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Development and in vitro characterization of esomeprazole floating gastro retentive microspheres

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ABSTRACT

The present study was to prepare and evaluate the floating microspheres of Esomeprazole magnesium trihydrate as a model drug for prolongation of the gastric retention time for oral delivery. EMT is a proton pump inhibitor which acts by irreversibly blocking the (H+K+)-ATPase enzyme system of the gastric parietal cell. Its half life is 1-1.5 hrs. EMT poor absorption may be because of degradation in gastric acid which can be prevented by incorporation of sodium bi carbonate which is a systemic antacid and act as buffer. The EMT floating microspheres were prepared by double emulsion solvent diffusion method by using Ethyl cellulose and different grades of HPMC like K4M, K15M, using Dichloromethane and alcohol solvent systems. EMT Floating microspheres were evaluated for micromeritic properties, particle size, % yield, In-Vitro buoyancy, incorporation efficiency and drug release. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 10 hrs and the particle sizes of microspheres were found to be in the range of 67.24±4.57 µm to 106.35±5.67µm. Incorporation efficiency was found in the range of 54.75±3.51to 83.97±2.54. In-vitro release profile of optimized formulations follows first order non-Fickian (Anomalous) release indicates diffusion and dissolution controlled release. FT-IR and DSC studies revealed the absence of any chemical interaction between drug and polymers used. During the stability period selected microspheres were found to be stable with respect to Entrapment efficiency and drug release characteristics.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc (Garg et al.,2003) Gastro-retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs (Gangadharappa et al., 2007). Peptic ulcers are sores or eroded areas that form in the lining of the digestive (gastrointestinal) tract. They usually occur in the stomach (gastric ulcer) or in the duodenum (duodenal ulcer). The stomach and duodenal lining have several mechanisms that help prevent ulcers from developing, like coating of mucus (mucous layer) protects the stomach lining from the effects of acidic digestive juices, Food and other substances in the stomach neutralize acid and Certain chemicals produced by the stomach protect the cells lining the stomach. If the mucous layer is damaged or if acid neutralizing substances are not present in normal amounts, digestive juices can causerritation and breakdown of the stomach or duodenal lining, allowing an ulcer to form(Tripathi). An ulcer is the result of an imbalance between aggressive and defensive factors (Brunton et al., 2006). Proton pump inhibitors (PPI's) are highly effective in the management of acid related diseases. There are currently five different proton pump inhibitors available including Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole and Esomeprazole (Remington 2000). In the present study Esomeprazole was selected as the payload model drug to treat the peptic ulcer. Esomeprazole is a proton pump inhibitor. Its metabolism is mainly by liver and excretion by renal and fecal. It acts by irreversibly blocking the (H+K+)-ATPase enzyme system of the gastric parietal cell. Its half life is 1-1.5 hrs with poor absorption may be because of degradation and poor solubility (Muthusamy et al., 2005) The solubility and absorption can be improved with an increase in the gastric residence time and also by creating basic pH with incorporation of Sodium bi carbonate.

MATERIALS AND METHODS

Esomeprazole magnesium trihydrate was obtained as a Gift sample from Lantex Pharma, Hyderabad, HPMC K4M and K15M purchased from Colorcon Ltd. Goa.

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Ethyl Cellulose 20cps was Gift sample from Colorcon Ltd, Goa. All other chemicals and reagents were of analytical grade and were used as obtained.

Preparation of floating microspheres

The floating microspheres loaded with Esomeprazole magnesium trihydrate were prepared by double emulsion solvent diffusion technique. The polymer Ethyl cellulose in different ratios, HPMC different grades (K4M, K15M), magnesium Stearate and drug were dissolved in mixture of alcohol and Dichloromethane (1:1) and then the drug polymer solution was constantly stirred with magnetic stirrer to get a uniform solution. By adding tabulated amount of distilled water in which sodium bi carbonate was dissolved, drug-polymer solution w/o emulsion was formed. The w/o primary emulsion prepared was poured in to 70 ml of light liquid paraffin containing Span 80 as a surfactant with vigorous stirring at 800 rpm by a mechanical stirrer using four bladed propeller type stirrer for 2 hr. Magnesium Stearate was added to avoid the flocculation. Then the formulated microspheres were separated through vaccum filtration equipment and washed with n-hexane followed by petroleum ether till oil free microspheres achieved. Then collected microspheres were dried for 1 hr at room temperature and subsequently stored in desiccators for 24 hr (Dev et al., 2011).

