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Research article

FORMULATION AND EVALUATION OF GELATIN MICROSPHERES LOADED WITH FENOFIBRATE

Reshma Fathima K*, Minimol PV, Siva Kumar R, Sreethu K Sreedharan, B.Vijayakumar

Grace College of Pharmacy, Kodunthirapully, Palakkad, Kerala, India.

ABSTRACT

The main aim of the study is to develop sustained release microspheres loaded with Fenofibrate. The microsphere were developed using coacervation and phase separation method using gelatin as a polymer. Totally two formulations were developed and evaluated for FTIR, DSC, Scanning electron microscopy, percentage yield, percentage drug entrapment, *invitro* drug release studies. The results of the study indicate that the microspheres having good flow property (24°11'' and 25°22'').The particle size were ranged from 5-10µm. The encapsulation efficiency was found to be 70% for F1 formulation and 97% for F2 formulation. The *invitro* release study were carried out using pH 6.8 phosphate buffer for the period of 12hrs. The F2 formulation released the drug over the period of 12hrs. In conclusion, F2 formulation suitable for oral sustained release of Fenofibrate.

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Corresponding Author

Reshma Fathima. K
Grace College of Pharmacy, Kodunthirapully, Palakkad, Kerala, India.

Email:- fathimaresh786@gmail.com

INTRODUCTION

Sustained drug delivery system is often used to reduce frequency of dose, to reduce side effects and there by obtaining a maximum therapeutic effect. One of the methods of controlling the rate of drug release by microencapsulation. Microspheres can be defined as solid spherical particles ranging from 1-1000Mm. This particle consist of core material the drug and the coating material. The coating material can be of various types ranging from natural polymer such as gelatin. Gelatin is obtained from collagen and can be used as a coating material in micro encapsulation as it is biodegradable, water soluble, non antigenic and also economical.

Fenofibrate used as hypolipedimic drug used for the treatment of atherosclerosis. Normal dosage regimen varies from 140mg to 200mg. The biological half- life of drug is 6-8 hr, it require frequent dosing to maintain the therapeutic effect. Also the physicochemical properties of the drug unsuitable for formation of capsule dosage form. So the drug was chosen as a model drug for improved physicochemical properties of the formulation, patient compliance for the development of capsule dosage form. The aim of the study was to develop and evaluate gelatin microsphere loaded with Fenofibrate (FNO) for improved physicochemical properties of formulation to facilitate developed capsule dosage form and better patient compliance.

Various methods have been reported for microencapsulation, of which coacervation phase separation method by temperature change was utilized to prepare microspheres, which were characterized by optical microscopy. Effect of various process variables on microsphere size was analyzed. From this study the optimum conditions for preparation of drug loaded microspheres were established and different batches of microspheres with varying drug polymer ratios were

prepared and they were characterized by optical microscopy and scanning electron microscopy. The microspheres were analyzed for drug entrapment and *invitro* release pattern.

MATERIALS AND METHODS

Materials

Fenofibrate were obtained as gift sample from Alkem pharmaceuticals Pvt Ltd. Mumbai. Gelatin (I.P. Grade) were obtained as gift sample from nice chemicals. Methanol was purchased from nice chemicals, Bangalore. Tween 20 was purchased from Prowess lab chemicals. Liquid paraffin was purchased from Prowess lab chemicals. Formaldehyde was purchased from nice chemicals, Bangalore. Hydrochloric acid was purchased from nice chemicals, Bangalore and all chemicals were of analytical grade.

Methods

Preformulation studies

Before development of any formulation, it is mandatory to carry out preformulation studies to find any changes in the drug characteristics and stability of a drug candidate for formulation development. The drug was characterized for the physicochemical and spectral properties and was compared with standard (Aulton ME, 2002; Hadkar, 2008 and Rowe RC *et al*.).

Physical appearance

Physical appearance of drug was observed and compared with the Pharmacopoeial specifications.

Melting point

Melting point of drugs was determined using scientific melting point apparatus.

Compatibility Study

Compatibility study was performed using FTIR and DSC. The details are given below.

Fourier transforms Infrared Spectrum (FTIR)

FTIR spectra of the mixture of the drug and the excipients in the ratio 1:1 were compared by using the same procedure done in pure drug. (Fig 1-3)

Differential scanning calorimetric analysis

The thermal behavior of Fenofibrate, were studied using Shimadzu D.S.C TA60 WS Thermal Analyzer. Accurately weighed samples of Fenofibrate (8.00mg), was run at the scanning rate of 15°C/min and 20˚C/min over a temperature range of 100°C to 300°C respectively. Nitrogen was used as purge gas through DSC cell. (Fig 4, 5)

