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Vol. 8(9), pp. 246-258, 8 March, 2014
DOI: 10.5897/AJPP2014.4006
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Preparation of magnetic microspheres of mesalamine by phase separation emulsion polymerisation technique

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Received 13 January, 2014; Accepted 20 February, 2014

The study involved magnetic microspheres of mesalamine prepared by phase separation emulsion polymerization (PSEP) method technique. Magnetic microspheres were prepared by PSEP method to target them to the colon. Three polymers namely Eudragit S 100, ethylcellulose and chitosan were used for the preparation of magnetic microspheres. Magnetite content and entrapment of mesalamine was evaluated. Eudragit S 100, ethylcellulose and chitosan were used as polymers. Fourier transform infrared spectroscopy (FTIR) spectrum of drug and polymer was taken to visualize the compatibility of drug and polymer. Scanning electron microscope (SEM) images show the uniformity and particle size of the microspheres formed. The *in vitro* release study was carried out in phosphate buffer pH 6.8. The various results obtained were fit into the mathematical models and the Higuchi model was found to be most suitable for the formulations. Chitosan magnetic microspheres prepared by phase separation emulsion polymerization were found to be best in all the evaluation parameters (practical yield, magnetite content, magnetic responsivity of microspheres, particle size, *in vitro* release studies). They contain maximum magnetite content which is the utmost feature for the magnetic microspheres. Microspheres can be targeted by the external magnetic field applied due to magnetite entrapped. Thus toxicity and reticuloendothelial clearance can be minimized.

Key words: Chitosan, Eudragit S 100, ethylcellulose, magnetic, phase separation emulsion polymerization (PSEP)

INTRODUCTION

Magnetic microspheres play a compromising role in controlled and novel drug delivery. Polymeric controlled drug delivery systems have evolved as one of the most attractive areas in drug delivery research. The drug release is controlled by properties of the polymer-drug system and also by other factors like pH, enzymes etc (Khar and Diwan, 2001). Despite several advantages offered by the controlled drug release, one important problem pertinent to the entire field is that all the systems so far developed give release rates that are constant or decrease with time. Increased delivery on demand will be very beneficial in certain situations. This increased delivery

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on demand can be achieved by using external feedback control systems such as magnetic control.

Tyle (1988) proposed the concept of magnetic drug targeting. Magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body. Magnetic microsphere is a newer approach in pharmaceutical field. Traditional radiation methods use highly penetrating radiation that is absorbed throughout the body, thus causes harm to the body. Its use is limited by toxicity and side effects. The aim of the specific targeting is to enhance the efficiency of drug delivery and to reduce the toxicity and side effects. Localization of the drug to the localised disease site is the important feature of this delivery system. This larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug (Vyas and Khar, 2004).

Techniques used in preparation of magnetic microspheres

Given the enormous advantage of multiparticulate system over single-unit oral dosage forms, extensive research has focused recently on refining and optimizing existing techniques for the formulation of magnetic microspheres as well as on the development of novel manufacturing approaches that use innovative formulation and processing equipment (McBride et al., 2013). Magnetic microspheres are prepared mainly by two methods namely: phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE), by using mixture of water soluble drugs (for lipophilic drugs, along with the dispersing agent) and 10 nm magnetite (Fe_3O_4) particles in an aqueous solvent of matrix material, which are about 1.0 µm in size that is small enough to allow them to be injected intravenously without any occlusion in the micro vascular. These microspheres are nontoxic and nonreactive with blood components (Salim et al., 2010). They can be stabilized by heating or chemically cross linking albumin to achieve a wide spectrum of drug release kinetics. These are infused into an artery, supplying a given target site. A magnet of sufficient field strength is then placed externally over the target area to localize the microspheres at the capillary bed in this region. In order to localize microspheres in a fast-moving arterial system, generally greater field strength is required. There are mainly two techniques, which are commonly employed for microspheres preparation (Ishida et al., 1983). Preparation of magnetic microspheres by phase separation emulsion polymerization method is shown in Figure 1.

MATERIALS AND METHODS

Mesalamine was obtained as a gift sample from IPCA Laboratories Ltd. Chitosan (Sigma Aldrich), Ethylcellulose (CentralDrugHouse, NewDelhi), Eudragit S 100 (Alphachemika), goethite (Shree Surya minerals), nitrogen gas (Deluxe industrial gases, pune). All the reagents were of analytical grade.

Preparation of magnetite

Figure 2 shows the procedure for preparation of magnetite (Kahani et al., 2009).

Formulation of magnetic microspheres

Drug polymer interaction studies

Compatibility of drug with polymers was checked by Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies. The FTIR spectrum of mesalamine is shown in Figure 3. Figures 4, 5, 6 and 7 show that there is no interaction between drugs and polymers used. DSC studies were done to estimate the compatibility. Melting point of the drug was found to be 280°C. Microspheres were prepared by phase separation emulsion polymerization method. Several batches of magnetic microspheres were prepared in different drug: polymer ratio using three polymers separately namely chitosan, eudragit S 100, ethylcellulose (Kakar et al., 2013). The scheme for preparation has been summarized in Table 1.

Characterization of magnetic microspheres

Determination of percentage yield

Magnetic microspheres prepared by PSEP were dried and weighed (Lalit and Tapar, 2011).

Percentage yield = Practical yield / Theoretical yield × 100

Figure 8 and Table 2 shows the representation of percentage yield.

Flow properties of magnetic microspheres

Carr's index, angle of repose and Hausner's ratio were evaluated by fixed funnel method and compared with the standard values (Table 3) (Vimal et al., 2009).

Drug content and entrapment efficiency

Weighed amount of microspheres were digested with phosphate buffer and analyzed for the drug content (Kahani et al., 2009). Figure 9 and Table 4 shows the entrapment efficiency.

Entrapment efficiency = Experimental drug content / Theoretical drug content × 100

Particle size determination

Particle size was determined by SEM. Particle size is represented in Table 5. SEM pictures are shown in Figures 10, 11 and 12.

