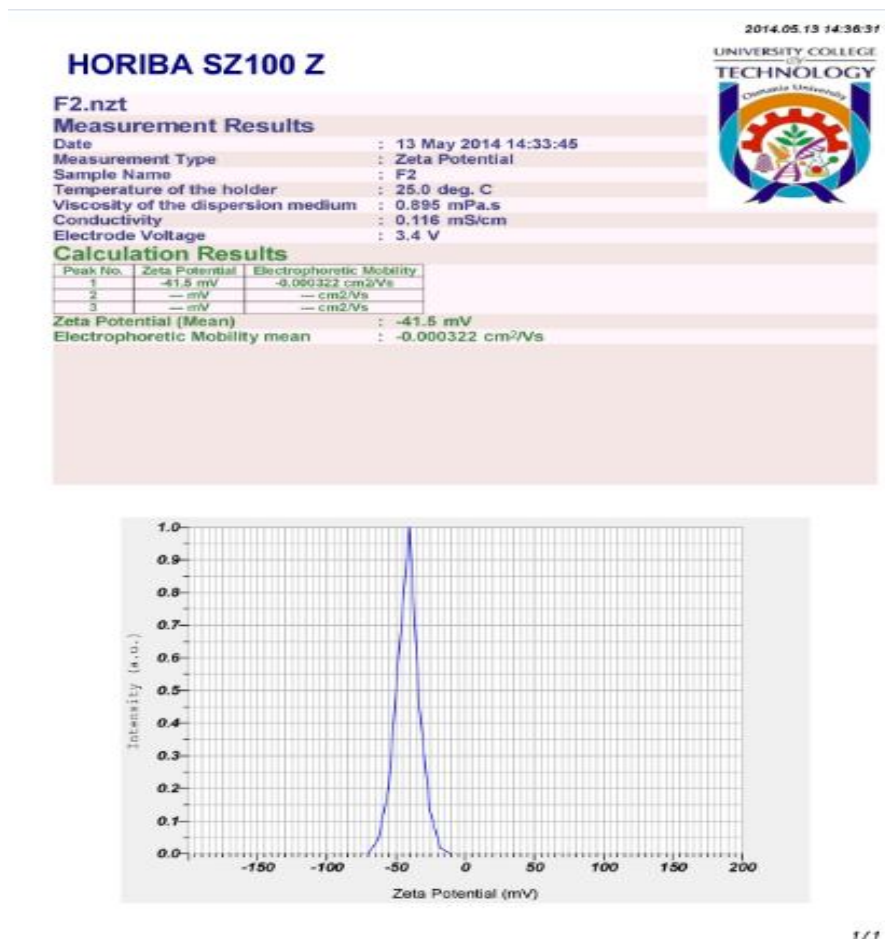


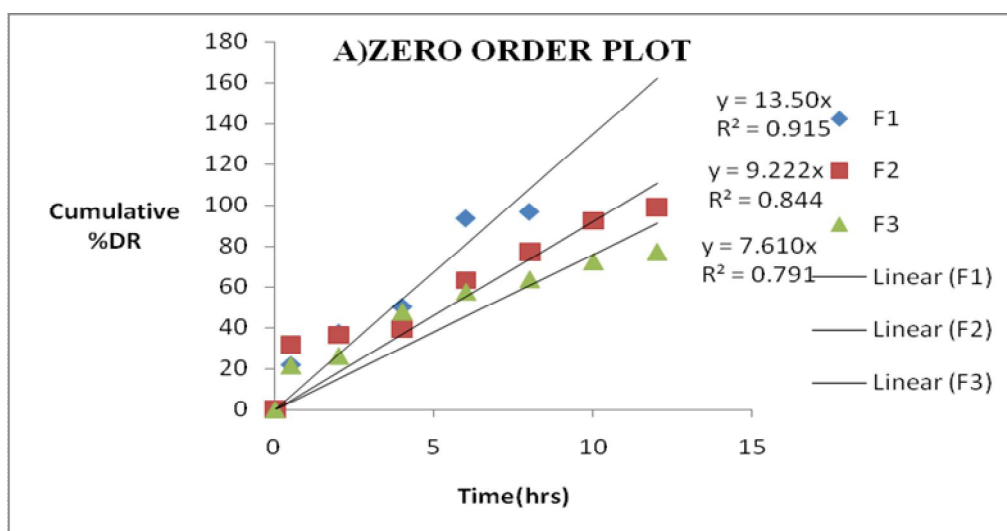
Fig.4- Zeta potential of Aspirin loaded ethyl cellulose nanoparticles by solvent evaporation technique for F2 formulation.