Characterization of floating microspheres

Micromeritic study

The prepared microspheres were characterized for their micromeritic properties such as tapped density, bulk density, % compressibility index, angle of repose (Tamizharasi et al., 2011).

Angle of repose

The angle of repose θ of the microspheres, which measures the resistance to particle flow was calculated as:

$$\text{Tan } \theta = h/r$$

Where h= height of the pile, r = Radius of pile formed by floating microspheres.

Tapped density and compressibility index

The tapping method was used to calculate tapped densities and compressibility index using tapped density.

Tapped density = Mass of floating microspheres / Volume of floating microspheres after tapping

%Compressibility index = $[1\text{-}V/V_0] \times 100$

Where V and V_0 are the volumes of the sample after and before the standard tapping

respectively.

Determination of practical yield

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of the microspheres (Karthikeyan et al., 2010).

$$\text{Practical yield} = \frac{\text{Actual weight of product}}{\text{Weight of excipient \&drug}} \times 100$$

***In vitro* buoyancy**

Floating microspheres (equivalent to 100 mg) were dispersed in 900ml of 0.1 N hydrochloric acid solution (pH 1.2) containing tween 80 (0.01 W/V %) / tween 20 (0.02W/V %) at 37°C.

The mixture was stirred with a paddle at 100rpm and after 12 hr, the layer of buoyant microspheres (Qf) was pipetted and separated by filtration simultaneously sinking microsphere (Qs) was also separated. Both microspheres type were dried at 40°C overnight.

Each weight was measured and buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microsphere.

Buoyancy (%) = Qf / (Qf + Qs) x 100

Where Qf and Qs are the weights of the floating and settled microspheres, respectively. All the determinations were made in triplicate (Sato et al., 2004; Jain et al., 2006).

Incorporation efficiency (IE)

To determine the incorporation efficiency, microspheres were taken, thoroughly triturated and suspended in a minimal amount of alcohol. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 302 nm (Srivastava et al., 2005).

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Particle size and shape analysis

Particle size analysis: The particle size of microspheres was determined by optical microscopy method; approximately 100 microspheres were counted for particle size using a calibrated optical microscope.

The microspheres were uniformly spread on a slide. The particle size of the microparticles was measured, along the longest axis and the shortest axis (cross shaped measurement). Average of these two readings was given as mean diameter of particles. The diameter of a minimum number of 100 microspheres in each batch was calculated.

Scanning electron microscopy

The external and internal morphology of the microspheres were studied using scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The stub containing the coated samples was placed in the scanning electron microscope (JSM- 6360A; JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 20 kV (Karthikeyan et al., 2010).

In vitro Release Studies

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. 5 ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with 0.1 N HCI and analyzed spectrophotometrically at 276 nm to determine the concentration of drug present in the dissolution medium (Sato et al., 2004).

FTIR and DSC study

FTIR spectral analysis of pure stavudine and stavudine loaded nanoparticles was performed by means of the KBr method employing a FTIR spectrometer (Shimadzu Corporation 8600, Japan). The thermal behavior of the polymer, drug, and formulated nanoparticles were analyzed using a DSC (Shimadzu DSC-60) instrument. About 5 mg of polymer, drug (EMT), floating microspheres formulation containing polymer drug mixture was weighed, crimped into an aluminum pan and analyzed at a scanning temperature range from 50 to 600˚C at the heating rate of 10˚C/m. Baseline optimization was performed before each run. Indium was used as the standard reference material to calibrate the temperature and energy scale of the apparatus (Basu et al., 2008; Liu et al., 1989).