Determination of magnetite content

Determination of magnetite content in prepared magnetic microspheres was conducted by employing a conventional titrimetric method using thiosulphate and potassium iodide for quantitative analysis. It was observed that the entrapment of magnetite increased

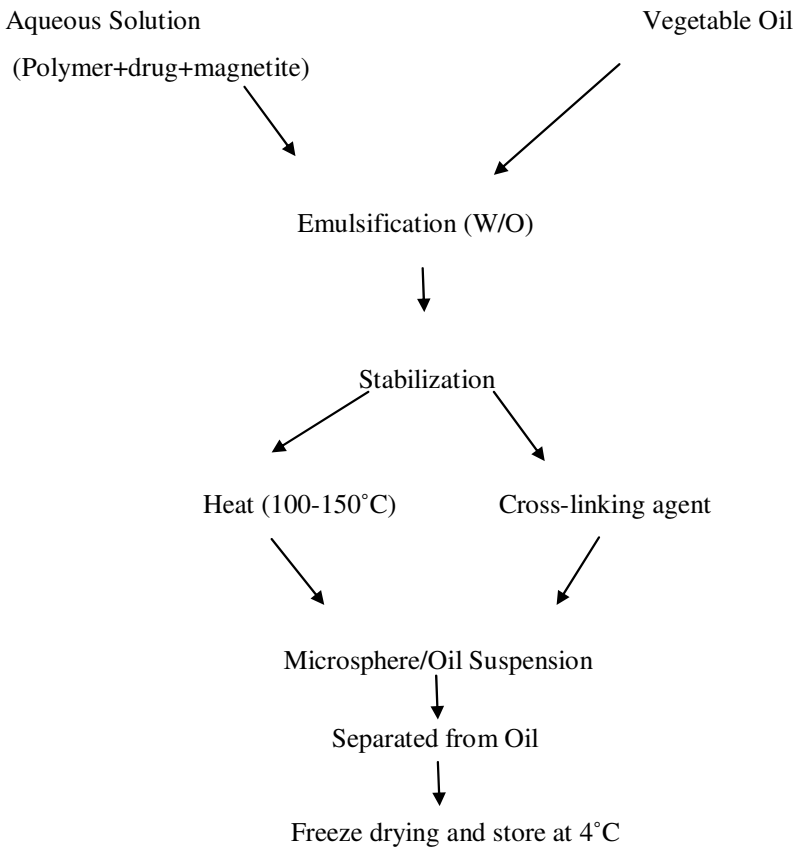

Figure 1. Preparation of magnetic microspheres by phase separation emulsion polymerization.

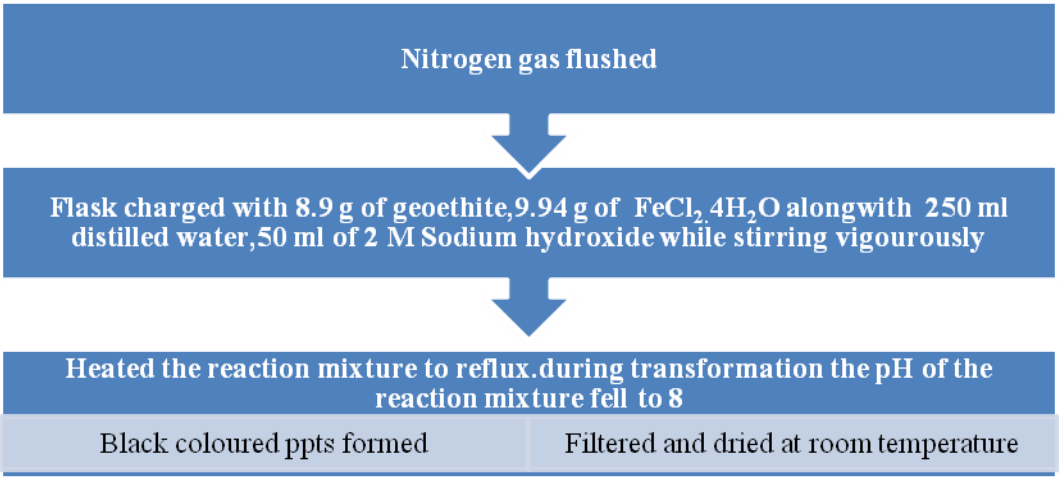

Figure 2. Procedure for preparation of magnetite.

with increase in concentration of polymer added in consecutive formulations. Maximum magnetite content was found for formulation F 3 (Vyas et al., 2013). Representation of percentage magnetite content is shown in Figure 13 and Table 6. Each ml of 0.1 N sodium thiosulphate is equivalent to 0.005585 g of ferric ion.

Dissolution studies

The dissolution studies were carried out in basket type apparatus. Phosphate buffer pH 6.8 was used. Accurately weighed 100 mg microspheres were introduced in phosphate buffer solution 900 ml.

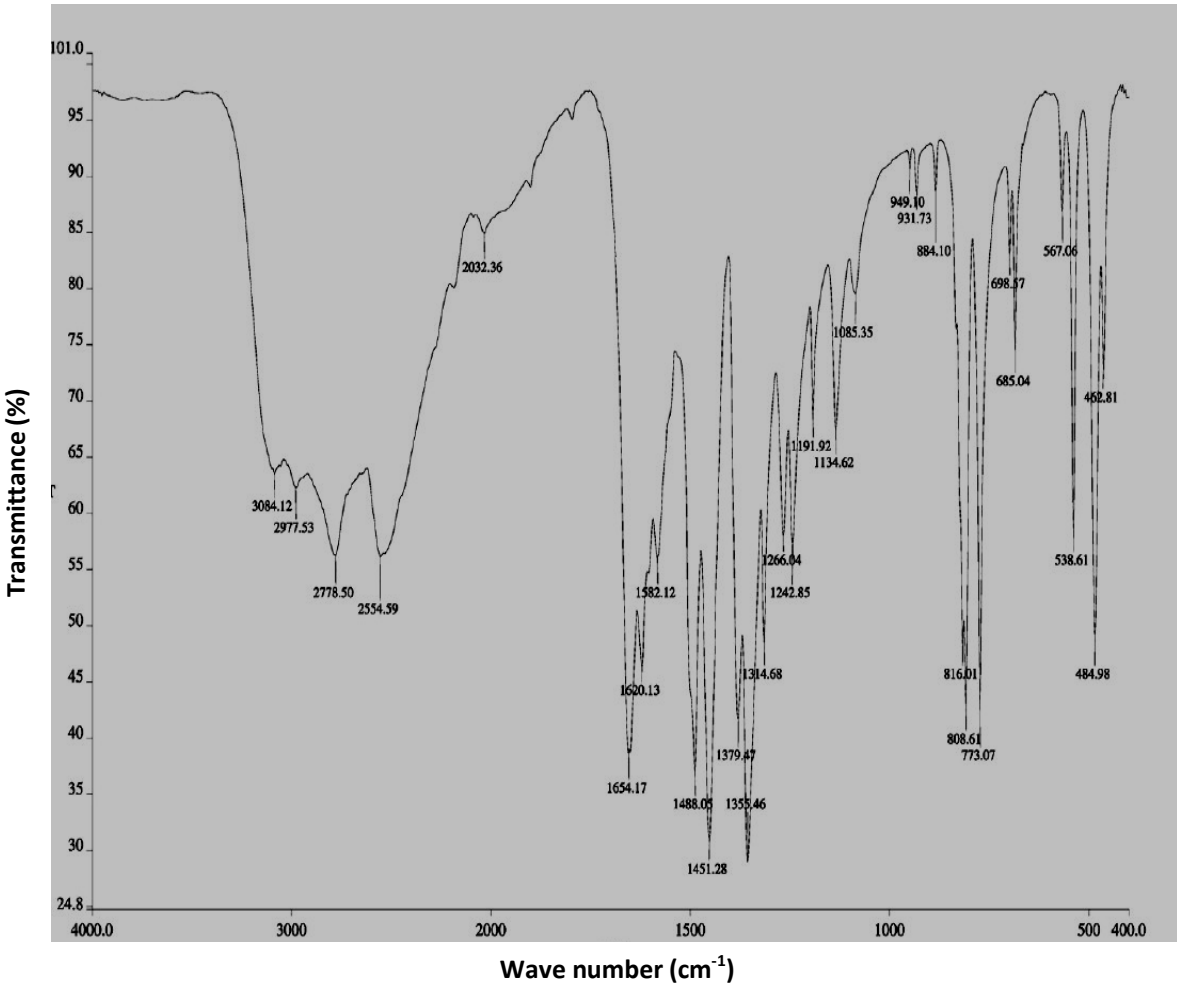

Figure 3. FTIR spectrum of mesalamine.