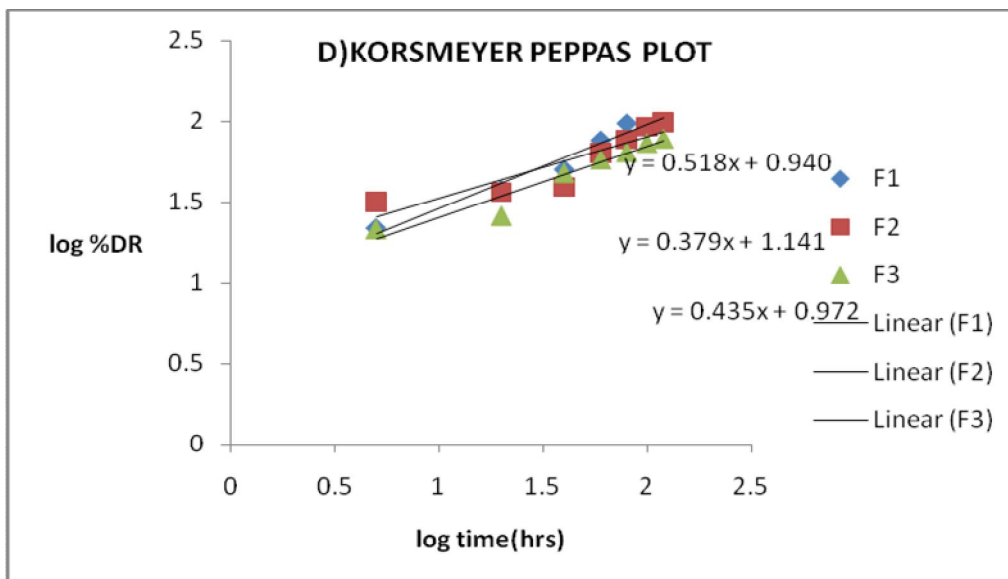
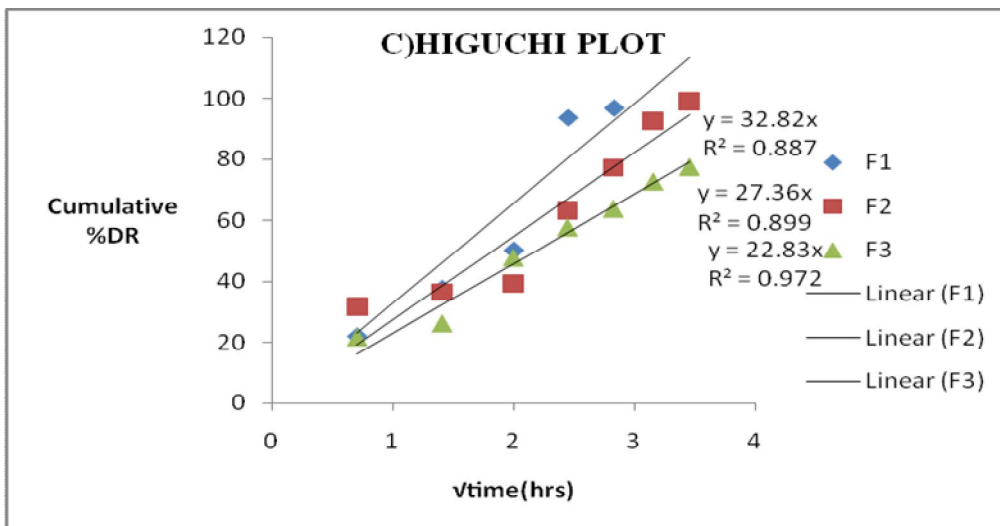
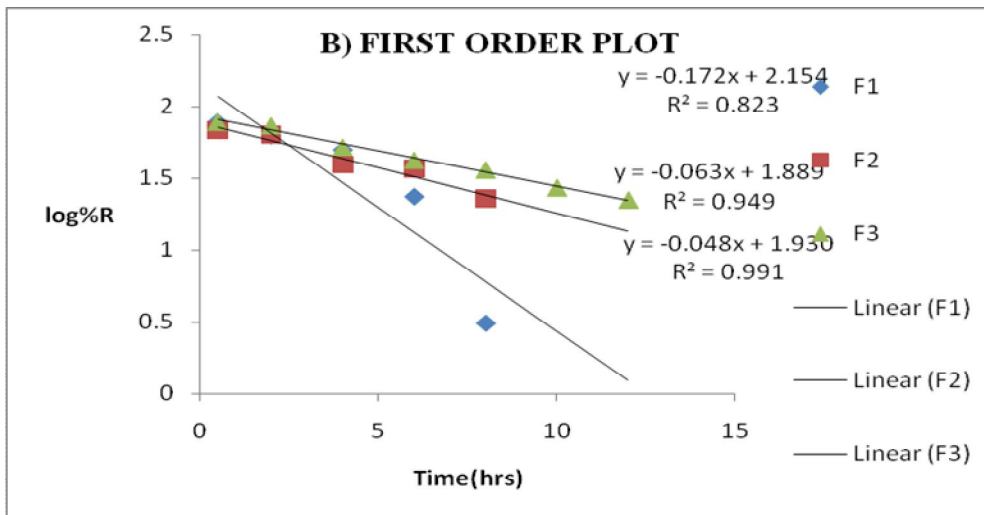
Invitro Drug Release Studies: The invitro release data of the two formulations were compared. In F1 formulation the drug release was 96.2% continued up to 8hrs In F2 formulation the sustained release nature was further improved up to 12hrs, 99.2% of drug has been released from F2 formulation. In case of F3 formulation 77.24% of drug has been released for a period of 12hrs.