Formulation of microspheres

Microspheres were prepared by emulsion-coacervation technique, which contains an aqueous and oily phase.1gm of gelatin was weighed and dissolved in 10ml of distilled water.100mg of drug was dispersed to the above solution. This mixture was heated to 50℃ (care to be taken to prevent overheating).15ml of liquid paraffin was heated to 50℃ and stirred at 500rpm. To this added 1ml of tween 20 and stirred to obtain a uniform mixture.The prepared drug-polymer phase was added drop wise to the oily phase, which was continuously stirred at 500rpm. The stirring was continued for 5min for uniform distribution of drug polymer solution. The temperature of the above solution was lowered to 10ºC and the stirring was continued for 2 hours. After the first hour, 1.5ml formaldehyde was added and stirring was continued for another 1 hour. The mixture is tightly closed and kept at a temperature for 4ºC for 24 hours, after which the mixture washed with ice-cold isopropyl alcohol several times to remove oily phase of the microspheres and dried.

Evaluation of microspheres

The results of the studies were presented in Table 2, 3

Bulk characterization

The bulk density, tapped density, Carr's Index, Angle of repose and Hausner's ratio were determined for all the formulation.

Percentage Yield (%Y)

Dried microspheres were accurately weighed and the percentage yield of microsphere were calculated (Swansi B *et al*., 2011).

$$\text{Percentage yield} = \frac{Practical\ yield}{Theoretical\ yield} \times 100$$

Entrapment Efficiency (%)

Accurately weighed 100mg of microsphere were dissolved in 100ml PBS pH6.8. The solution was kept overnight and was filtered through whatman filter 0.45µm. The drug concentration was determined by UV spectrometer at maximum wavelength of 290nm. The following equation was used to calculate % drug entrapment (Swansi B *et al*., 2011).

$$\%\text{Drug Entrapment} = \frac{\text{practical drug content}}{\text{theoretical drug content}} \times 100$$

Scanning electron microscopy

The morphology of microspheres was investigated using Scanning Electron Microscopy (SEM). The samples were prepared by sprinkling the formulation on double-adhesive tape stuck to aluminium stub. The stub was placed in high-vacuum evaporator. The samples were then randomly scanned and photomicrographs were taken with

a Scanning Electron Microscope (Shivakumar HN *et al*., 2007)**.** (Fig 6,7)

***In-vitro* cumulative percentage drug release study**

The Fenofibrate release from the microspheres was evaluated by using the US Pharmacopoeia Dissolution capsule to get the final weight of 475mg each of the capsules was transformed into dissolution media. The 5ml samples were withdrawn at predetermined time intervals with dissolution media replacement and were filtered through 0.45µm whatman filter paper. The drug content was determined spectrophotometrically at 290nm on shimadzu UV/ Vis- spectrophotometer (Nath B *et al.*, 2011).

Apparatus-II Paddle (XVIII) in 900ml mixture of PBS pH 6.8 with 1% SLS in 9:1 at 37°C ± 0.5 temperature. The rotational speed of dissolution apparatus was maintained at 100rpm. Each run was carried out in triplicates. Accurately weighed 243mg of microspheres were filled in a "0" size

Table 1. Formulation of microspheres

Formulation	Drug(mg)	Polymer(mg)	Tween20(ml)
F1	200	1000	1
F2	200	1500	1

Table 2. Bulk characterization evaluation of fenofibrate microspheres

Sl.no	Parameter	Fenofibrate microspheres	
		F1	F2
1	Angle of repose	24.11	25.22
2	Bulk density	0.26	0.31
3	Tapped density	0.33	0.39
4	Carr's index	20	22
5	Hausner's ratio	1.25	1.30

Table 3. Dissolution data of Fenofibrate microspheres

S. No	Time (hr.)	F1	F2
1	0	0	0
2	0.5	4.07	5.45
3	1	12.87	7.29
4	2	27.31	14.49
5	3	33.14	19.34
6	4	38.79	25.06
7	5	45.25	37.06
8	6	50.93	46.80
9	7	54.99	56.51
10	8	55.87	62.24
11	10	57.47	65.26
12	12	60.17	67.39