Aliquots were taken at different time intervals and percentage drug release analysed by UV Spectrophotometer at 230 nm (Zhang et al., 2007). Figure 14 represents the comparison of dissolution studies conducted on formulations F1, F2 and F3. Table 7 shows the percentage release of formulations.

In vitro study of release kinetics of magnetic microspheres

In the present study the raw data obtained from *in vitro* drug release study was analyzed wherein data were fitted to different equations in kinetic models to study the release kinetics of the optimized formulation. The kinetic models used were zero order, first order, Higuchi's equation, Hixon Crowell and Korsemeyer Peppas model. F 3 formulation best suits Higuchi model.

Zero order release kinetics

The zero order graphs were plotted between % cumulative drug release (CDR) versus time and are presented in Figure 15.

First order release kinetics

The first order graphs was plotted between log cumulative percent-tages of drug remaining versus time and are represented in Figure 16.

Higuchi model release kinetics

The Higuchi model graph was plotted between % cumulative drug release (CDR) versus square root of time and are shown in Figure 17.

Korsemeyer Peppas model release kinetics

The Korsemeyer Peppas model graph was plotted between log of time versus % cumulative drug release (CDR) and is shown in Figure 18.

Hixon Crowell model

The Hixon Crowell model graph was plotted between time vs. cube root of amount remaining and is shown in figure 19.

RESULTS

Magnetic microspheres could be better retained due to its

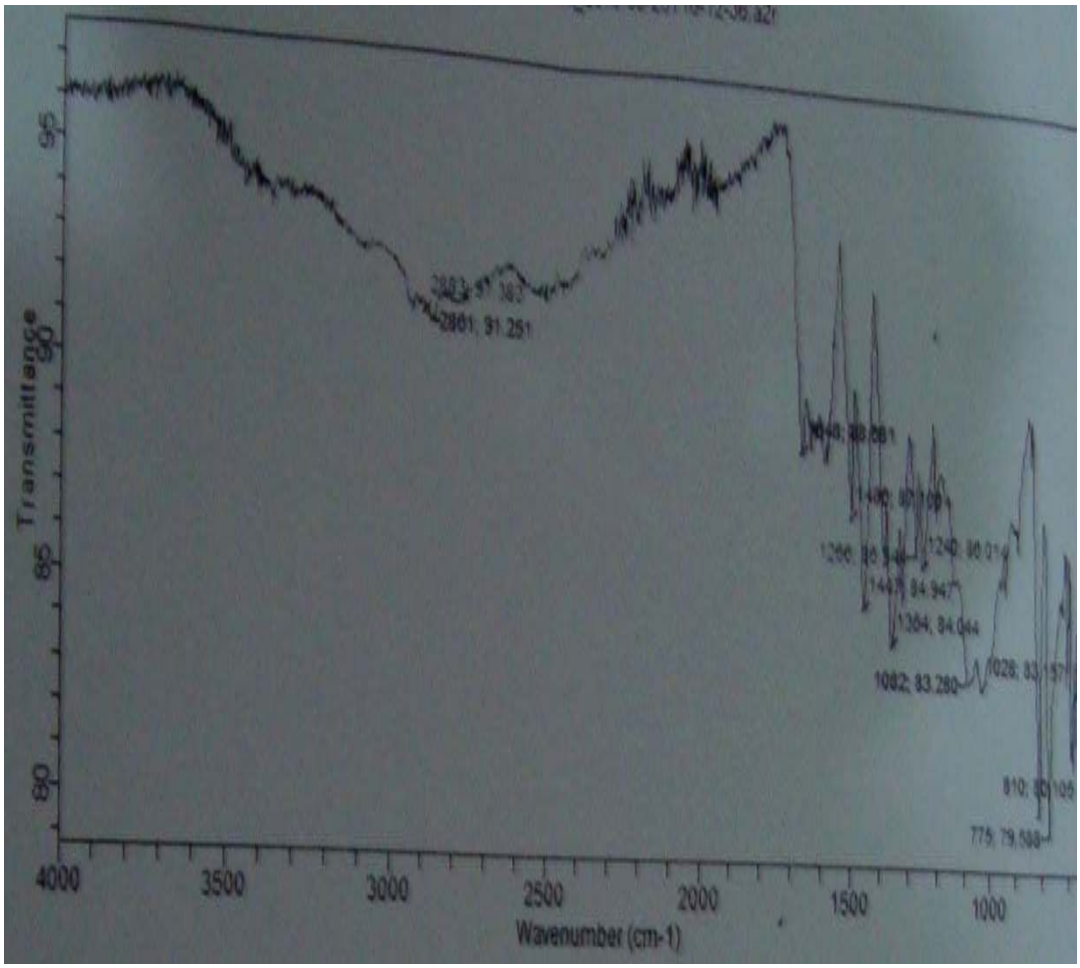

Figure 4. FTIR spectrum of physical mixture of chitosan and mesalamine.

Table 1. Composition of Magnetic microspheres.

Formulation code	Magnetite (mg)	Polymer (mg)	Drug (mg)	Polymer: Drug ratio	Method
F1	50	Chitosan (125)	125	1:1	PSEP
F2	50	Chitosan (84)	166	1:2	PSEP
F3	50	Chitosan (63)	187	1:3	PSEP
F4	50	Ethylcellulose (125)	125	1:1	PSEP
F5	50	Ethylcellulose (84)	166	1:2	PSEP
F6	50	Ethylcellulose (63)	187	1:3	PSEP
F7	50	Eudragit (125)	125	1:1	PSEP
F8	50	Eudragit (84)	166	1:2	PSEP
F9	50	Eudragit (63)	187	1:3	PSEP

more magnetite content. Chitosan microspheres were found to be best. The better sustained release was found for formulation F3.

1. 5-ASA was found to be compatible with chitosan, ethylcellulose, eudragit S 100 for the preparation of magnetic microspheres.

2. Solubility of 5-ASA was found to be optimum at neutral pH.

3. Chitosan is a most suitable and compatible polymer for the preparation of magnetically responsive polymers of 5-aminosalicyclic acid.

