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Formulation And Evaluation of Polymeric Microspheres Ofeprosartan Mesylate

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Abstract

Eprosartan mesylate (ESM) is a BCS-class II drug that is insoluble in water and has a low bioavailability (13%). The aim of the present work was to prepare the microspheres of Eprosartan mesylate improving solubility and hence bioavailability. The microspheres of Eprosartan mesylate was prepared by solvent evaporation technique with Eudragit RL 100 by using various ratios (1:1, 1:3 and 1:5).Microspheres was evaluated by Fourier Transform infrared spectroscopy (FTIR), Scanning electron microscopy (SEM),Differential scanning electron microscopy, Saturation solubility and *in-vitro* studies. The solid state characterization revealed that no drug polymer interaction and the formulations F2 shows (1:3) better in vitro drug release from other formulation. Among these three formulations F2 shows better sustained release than F1 and F3. As a result, drug loaded microsphere appear to be a promising approach for increasing the solubility and bioavailability of Eprosartan mesylate.

Keywords: Microspheres, Eprosartan mesylate, Solvent Evaporation method, Bioavailability enhancement.

Introduction

One of the most difficult aspects of drug development is increasing the oral bioavailability of poorly water soluble drug. For decades, pharmaceutical dosage forms such as tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables have been used to deliver the majority of drugs to patients. Some of the issues can be solved by creating a regulated drug delivery system that boosts a medicine's therapeutic efficacy while reducing side effects. Some of the problems are overcome by developing a controlled drug delivery system which increases the therapeutic efficacy of a given drug while minimizing side effects.Drugs that are rapidly absorbed from the gastrointestinal tract (GIT) and also have a short half-life are quickly excreted from the bloodstream, require frequent dosing[1, 2]. To alter this drawback, the oral sustained release (SR) formulations have been developed in an attempt to release the drug slowly into the GIT for prolonged period of time [3,4]. Eprosartan mesylate (EM) is used for the treatment of high blood pressure that acts as a "angiotensin II receptor antagonist." Eprosartan is reported to be more tolerated than enalapril when compared to other

angiotensin II receptor antagonists [5].It's an antihypertensive drug with a 13 % oral bioavailability [6,7]. It's a BCS Class II drug that's insoluble in water.

Microspheres have been promising approaches for achieving oral sustained release. As a coating material or carrier, the microsphere requires a polymeric component. A number of various substances both biodegradable and non-biodegradable have been demonstrated for the preparation of microsphere.It not only reduces the drug's dose by rapidly reaching the active biological sites, but it also lowers toxicity [8].According to the literature review, the Eudragit RL100 and PVA (polyvinyl alcohol) in water for Eprosartan mesylate were not investigated for microsphere in varied ratios using chloroform as the solvent.Biodegradable polymer microspheres for controlled drug delivery have got much attention due to their outstanding clinical benefits: lowering dose frequency, improving patient convenience and acceptance for patients, as well as drug targeting to particular region [9, 10,and 11].
Among the different microsphere preparation processes, the solvent evaporation method is one of the most used. Microspheres can be made by extracting or evaporating the organic solvent from dispersed oil droplets that contain both polymer and drug during the solidification process.The art of the preparation process has significant impacts on the attributes of drug loaded microspheres such as surface morphology, particle size, encapsulation efficiency and *in-vitro* release profiles [12-16]. Hence, the goal of the study was to develop the Eprosartan mesylate microsphere by utilizing polymer like Eudragit RL 100 for sustained effect of Eprosartan mesylate.

Methodology

Microspheres were formulated by solvent evaporation method. Required amount of polymer were added to a chloroform solution in the drug. The aqueous phase was prepared by dispersing PVA (polyvinyl alcohol -0.2 %) in water. The drug – polymer solution was mixed to the aqueous phase with constant stirring. A magnetic stirrer was used to carry out this process at [Remi,Vasai,(India)] at 500 rpm for 1 min to form an emulsion. The resultant solution was added into 80 ml of PVA aqueous solution (0.2%, w/v) and magnetically agitated at 550 rpm at 25 ◦C for further 3 h under atmospheric pressure. In addition, saline solution (2%, w/v) was also added to modulate the osmotic pressure. The solidified microspheres wereseparated by centrifugation which were then rinsed thrice using de-ionized water before being lyophilized (Christ Alpha 1–2, Martin Christ Co., Germany) overnight to get a free flowing water dispersible powder. Finally the driedwas taken out for examine physicochemical characters and *in- vitro* releasestudy.