Fig 1. IR spectrum of Fenofibrate

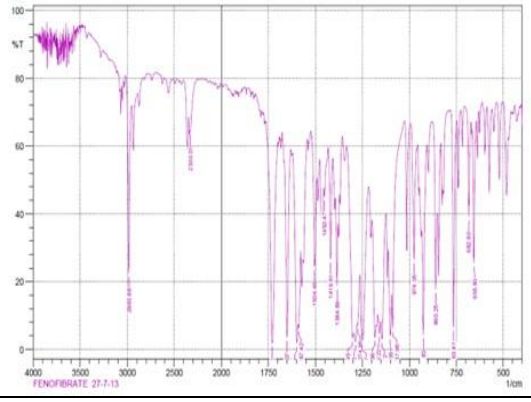


Fig 2. IR spectrum of Gelatin

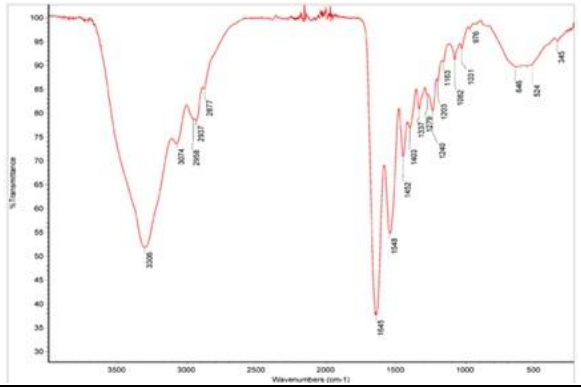


Fig 3. IR spectrum of Fenofibrate + Gelatin

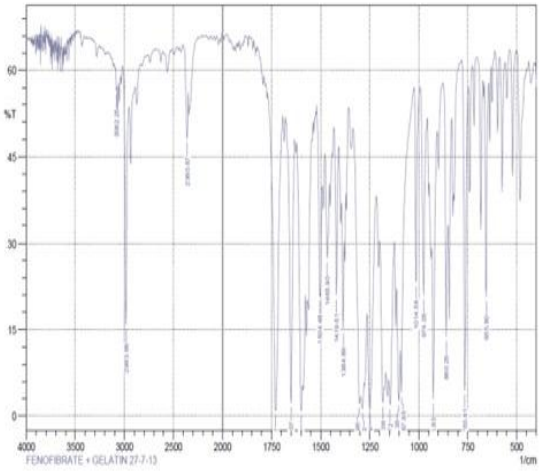


Fig 4. DSC curve of Fenofibrate

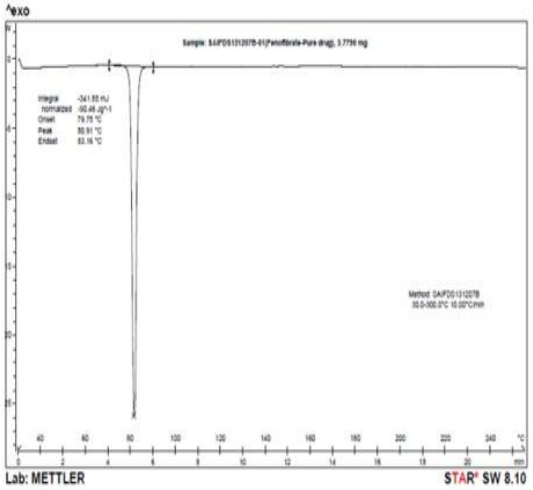


Fig.5. DSC curve of prepared microspheres

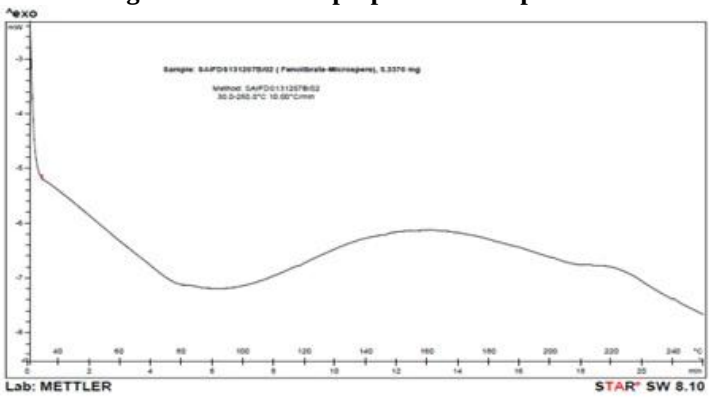


Fig 6. SEM images of Fenofibrate pure drug

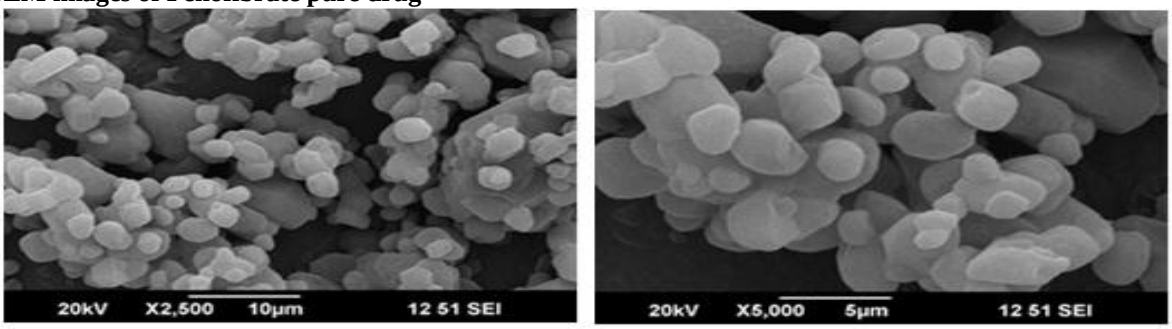


Fig 7. SEM images of prepared microspheres

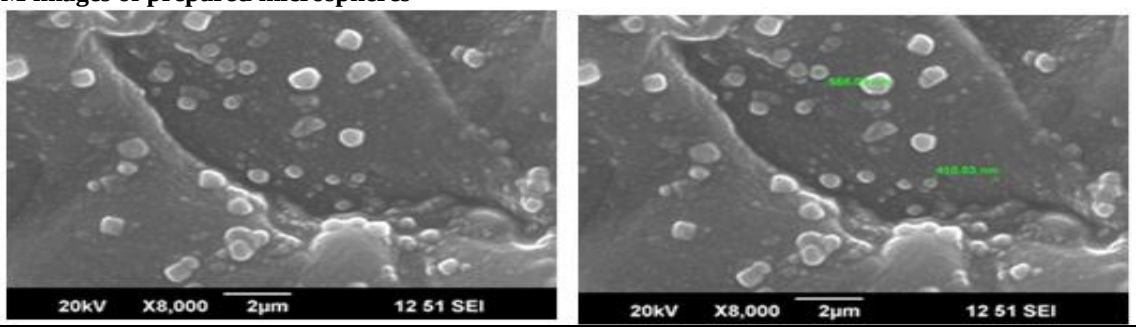
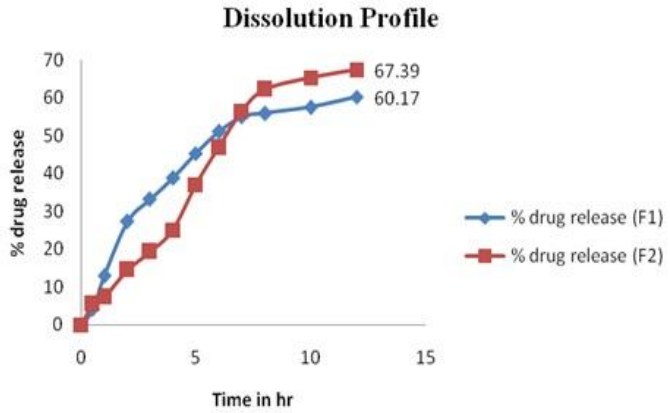


Fig 8. Dissolution profile for Fenofibrate microspheres



RESULTS AND DISCUSSION

The fenofibrate microsphere was successfully prepared using coacervation and phase separation method. FTIR and DSC studies indicate that the drug was compatible with polymer. The principal IR absorption peaks of drugs were observed in the spectra of the physical mixtures of the drug and the excipients. The IR spectral study indicated no interaction between the drug and the excipients, confirming the stability of the drug in the formulation. Differential Scanning Calorimetry (DSC) is a useful method that enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic transformations). The DSC of FNO exhibited broad endothermic peak at 80.91°C indicates melting point of FNO. Lack of sharp melting peak in the DSC of a FNO in the fig 4 indicates that the FNO is present in an amorphous rather than crystalline form of FNO. The shape and surface morphology of Fenofibrate pure drug and microsphere was investigated using scanning electron microscopy (SEM) and the shape and surface morphology were studied. It showed that the microspheres were nearly spherical in shape and the surface was