4. Percentage practical yield increases as the ratio of polymer to the drug added increased.

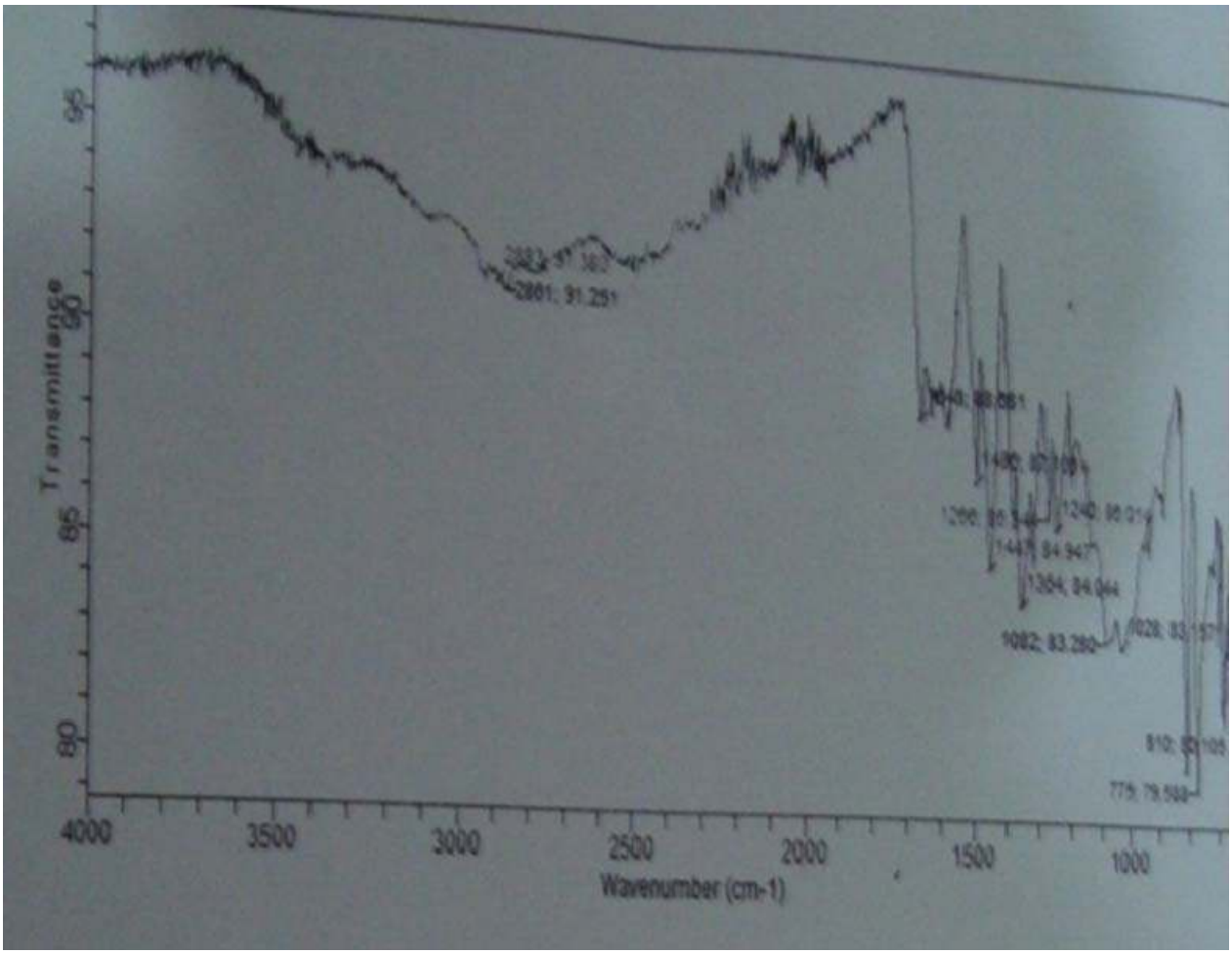

Figure 5. FTIR spectrum of physical mixture of ethylcellulose and mesalamine.

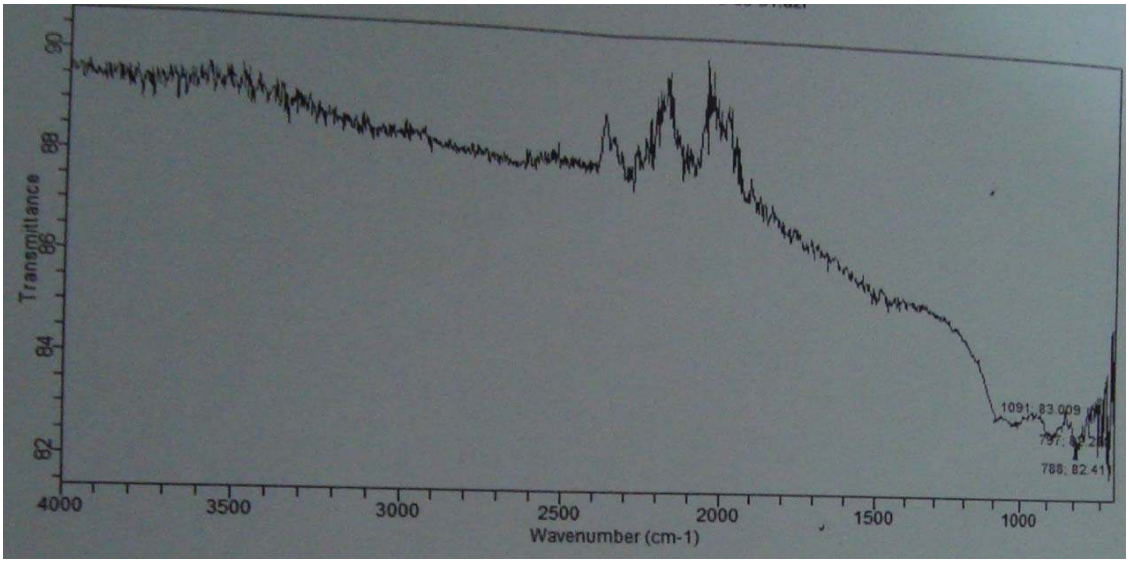

Figure 6. FTIR spectrum of physical mixture of Eudragit S 100 and mesalamine.