Determination of drug release kinetics

The mechanism of release from optimized formulation was determined using the following mathematical models: zero-order kinetics, first- order kinetic, Higuchi kinetics, and the Korsmeyer-Peppas. The regression coefficient and slope values were determined.

Stability studies

The stability study of the Nanoparticles was carried out according to ICH guidelines at Refrigeration Temperature (4-80C), Room Temperature (25±20C) and oven Temperature (45±20C) for 30 days by storing the samples in stability chamber (Lab-Care, Mumbai).

RESULTS AND DISCUSSION

The floating microspheres loaded with Esomeprazole magnesium trihydrate were prepared by double emulsion solvent diffusion technique (Table 1). This method produces good yield, which indicates minimum loss of microspheres during the preparation and recovery.

Micromeritic properties of the prepared microspheres were evaluated for bulk density, tapped density, Carr's index and angle of repose. The results suggest that all the values are within the range, which indicates good flow properties the values were given in table 2. The Entrapment efficiency and mean particle size in all the formulations were found to be between 67.24± 4.57 to 106.35± 5.67 µm and 54.75±3.51 to 83.97±2.54%. The results showed that, the entrapment efficiency was increases with increase in polymer concentration (Table 3).

The floating buoyancy of the developed formulations of Esomeprazole floating microspheres were found to be in the range of 67.52±2.87 to 75.35±2.34%. The floating buoyancy was showed increase in polymer concentration increases the floating buoyancy. The SEM analysis confirmed that the prepared microspheres were spherical in shape (Fig 1, 2 &3).

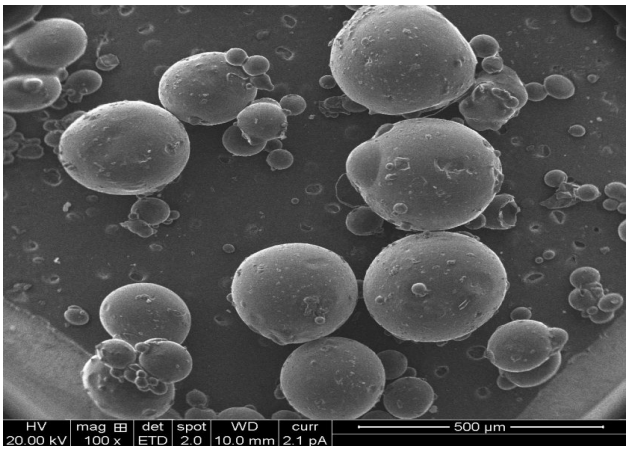

Fig. 1: SEM Photograph of EMT floating Microspheres in group.

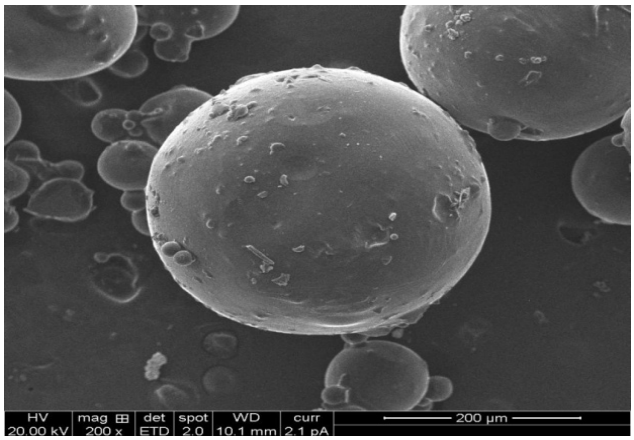

Fig. 2: SEM Photograph of EMT floating single Microsphere.

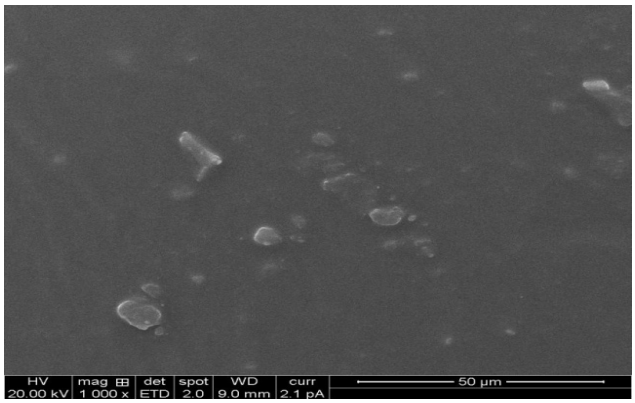

Fig. 3: SEM Photograph of EMT floating microsphere surface morphology.

