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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF ENALAPRIL MICROSPHERES

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ABSTRACT

The present work was carried out to prepare and evaluate microspheres drug delivery system of Enalapril of using various polymers in various proportions. The following experimental protocol was therefore designed to allow a systemic approach to the study. In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.The development process of oral controlled drug delivery system is precluded by several physiological difficulties, such as an ability to restrain and localize the drug delivery system within desired region of the gastrointestinal tract and the highly variable nature of gastric emptying process8. Therefore the scientific framework required for the successful development of an oral drug delivery system consists of basic understanding of (i) physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug; (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed. In vitro dissolution studies are performed for Prepared Microspheres by using modified dissolution method apparatus with solvent 0.1% SLS solution. The dissolution rate was found to increase linearly with increasing concentration of polymer. The optimized formulations are (F6). Formulation have recorded drug 98.9 respectively in 12 hrs. analyse the drug release mechanism the in-vitro release data was fitted into various release equations and kinetic models zero order, first order, Higuchi and Korsmeyer Peppas model.

INTRODUCTION

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity or targeting the delivery of drug to a tissue. A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics[1].

Microspheres are defined as particulate dispersions or solid particles with a size in the range of 10-1000mcm. The drug is dissolved, entrapped, encapsulated or attached to a microspheres matrix[2]. Depending upon the method of preparation, microspheres or microcapsules can be obtained. Microcapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while Microspheres are matrix systems in which the drug is physically and uniformly dispersed[3].

In recent years, biodegradable polymeric Microspheres, particularly those coated with hydrophilic polymer such as poly(ethylene

glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes[4].

The major goals in designing microspheres as a delivery system are 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[5]. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability[6].

On the other hand, polymeric Microspheres offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties[7]. The advantages of using microspheres as a drug delivery system include the following;

Particle size and surface characteristics of Microspheres can be easily manipulated to achieve both passive and active drug targeting after parenteral administration[8]. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects[9].

Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance[10-12].

Materials: Enalapril was procured from A-Z Pharmaceuticals, Mumbai, India. HPMC, Calcium Carbonate, Sodium Bicarbonate, Ehthyl Cellulose were purchased from S.D. Fine Chemicals Ltd, India.

Methods:

Preformulation Studies

The word preformulation is self explanatory, meaning the scientific study that is performed before formulating a dosage form to understand the properties of drug and its interaction with excipients. Preformulation testing is the first step in the rational development of dosage forms of the drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms[13].

FT-IR Spectroscopy

Infrared (IR) spectral matching studies are employed to detect any possible interaction between drugs and the polymers or excipients. In the present, the compatibility between the drug Enalapril with different polymers and were evaluated with help of FTIR. The samples were scanned from 4000 to 400 cm -1in FT-IR spectrophotometer. Similarly the IR spectra of all the individual drug and prepared nanocrystals were also recorded. Physical appearance of the samples and appearance or disappearances of peaks in the spectra were observed to access any possible physical and chemical interaction[14].

Differential Scanning Calorimetry (DSC)

The thermal properties92 of the lyophilized powder samples were investigated with a DSC-41 apparatus (Shimadzu, Japan). The scanning temperature for each lyophilized powder sample was set from 25 to 200˚C with a heating rate of 10 ˚C/min. 10 mg of each sample was analyzed in an open aluminium pan and magnesia was used as reference. In order to evaluate the internal structure modifications after nanosizing process, thermal analysis was performed on Enalapril & the excipients[15].

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to characterize the particle morphology of the unprocessed drug as well as the fabricated drug Microspheres. A small fraction of each drug powder sample was fixed on a double-

sided conductive carbon tape and sputter-coated with 5 nm of a Pt–Pd alloy. Micrographs were obtained on a Zeiss DSM 982 Field Emission Gun Scanning Electron Microscope (Carl Zeiss AG, Germany).

Particle size distribution

The size of drug Microspheres was measured immediately after precipitation by dynamic laser light scattering (Microspheres size analyzer, Malvern). Before analysis, the drug suspension was diluted by purified water to 0.2 mg/ml. Graphic mean size (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis.

Method of Preparation

Enalapril drug microspheres were prepared by Emulsion followed by Solvent evaporation method and different types of polymers were used[16-17].