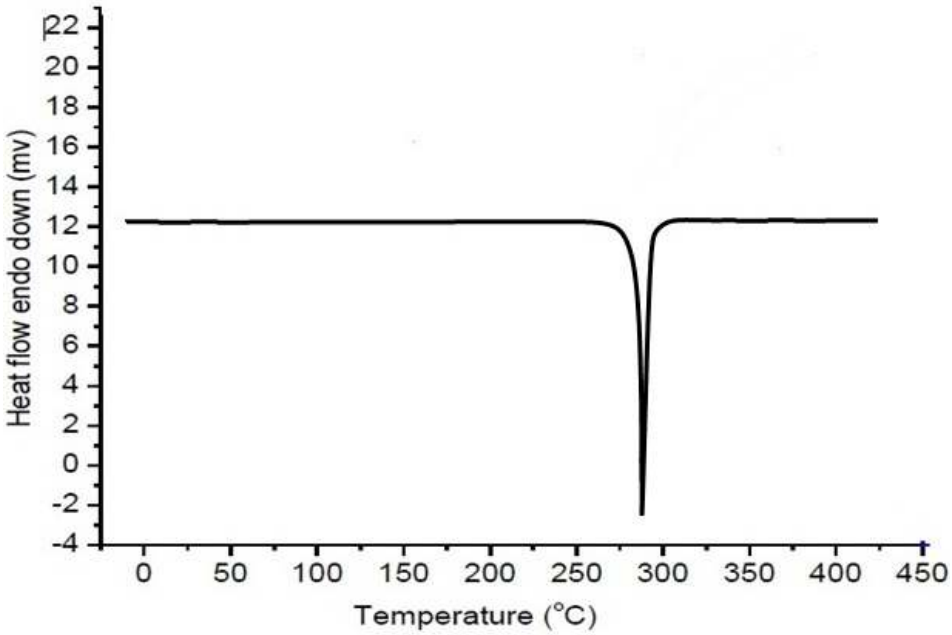

Figure 7. DSC thermogram of physical mixture of drug and chitosan.

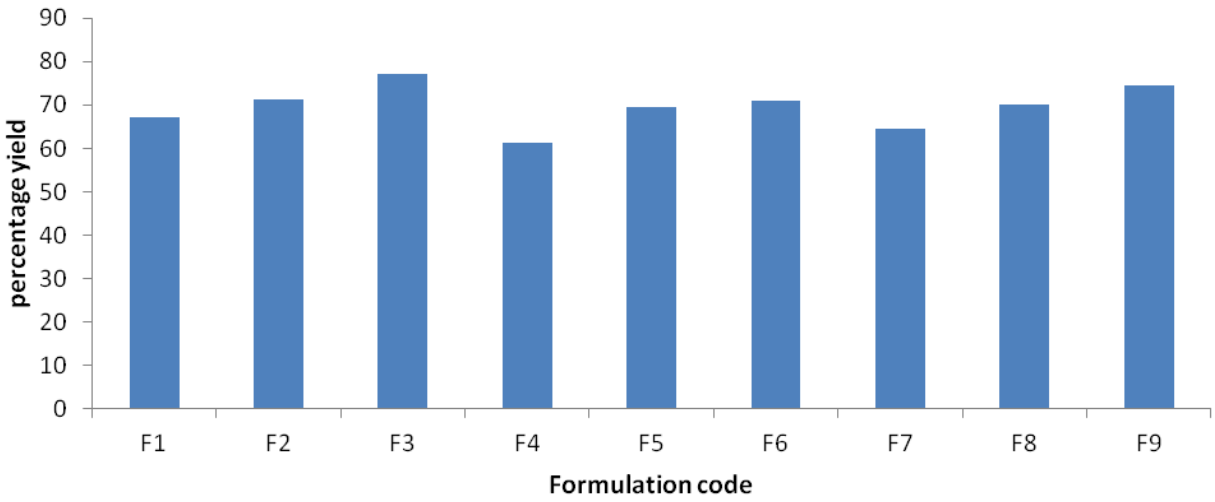

Figure 8. Percentage yield of formulations.

Table 2. Percentage yield of magnetic microspheres.

Formulation code	Percentage yield
F1	67.16
F2	71.14
F3	77.18
F4	61.27
F5	69.58
F6	71.09
F7	64.40
F8	70.23
F9	74.45

5. Particle size revealed that microspheres were in size ranging from 10 to 100 µm.
6. Increase in the amount of polymer added to the formulation increases the entrapment efficiency of both the drug and magnetite.
7. Increase in swelling ratio of microspheres was reported with increase in concentration of polymer with time.
8. The prepared magnetic microspheres of 5-amino-salicyclic acid were found to be magnetically responsive. The magnetic responsiveness increases with increase in entrapped magnetite content.
9. Overall, the curve fitting into various mathematical model

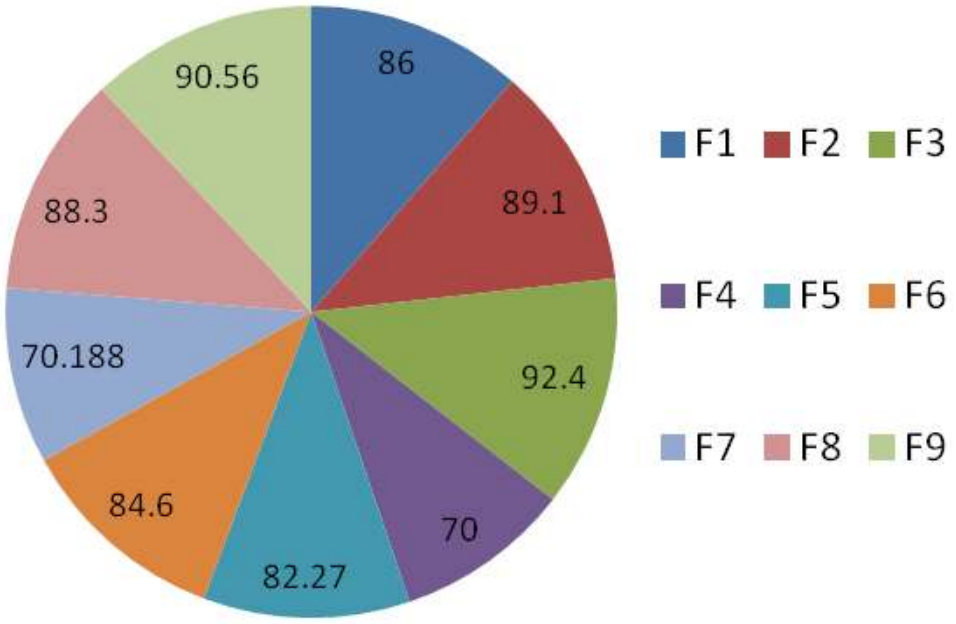

Figure 9. Entrapment efficiency of magnetic microspheres.