Table. 1: Formulation Table of EMT floating microspheres.

Code	Ingredients									
	Drug (mg)	Ec (mg)	HPMC K4M (mg)	HPMC K15M (mg)	$NaHCO_3$ (mg)	Mg. Stearate (mg)	H_2O (ml)	Alcohol: DCM (1:1)ml	Liquid paraffin (ml)	Span 80
F1	200	100	100	---	400	300	4	12	70	0.5%
F2	200	300	100	---	400	300	4	12	70	0.5%
F3	200	500	100	---	400	300	4	12	70	0.5%
F4	200	100	---	100	400	300	4	15	70	0.5%
F5	200	300	---	100	400	300	4	15	70	0.5%
F6	200	500	---	100	400	300	4	15	70	0.5%

Table. 2: Micromeritic properties of EMT floating microspheres.

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index	Angle of repose
F1	0.407±0.01060	0.442±0.0197	8.270±1.019	21.300±1.060
F2	0.669±0.0127	0.780±0.0282	14.144±4.745	19.940±0.410
F3	0.443±0.0098	0.513±0.0183	13.055±5.734	19.805±0.855
F4	0.434±0.0183	0.465±0.0063	7.293±6.019	21.785±1.067
F5	0.426±0.0056	0.464±0.0169	8.148±2.137	19.335±0.445
F6	0.467±0.0127	0.534±0.0106	12.504±4.234	21.465±0.473

Table. 3: Characterization of Percentage yield, Incorporation efficiency, buoyancy and particle size of EMT floating microspheres.

Formulation Code	Practical Yield (%)	Incorporation Efficiency* (%)	Buoyancy (%)	Mean particle size* (µm)
F1	75.63	54.75±3.51	67.52±2.87	67.24± 4.57
F2	78.69	67.84±2.19	68.65±1.02	74.56± 8.62
F3	83.06	75.16±3.06	69.20±2.60	75.17± 3.05
F4	77.09	72.75±1.96	72.10±2.68	85.73± 4.15
F5	81.07	80.19±1.57	73.65±1.54	95.43± 2.59
F6	86.73	83.97±2.54	74.05±1.84	106.35± 5.67