Preparation of Polymer and drug Solution

- ❖ Weighed the required amount of polymer and placed in a dry beaker.
- ❖ Required quantity of solvent (methanol) was taken in a measuring cylinder.
- ❖ Now, methanol was added to the beaker containing polymer slowly.
- ❖ Then, it was stirred with glass rod continuously to form polymer solution.
- ❖ Add accurately weighed amount of Enalapril 20mg and mix thoroughly.

Preparation of aqueous solution

Weighed the required amount of SLS 1g in 1000mL of water and mix then kept a side for removing air bubbles

A. Simple Mixing

Enalapril Microspheres were prepared by using Emulsion followed by solvent evaporation technique as an effective technology in preparation of microspheres. Polymers dissolved in chloroform then 10mg of drug of Enalapril was completely dispersed in polymer solution and 1 % SLS solution add to this under stirring at 400-500 rpm up to 20min then beaker placed into probe sonicatoe for 15min after sonication kept for continuous stirring by magnetic stirrer and temperature was maintained at 10˚c by using ice bath. Microspheres occurred immediately upon mixing.temperature was maintained at 10˚c by using ice bath. Microspheres occurred immediately upon mixing.

Evaluation Parameters

Assay

Weigh accurately about 0.3 g of Enalapril dissolve in exact 40 mL of methanol and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration, Endpoint Detection Method in Titrimetry). Each mL of 0.1 mol/L sodium hydroxide VS = 35.419 mg of C16H13Cl2NO4. Enalapril, when dried, contains not less than 99.0% and not more than 101.0% of Enalapril.

Swelling study

The swelling ration of prepared tablets were measured by gravimetrically by weighing the tablets prior to and after swelling[18]. The microspheres were weighed and then placed in suitable buffer solution. The wet weight of the swollen microspheres were determined by blotting them with filter paper to remove moisture adhering to the surface, immediately followed by weighing on electronic balance. All experiments were done in triplicate. The swelling ration of the tablets were calculated from the following equation

Swelling Ratio= ((W_t-W_0))/W_0

Where, Wt is the weight of the microspheres at appropriate intervals

W0 is initial weight of the microspheres

Drug loading & Encapsulation Efficiency

The prepared Naproxen microspheres were subjected to preliminary characterization such as drug loading and encapsulation effeciency. The evaluated parameters were within the acceptable range for all the formulations. F6 formulation shows maximum % encapsulation efficiency compared to other formulations due to rate of more drug loading is more in F3 formulation respectively. The rate of polymer ratio also influence on drug loading and encapsulation efficiency[19].

Dissolution Test

The *in-vitro* dissolution studies[20-21] were carried out using dissolution test apparatus containing 900 mL of microspheres solution. The studies were carried out for 12 hr. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.05 °C. Basket rotation was adjusted to 75 rpm. At definite intervals, 10 ml samples were withdrawn and analyzed spectro photo metrically at 209 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was