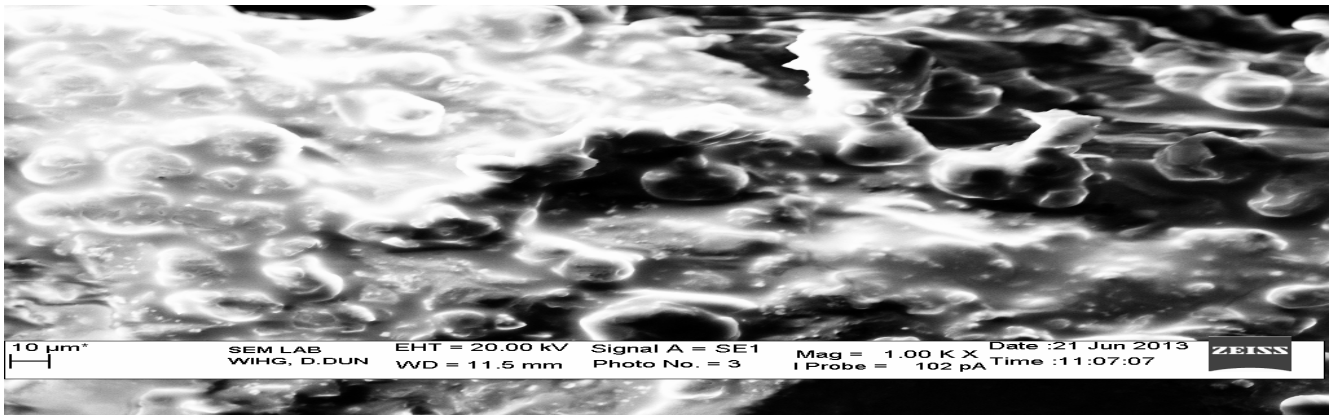

Figure 10. SEM image of F1 formulation.

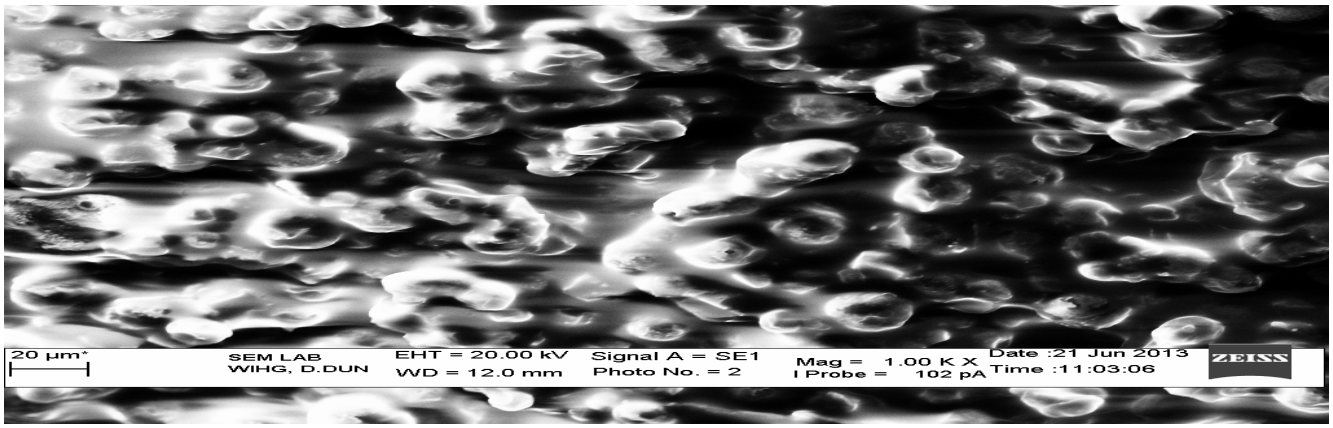

Figure 11. SEM image of Formulation F2.

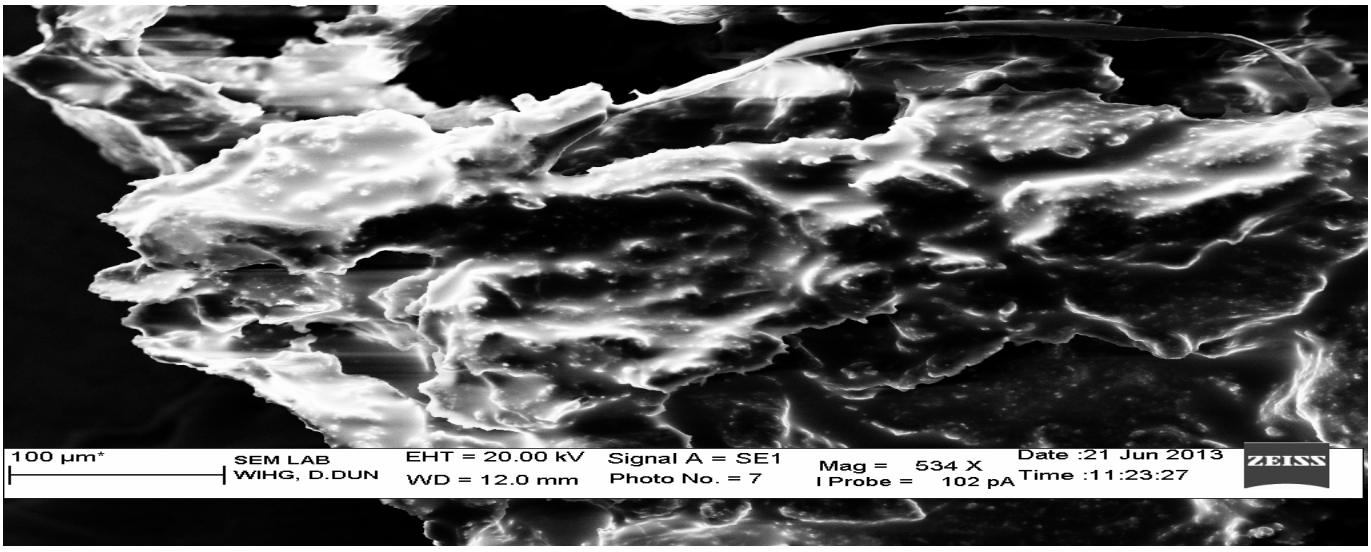

Figure 12. SEM image of formulation F3.

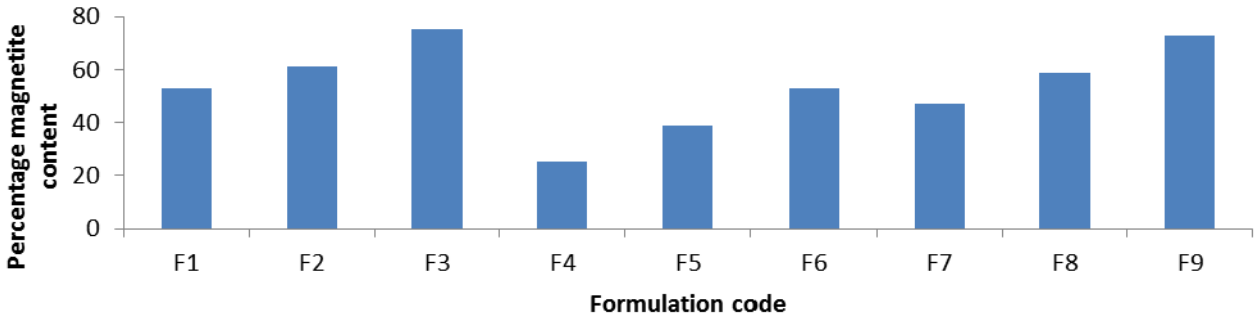

Figure 13. Percentage magnetite content entrapped.