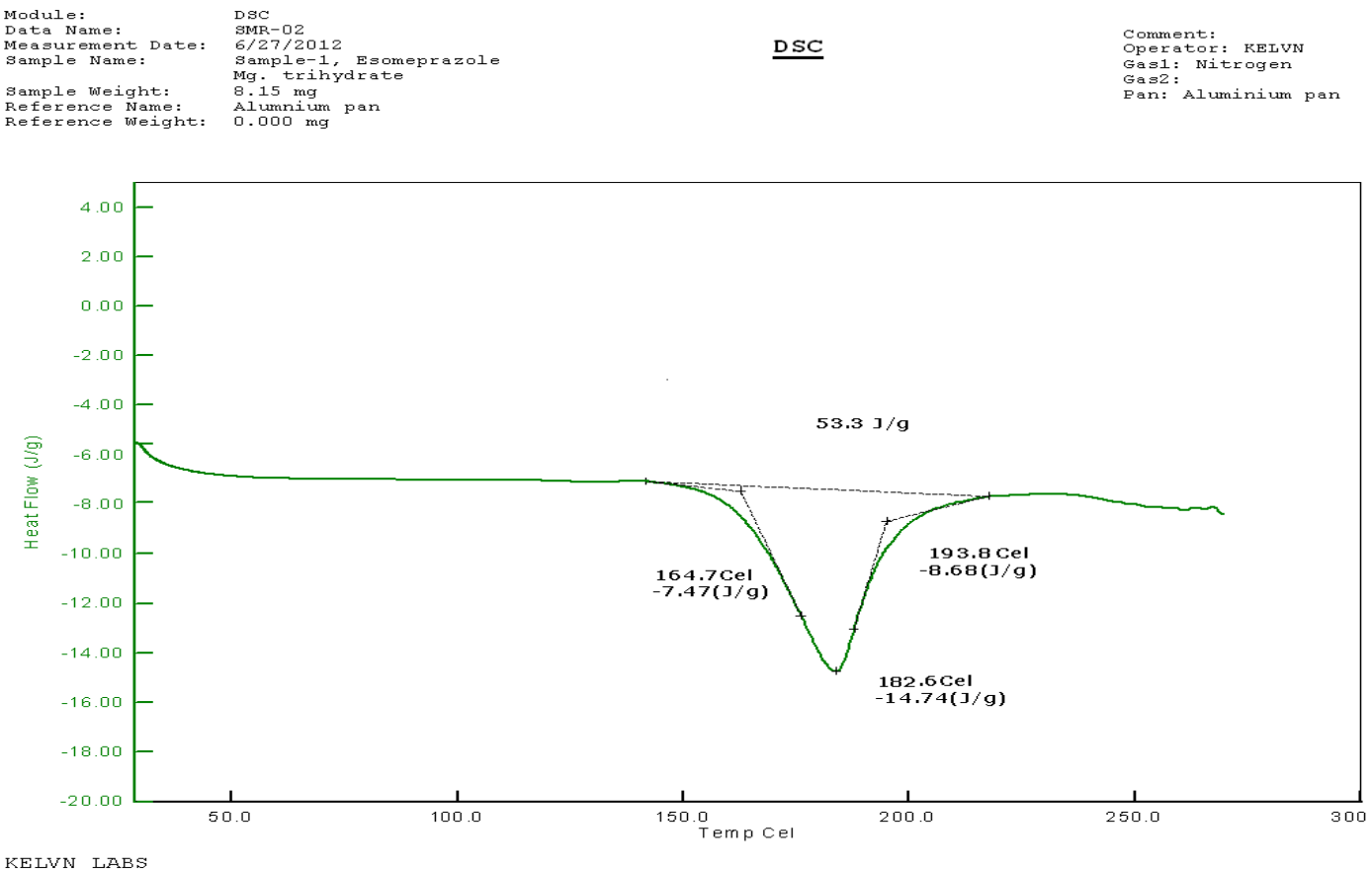

Fig. 4: DSC Thermogram of Pure EMT.