found to be smooth. The Micromeritic properties of bulk density, tapped density, Hausner's ratio, angle of repose were evaluated. The microencapsulation process altered the micromeritics property. The prepared formulation showed good flow property. The percentage yield was calculated as per the equation and it was found to be 74 % and 76% in formulation F1 and F2 respectively.% Drug entrapment of drug entrapped within the polymer matrices were in the range of 70-97 %. An entrapment efficiency depends on the drug solubility in the solvent system used for processing. The drug release from microspheres in phosphate buffer pH 6.8 has been shown in Figure 8. *In vitro* drug release from F1and F2, were in the range of 60 and 68% within 12hours respectively. No formulation is showing burst release which indicates the absence of free particles on the surface of microspheres which further confirmed by SEM study. The trail revealed that low level of gelatin (25%) failed to produce microsphere with acceptable physical characteristic where as high level of stearic acid (100%) resulted in microsphere that exhibited high percentage of drug release. As the level of paraffin oil increases the particle size of microsphere increases due to tackiness which in turn decrease the % drug release from the microsphere.

CONCLUSION

The Fenofibrate microspheres were successfully developed by coacervation and phase separation technique using gelatin as a polymer. In conclusion F2 formulation releases the drug over the periods for 12 hrs with improved characterization of the formulation. The formulation facilitate the design of hard gelatin capsule with improved patient compliance.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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