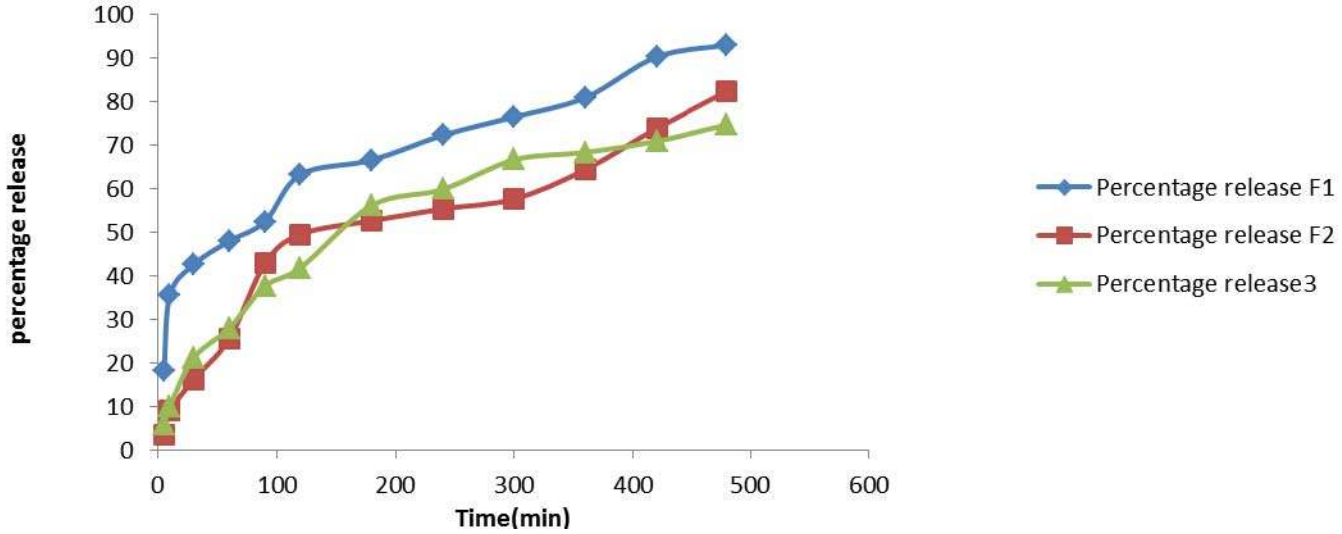

Figure 14. Comparison of dissolution study of formulations F1, F2 and F3.

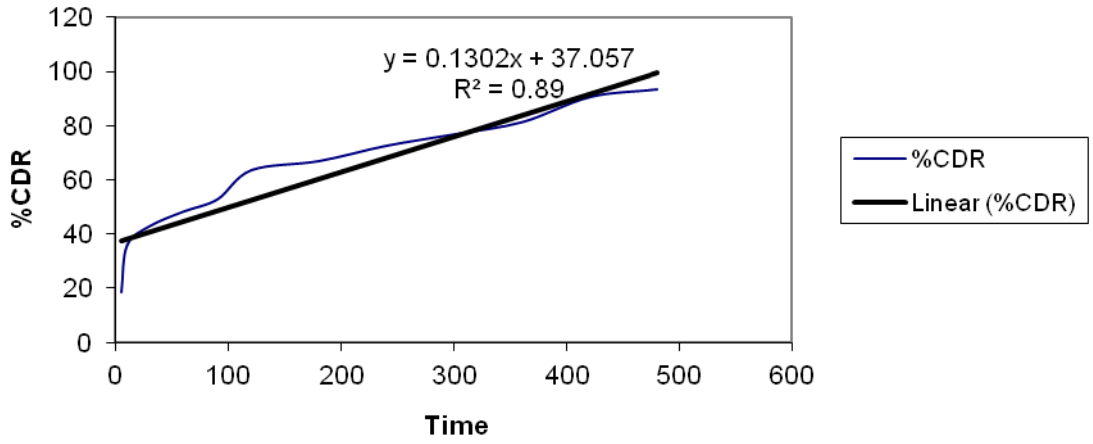

Figure 15. Zero order release kinetics of magnetic microspheres.

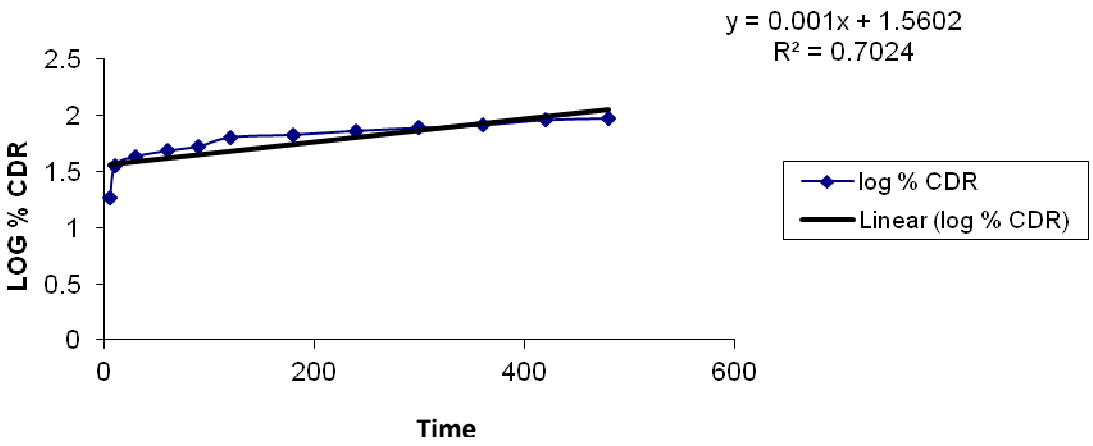

Figure 16. First order release kinetics magnetic microspheres.

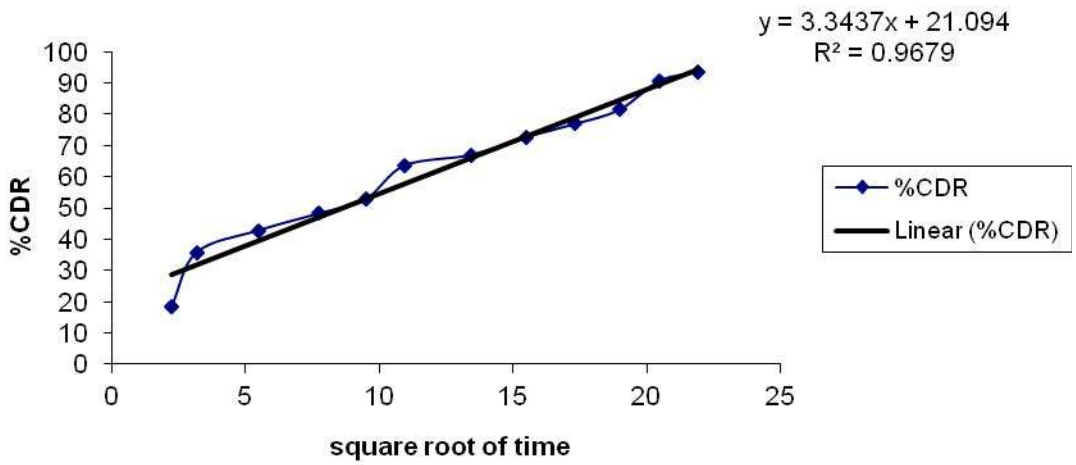

Figure 17. Higuchi model release kinetics of magnetic microspheres.