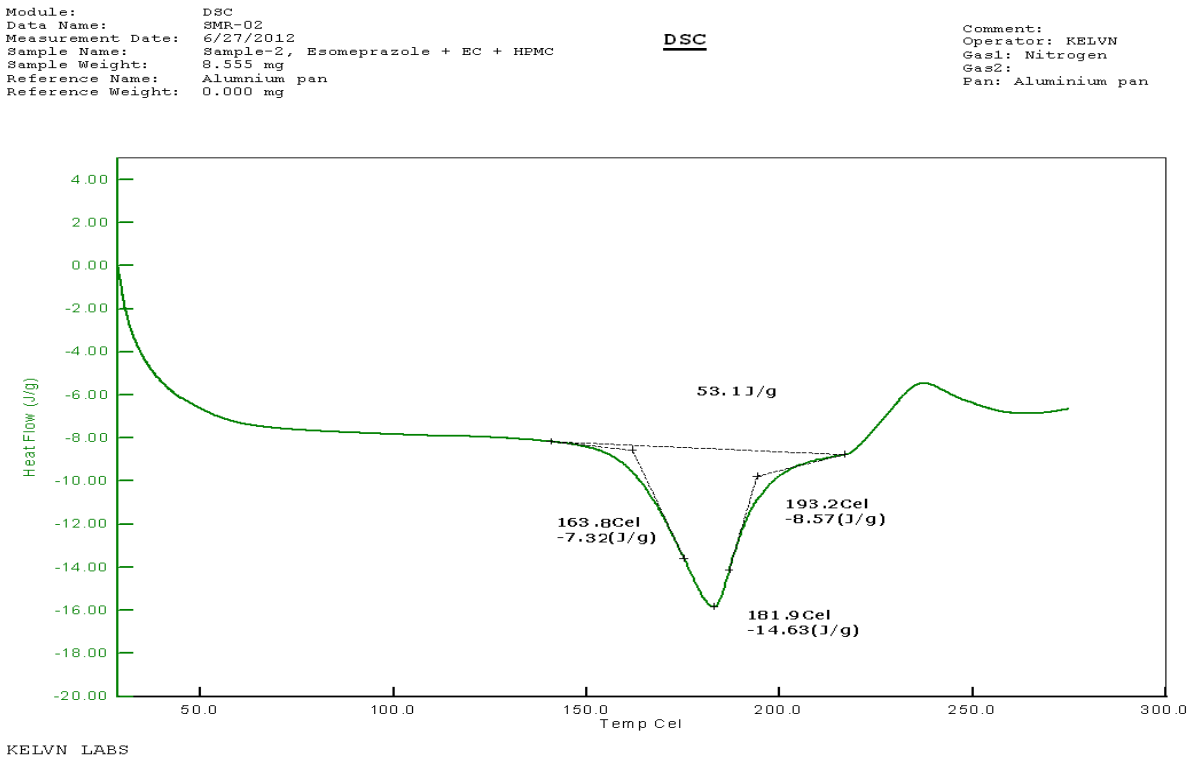

Fig. 5: DSC Thermogram of Optimized formulation F10.