Evaluation of microsphere

FT-IR spectroscopy

FT- IR spectra was recorded on the sample scannedby KBr disks (2 mg sample in 200 mg KBr disks) using Fourier Transform Infra-Red spectrometer.To assess the chemical integrity and compatibility of the drug with the polymer in the microspheres, the samples were scanned over a frequency range of 4000-400 cm-1[17, 18].

Particle size distribution

The measurements of different particle size of microsphere formulations were performed by using Microtac blue wave particle size analyzer. The samples have to be diluted with de-ionized water before measurement to obtain a suitable concentration. The formation of micro-sized particles was confirmed by the obtained results from particle size distribution.

Zeta potential analysis

The particle charge was one of thein assessments for the stability of microsphere. The large numbers of particles were uniformly charged, and then electrostatic repulsion between the particles will increases, hence, the formulation's physical stability also improves. Malvern Zetasizer was used to determine the zeta potential of the formulated microsphere.The samples were diluted with de-ionized water before measurement.

Saturation solubility

The saturation solubility measurement was performed on both pure drug and different microsphere formulations. 50 mg of pure drug and microsphere equivalent to 50 mg of Eprosartan mesylate were placed separately into a 25 ml stoppered conical flask containing 10 ml distilled water. In a rotary shaker, the flasks were sealed and agitated for 24 hours at 37 °C or equivalent for two days. After the required time interval, the samples were collected, and suitably diluted and analyzed on a UV spectrophotometer at 233 nm was used to examine the samples.

Scanning electron microscopy

The scanning electron microscopy (SEM) was used to analyzing size and morphology. The particle size analyses of microspheres were evaluating the confirmation of the micro-sized formulation. The sample was adhered on a double sided adhesive tape stuck to an aluminum stub and the stubs were platinum coated. The stub containing sample is placed in scanning electron microscopy chamber, where the surface morphology was examined.

***In-vitro* drug release studies**

The *in-vitro* release study on Eprosartan mesylate and microsphere formulations were performed in USP dissolution apparatus using paddle method (Type II) at50 rpm. The dissolution study was performed inphosphate buffer (pH 7.4).The dissolution medium was 900 ml phosphate buffer and temperature was kept at 37±0.5°C.Predetermined weights of pure Eprosartan mesylate and microsphere that were equivalent to 300 mg of ESM were taken and introduced into the dissolution medium. The Sample (5ml) was withdrawn at specific time intervals and replaced with a same volume of freshly prepared dissolution medium and then filtered. UV-Visible spectrophotometer (Shimadzu) was used to evaluate the filtered samples at 233 nm. The dissolution study of unprocessed drug and different microsphere formulation was studied.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC200 F3 Maia®, Netzsch Instrument Co., and Germany) was used to analyze the materials' thermal characteristics.The samples were scanned under a dry nitrogen purge from 30 to 200°C in sealed aluminum pans at a heating rate of 10°C/min.

Result and discussion

FTIR Spectra was used to assess possibility of an interaction between drug and polymers. The FT-IR spectroscopy of pure Eprosartan mesylate, Eudragit RL 100 as well as physical mixture of the drug and their formulations were recorded. Eprosartan mesylate has distinct peaks that can be seen. Physical mixtures of Eprosartan mesylate, polymers, and their formulations all showed a similar peak. In combined spectra, there was no discernible shift, disappearance, or reappearance of peaks, indicating good drug–polymer compatibility and no possible interaction between Eprosartan mesylate and polymers. As a result, the polymer was suggested to be anacceptable forformulation of microsphere.

Particle size and Polydispersity index

The particle size has one of the most necessary features of microsphere and its mean particle size ranges from F1 (95.94), F2 (70.89), and F3 (106.3) (d.nm) for 1:1, 1:3 and 1:5 respectively.