replaced into the dissolution flask to maintain the sink condition

RESULTS AND DISCUSSIONS

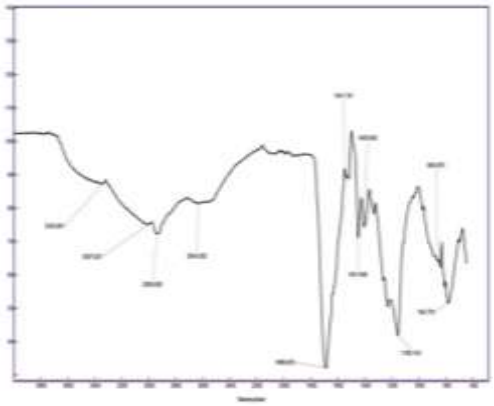


Fig. 1. IR spectra of Enalapril

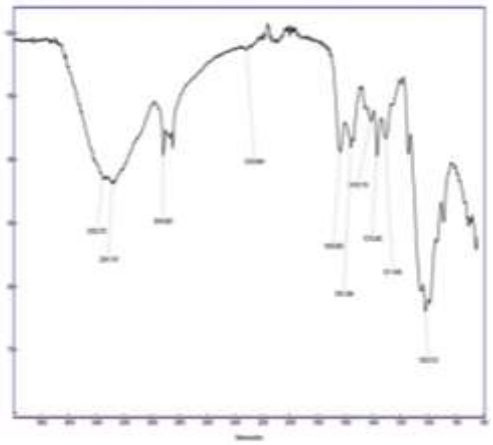


Fig. 2. IR spectrum of HPMC

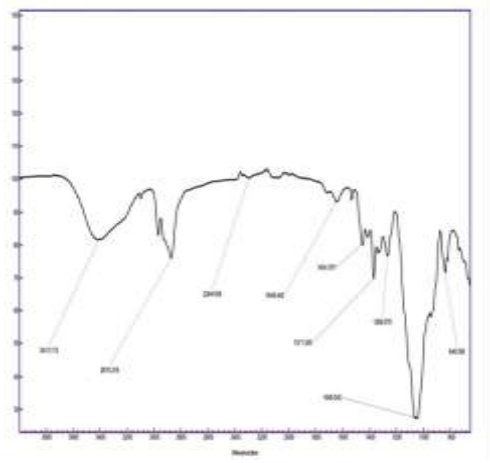


Fig. 3. IR spectrum of F6

DISCUSSION

The present investigation was under taken to formulate Enalapril microspheres Using various polymers HPMC, Ethyl Cellulose, PEG6000 SLN were prepared along with other additives. Solvent Evaporation method was used for the preparation of Microspheres. A total number of 9 formulations were prepared and evaluated.

Particle Size Analysis

The particle size analysis for the Enalapril fabricated microspheres using various polymers revealed that presence of stabilizer influenced the particle size. , Graphic mean (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis. Graphic Mean provides a less coarse-particle weighted mean particle size than mean diameter of the volume distribution. While it includes the median value, it can provide a different and possibly better control value since both small particles and large particles are included in the calculation. Smaller graphic mean (Mz) values indicating smaller particles were found when GMS (F6) was used at 10%. The Mz value for the formulation F6 was found maximum (209 nm) indicating bigger particles. The concentration of polymer found to influence the particle size. Increasing the concentration of most of the studied polymers from 6 to 10% decreased the particle size.

***In vitro* dissolution**

In vitro dissolution studies are performed for Prepared Microspheres by using modified dissolution method apparatus with solvent 0.1% SLS solution. The dissolution rate was found to increase linearly with increasing concentration of polymer. The optimized formulations are (F6). Formulation have recorded drug 98.9 respectively in 12 hrs.

Drug Release Kinetics

In vitro drug release data of all the Sustained formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table and plots shown in figures 7-9. From the above data, it can be seen that all the formulations have displayed first order release kinetics ('r' values in the range of 0.900 to

0.965). From Higuchi and Peppas data, it is evident that the drug is released by non-fickian diffusion mechanism (n<0.5). From the kinetic data of factorial formulations (table 2), it is evident that F6 formulation has shown drug release by zero order kinetics. The values of 'r' for Higuchi's equation of formulation. This data reveals that drug release follows non-Fickian diffusion mechanism Higuchi model.