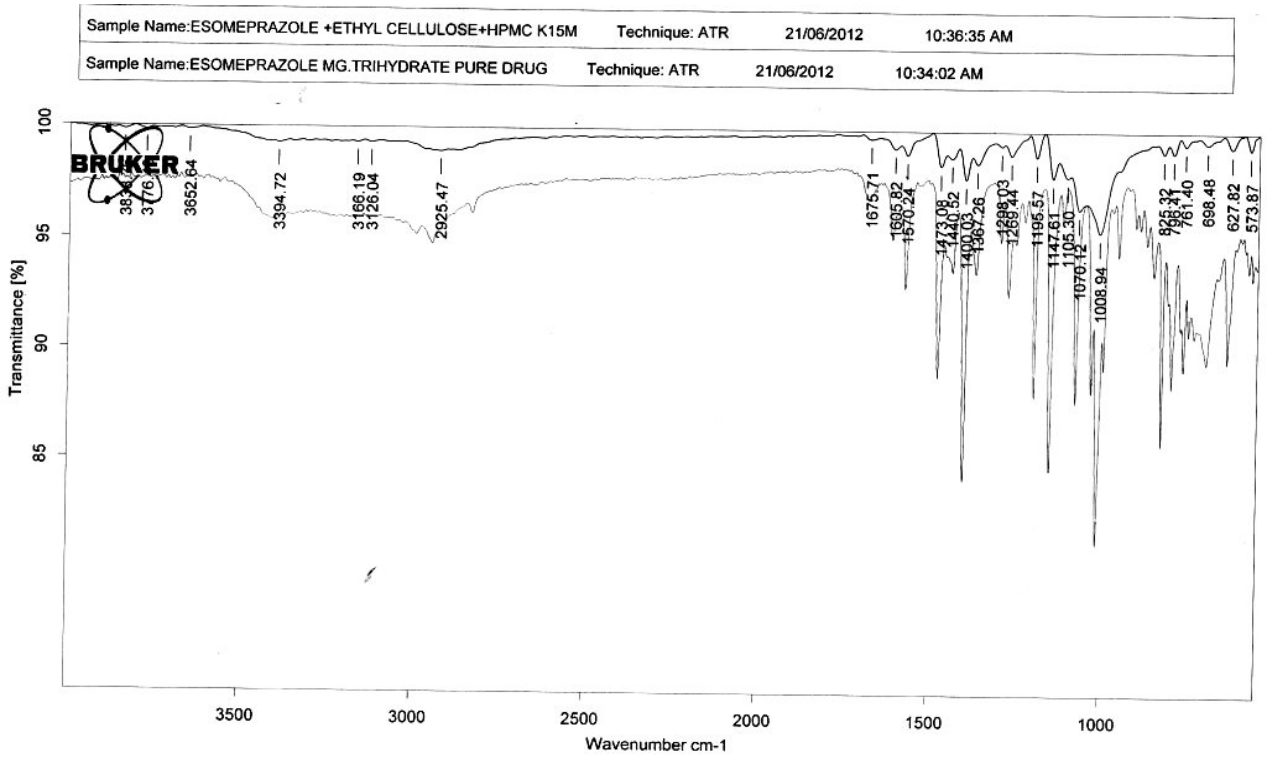

Fig. 6: FTIR Overlap spectra of optimized EMT floating microsphere .

FTIR and DSC thermograms (Fig 4, 5 & 6) were used for the characterization of drug and its formulations, FTIR peaks of pure drug and optimized formulation F5 peaks are almost all equal which indicates no interaction of the polymer with drug in its formulation. The DSC thermograms of the pure drug exhibited a broad endothermic peak in the range of 182.6^{0}C corresponding to the melting point of the drug The thermograms of the formulation F5 exhibited the endothermic peaks at 181.9^{0}C which is almost all equal to pure drug. From these observations it is quite obvious to conclude that the drug has not lost its properties and does not show any type of interactions with the polymers and excipients.

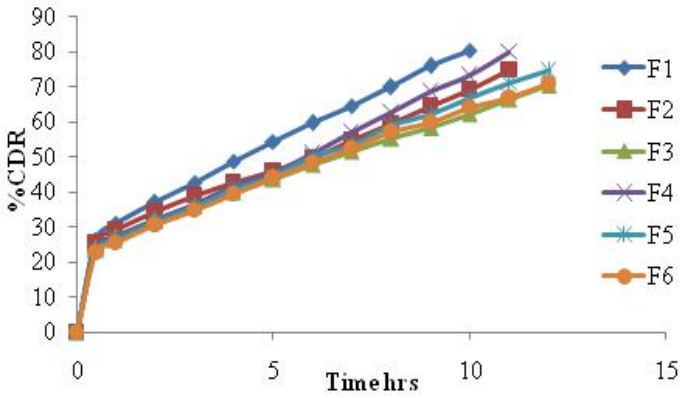

Fig. 7: *In vitro* drug release profile of EMT floating microspheres F1-F6.

The drug release profiles from the microspheres were as shown in Fig.7. The formulations F5, and F3 showed good release from the polymers. The percentage cumulative drug release after 12 hours was 74.342% and 70.289% respectively. However about 20% initial burst release was found within half an hour in all formulations. F5 released 74.342% of EMT in 12 hrs with an initial burst nearly 23.08% of drug within half an hour. Polymer concentration, viscosity affects the release of EMT.

Drug release kinetics was derived for best formulation from the in vitro profile. The optimized formulation follows the first order plots indicated by high regression value. The "n" value obtained from the Korsmeyer-Peppas model showed that the selected formulation followed the non-Fickian (Anomalous) release, which indicated that drug release from floating microspheres by diffusion and dissolution controlled release.

From stability studies minimal loss in the drug content was found in the EMT microspheres when stored at Refrigeration Temperature (4-80C), Room Temperature (25±20C) and oven Temperature (45±20C) for 30 days. This indicated that that Stavudine Nanoparticle formulation remains fairly stable at refrigeration, room and oven temperature.

CONCLUSION

Floating microspheres of EMT were prepared by double emulsion solvent diffusion technique using Ec, HPMC K4M and HPMC K15M. The entrapment efficiency, percentage of yield as well as particle size improved with combination of Ec+HPMC K15M than Ec+HPMC k4M. The FTIR and DSC studies revealed that no interaction between drug and polymer. Based on the entrapment efficiency, *in vitro* release F5 was found to be best formulation.

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