Polydispersity index shows degree of particle size distribution and promotes the physical stability of microsphere. Poly dispersity index of the formulations shows F1 to F3 were 0.359, 0.293 and 0.595 respectively. The formulation F2 indicates the smaller particle size (70.89) which suggests the good uniformity in particle size distribution.

It may be due to an increase in the viscosity of the solution containing the drug and polymer mixture, as well as a constant amount of solvents involved during solubilization. Here Particle size is especially influenced by Eudragit RL100.

It could be attributed to the increase in the viscosity of the solution containing drug and polymer mixture, as well as constant amount of the solvents used during solubilisation. Here Eudragit RL100 has more effect on particle size[19].

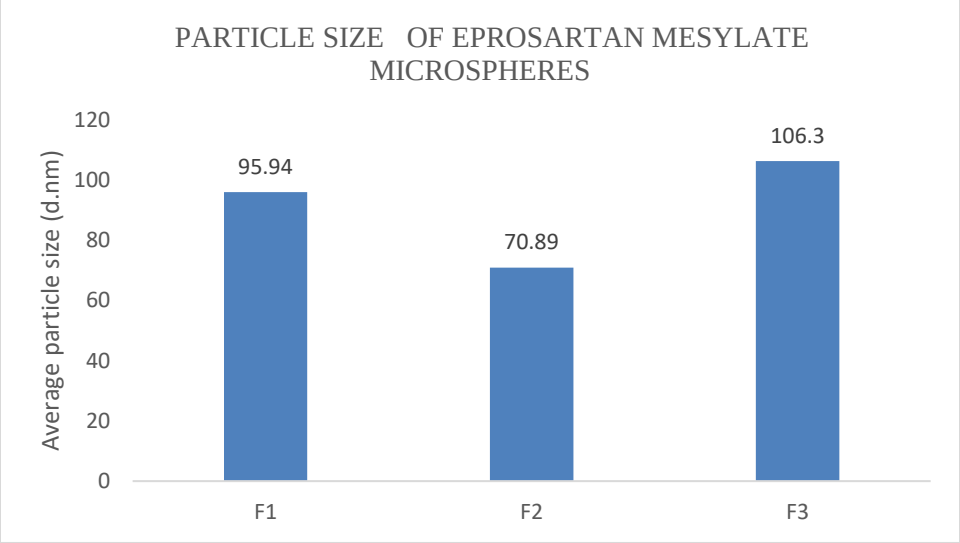

Figure 1

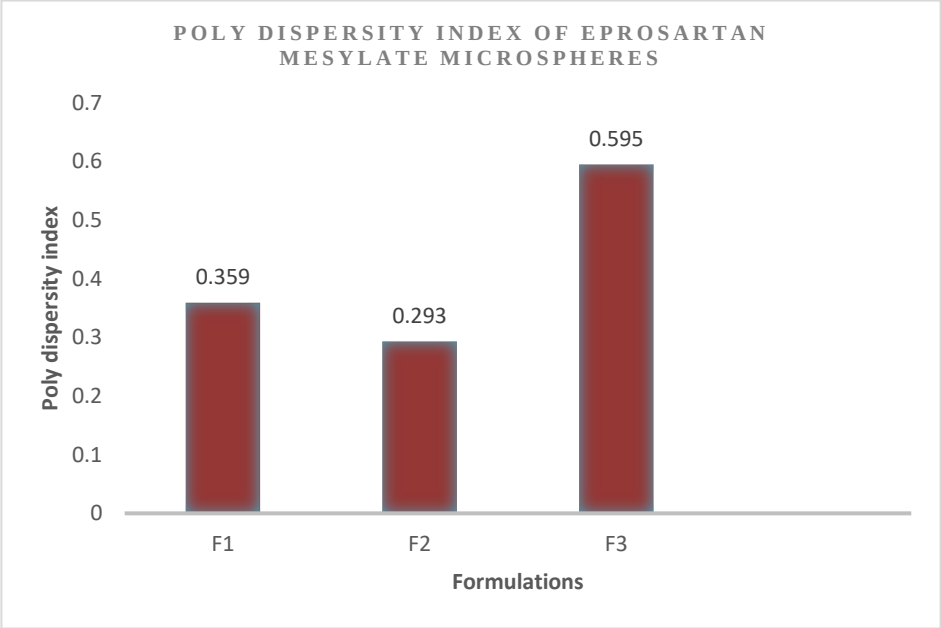

Figure 2

Zeta potential analysis:

The assessment of the zeta potential values (properly related to the double electric layer on the surface of colloidal particles) of a microsphere is necessary as indicates about the long term stability.Stronger repulsive forces are produced by extreme positive or negative zeta potential values, although repulsion between particles with similar electric charges prevents particle agglomeration and hence simple re-dispersion.A minimum zeta potential of ±20mV is required for simultaneous electrostatic and steric stabilization. The zeta potential study of microsphere formulations F1 - F3 were found to be in the range of F1 (-22.5 mV), F2 (-17.4 mV) and F3 (-26.9 mV) respectively, The zeta potential measurement indicates negatively charged due to double layer repulsion between the droplets and also it depends upon the pH and concentration, which indicates good physical stability of microspheres.

Drug content determination:

The drug particle of microsphere preparation was reduced to micro size. The drug content of Eprosartan mesylate F1, F2, and F3 were found to be in the range of 94.92%, 97.16%, and 89.37% during the formulation process. The results show that all microspheres had high drug content with a low standard deviation, and lower drug loss during the preparation process. It revealed that the drug is evenly dispersed in the powder formulation. Hence this method was used in the study appears to be reproducible for preparation of microsphere.

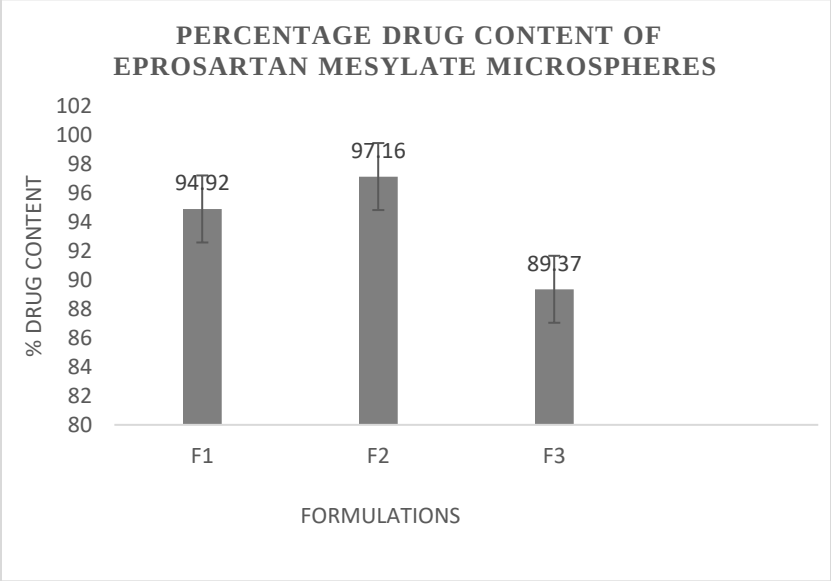

Figure 3

Saturation solubility

Microsphere solubility profile enhances dissolving rate and solubility, whereas reduction of size leads to improved dissolution. Eprosartan mesylate has a solubility of 22.34% and the formulations showed in F1 81.31%, F2 88.13% and F3 76.26% in phosphate buffer. The amorphous nature of the drug after solvent evaporation is indicated by the saturation solubility study of crystallization investigation, which indicates that microspheres were demonstrating greatest solubility relative to pure drug is due to the amorphous form of drug after solvent evaporation.

The improved solubility with an increase in all carrier proportion. This could be due to good wetting ability associated with polymer ratios (1.1, 1:3, 1:5) of microspheres. Eudragit RL 100 (1:3, F2) microspheres have very tiny particle size, resulting in the large encapsulation surface area, so as the proportion of carrier increases; a large surface is exposed for the drug crystal adsorption. The order of improvement in solubility was F2 (1:3) > F1 (1:1) > F3 (1:5). **Figure 4** shows the solubility of produced microspheres in phosphate buffer (pH 7.4).