In order to determine the order of the drug release and know whether the drug release is diffusion controlled or dissolution controlled and to determine the mode of diffusion. The drug release data was fitted for various kinetic models for Zero order, First order, Higuchi and Korsmeyer peppas plots for all the formulations are shown in graphs. From the plots the drug release follows first order kinetics and the drug release followed fickian diffusion for F2 formulation.

Parameters determined from the Invitro Release Studies performed on Aspirin loaded Ethyl cellulose nanoparticles:

Formulation	Zero Order Plot(R^2)	First order Plot(R^2)	Peppas Plot(n)	Higuchi Plot (R^2)
F1=(1:1)	0.915	0.823	0.379	0.887
F2=(1:1.5)	0.844	0.949	0.518	0.899
F3=(1:2)	0.791	0.991	0.435	0.992





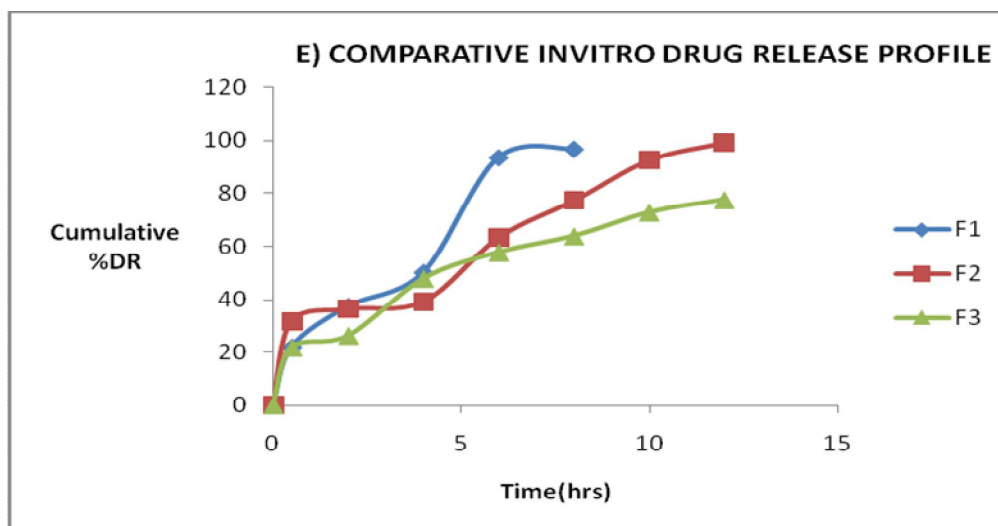


Fig.5 - Release kinetics of Aspirin loaded ethyl cellulose nanoparticles by solvent evaporation method of F1, F2 and F3 formulations. A) Zero order plot B) First order plot C) Higuchi plot D) Peppas plot and E) Comparative invitro drug release profile

DISCUSSION

In this present study Aspirin loaded ethyl cellulose nanoparticles were prepared by solvent evaporation method by using Tween 20 as an emulsifier agent and ethyl acetate as solvent. Three formulations were prepared by varying the concentrations of polymer. Each series of experiments were conducted to understand the influence of process parameters like solvent mixture, composition, concentration of the emulsifying agent and speed of stirring.

The effect of viscosity of polymer concentration on various parameters like yield, drug content, entrapment efficiency, loading capacity was compared. Entrapment efficiency and loading capacity of the formulations was found to be more for F3 formulation than F1 and F2 formulation. It was mainly because of the high concentration of the polymer. Invitro drug release studies were conducted by means of orbiter shaker. In F1 formulation the drug release was continued up to 8hrs indicating its sustain release nature and good drug releasing properties. In F2 formulation the sustained release nature was further improved up to 12hrs, 99.2% of drug has been released from F2 formulation. In case of F3 formulation 77.24% of drug has been released. On comparison even though sustained release property has been improved, the drug release was decreased in F3 formulation. This was mainly because of the high concentration of the polymer. As the polymer concentration increased the viscosity of the organic phase also increased which is mainly responsible for the sustained release nature

of the polymer. But the polymer at higher concentration is not supporting the complete release of the drug from F3 formulation.

CONCLUSION

From the results it was concluded that F2 formulation with Drug: Polymer ratio of 1:1.5 was considered to be the best formulation for the preparation of Aspirin loaded ethyl cellulose nanoparticles by solvent evaporation technique.

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