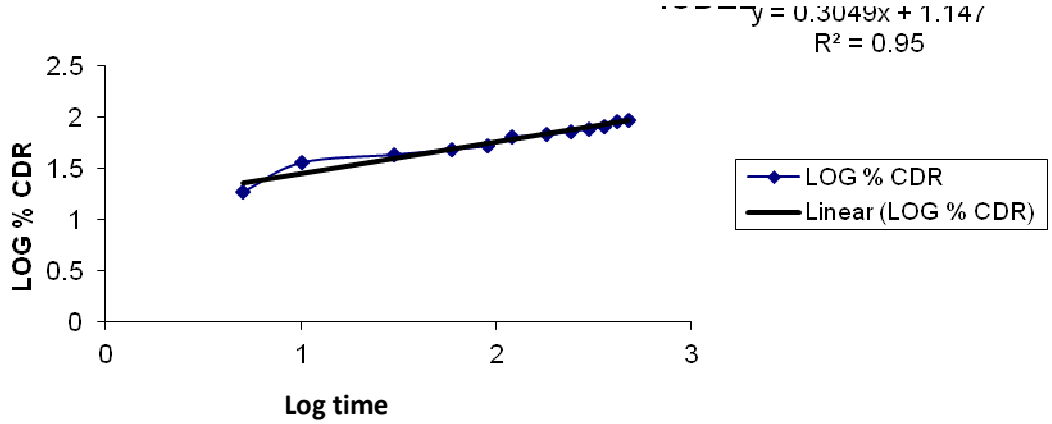

Figure 18. Korsemeyer Peppas model release kinetics of magnetic microspheres.

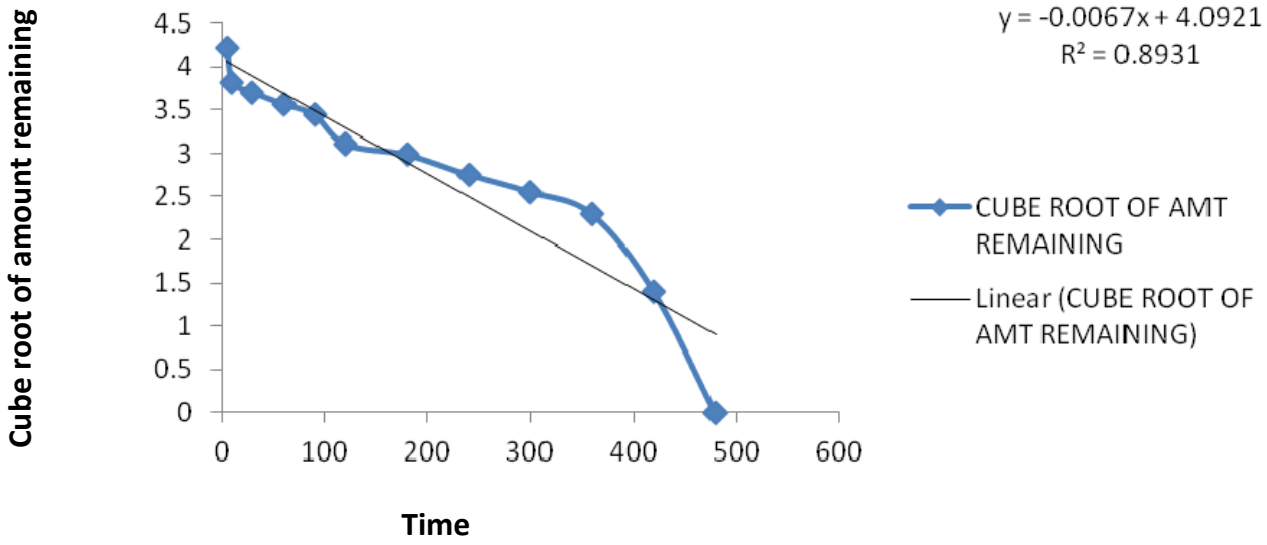

Figure 19. Hixon Crowell model release kinetics of magnetic microspheres.

Table 3. Flow characteristics of magnetic microspheres.

Code	Carr's index (%)	Hausner's ratio	Angle of repose	Flow character
F1	9.89	1.17	27.5	Excellent
F2	16.47	1.19	30	Good
F3	9.56	1.0	27.5	Excellent
F4	26.9	1.43	40.99	Passable
F5	27.3	1.23	42.28	Passable
F6	30.1	1.22	44.36	Poor
F7	10.6	1.2	27.6	Excellent
F8	19.8	1.4	25.5	Fair
F9	22.8	1.3	29.5	Fair

models was found to be average. It was found that formulation F-3 (chitosan 1:3) obeys Higuchi model.
10. On the basis of drug content, magnetic responsiveness, particle size morphology, *in vitro* release, release kinetics formulation F-3 (chitosan 1:3) was found to be most optimized.

Table 4. Drug content and entrapment efficiency of magnetic microspheres.

Formulation code	Drug content (%)	Entrapment efficiency (%)
F1	48	86.0
F2	31.3	89.1
F3	26.3	92.4
F4	43	70
F5	29.66	82.27
F6	26.33	84.6
F7	44.6	70.188
F8	31.3	88.3
F9	26.3	90.56

Table 5. Particle size of the formulated microspheres.

Code	Particle size (µm)
F1	10
F2	20
F3	100
F4	10
F5	20
F6	30
F7	10
F8	20
F9	100

Table 6. Percentage magnetite entrapped in magnetic microspheres.

Formulations code	Percentage magnetite entrapped
F1	51
F2	59
F3	73
F4	23
F5	37
F6	51
F7	45
F8	56.5
F9	70.605

Table 7. Percentage release of the formulated magnetic microspheres.

Formulation code	Percentage release
F1	95.00
F2	84.60
F3	76.10
F4	82.89
F5	76.98
F6	74.90
F7	86.67
F8	80.90
F9	76.90

DISCUSSION

As drug: polymer ratio increases the release of drug decreases due to formation of a rigid polymer matrix. Also, with increase in drug: polymer ratio particle size increases, thus surface area is decreased and release of drug is retarded. This proposed a method for targeted drug delivery by applying high magnetic field gradients within the body to an injected super paramagnetic fluid carrying the drug with the help of modest uniform magnetic field. 5-ASA was used as a model drug. In the present study, an attempt was made to formulate 5-ASA magnetic microspheres in order to study targeting efficiency, enhance bioavailability, reduce dose, thereby improving patient compliance.

Conflict of Interest

No competing interests were disclosed.

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