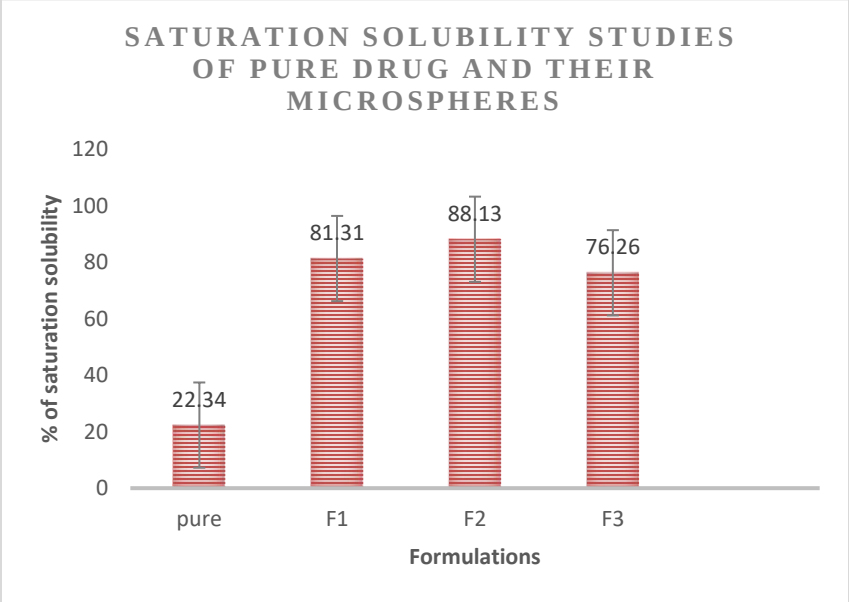

Figure 4

SEM studies

SEM was used to examine the morphologies and surfaces of the Eprosartan mesylate (Fig. 5A), Eudragit (Fig. 5B), and F2 (Fig. 5C) particles. The surface morphology of the microspheres was found in plain Eprosartan mesylate powder made up of irregularly shaped crystals with rough surface. The particles of formulation F2 appeared a numerous uniform spherically shaped particles below 1000 µm with smooth surfaces of drug-loaded microspheres could be seen with the solvent evaporation technique **(Fig. 5C)** similar findings have been reported [20].