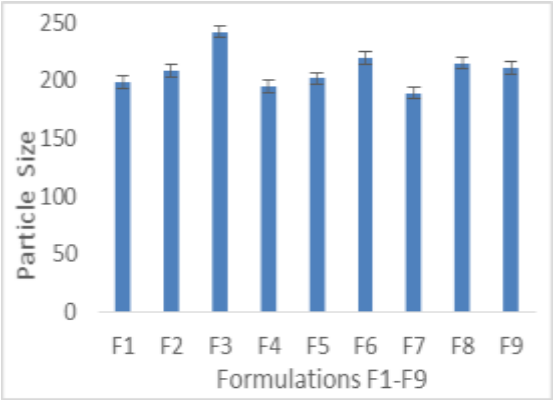


Fig. 4. Particle Size ranges of F1-F9

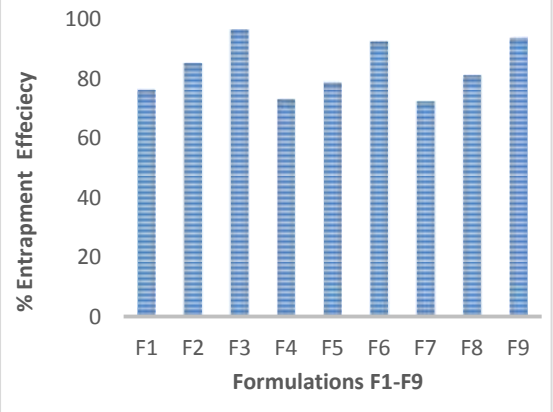


Fig.5. Entrapment Efficiency of F1-F9

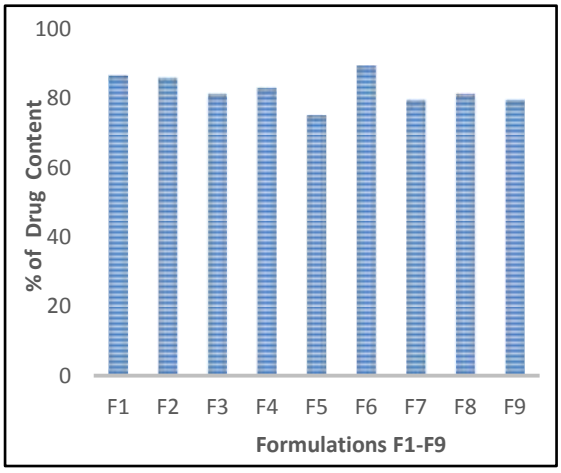


Fig.6. % of Drug Content of F1-F9

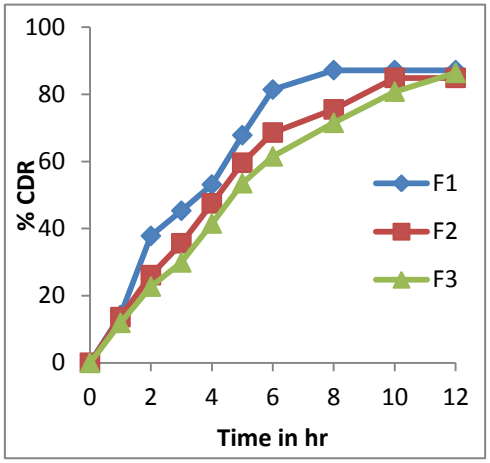
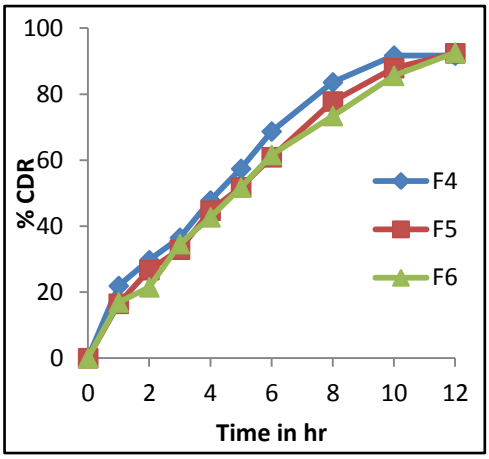


Fig.7. In-vitro drug release of F1-F3

Fig.8. *In-vitro* drug release of F4-F6



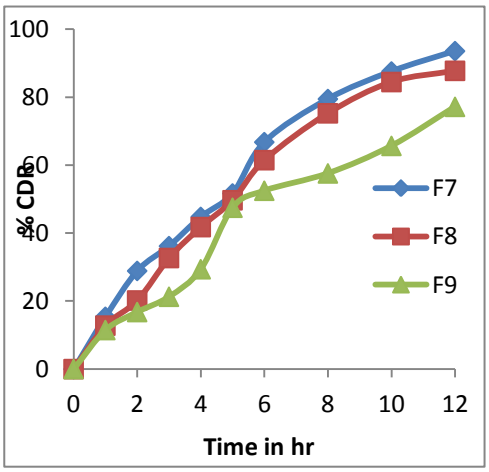


Fig 9: *In vitro* drug release of F7-F9

Table 1. Formulation of Enalapril Microspheres

Ingredients (mg)	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Enalapril (mg)	20	20	20	20	20	20	20	20	20
HPMC K4M	50	75	100	-	-	-	-	-	-
HPMC K 100	-	-	-	50	75	100	-	-	-
Ethyl cellulose	75	150	225	-	-	-	50	75	100
Dichloromethane	10	10	10	10	10	10	10	10	10
Methanol (ml)	10	10	10	10	10	10	10	10	10
2% SLS (ml)	50	50	50	50	50	50	50	50	50

Table 2. Kinetic analysis of dissolution data

Formulation code	Zero order	First order	Higuchi	Peppas	
F6	r^2	r^2	r^2	r^2	n
	0.99	0.8	0.96	0.99	0.8

CONCLUSIONS

Success of the In vitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance. From the results, formulation F9 containing Enalapril Microspheres using combination of polymers evolved as the optimized formulation and it releases more than 98.9% drug in 24hrs. IR spectroscopic studies indicated that there are no drug-excipient interaction in the optimized formulation. The optimized formulation F9 can be considered as a promising Sustained drug delivery system of Enalapril Microspheres providing nearly zero order drug release over a period of 12 hr.

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