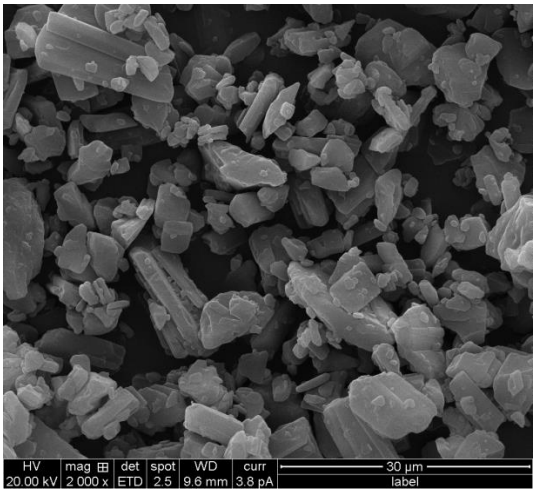

Figure 5 A

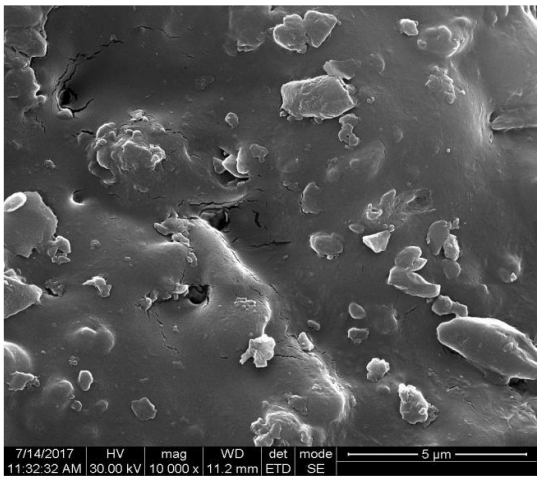

Figure 5B

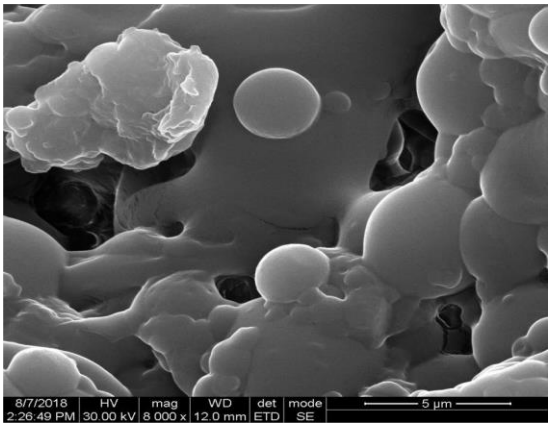

Figure 5C

Scanning electron microscopy photograph of pure drug A,Eudragit B and Formulation F2 C

Differential scanning calorimetry

DSC studies showed change in the crystallinity of Eprosartan mesylate compared to plain drug.DSC thermographs of the pure drug and formulation F2 shows the exhibited endothermic peaks around 134◦C due to the melting range of Eudragit. It appeared as an endothermic peak **(Fig.6A)**. In addition, an exothermic peak derived from crystal form into amorphous. Eprosartan mesylate -loaded microspheres formulated by solvent evaporation technique **Fig.6C**shows that the drug uniformly dispersed in the microspheres in the amorphous form microspheres. There was no incompatibility between Eprosartan mesylate and polymers because all peaks in the spectra were not considerably shifted. **Figures 6A, 6B, and 6C** demonstrate this.

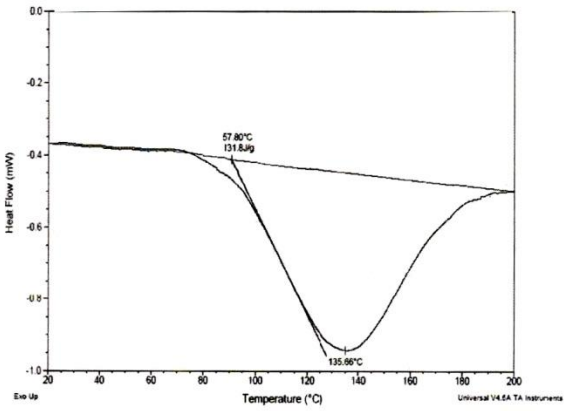

Figure 6A

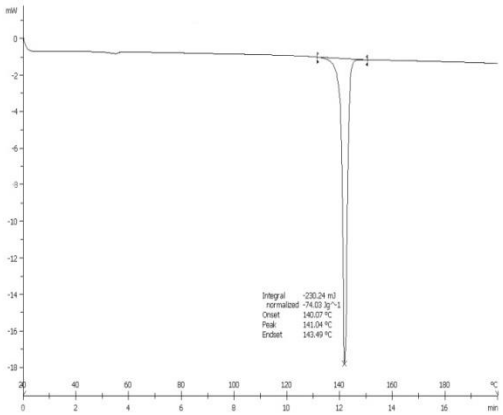

Figure 6B

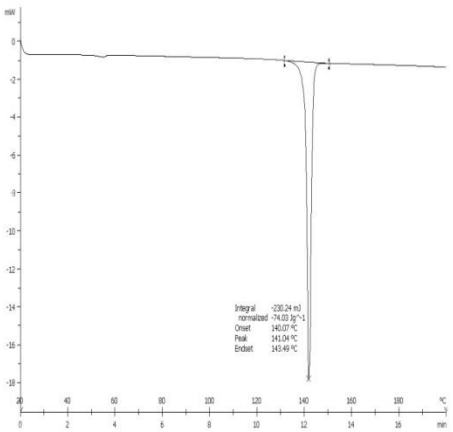

Figure 6C

DSC thermograph of pure drug , EudragitRL100 and Formulation F2 Microsphere

***In- vitro* dissolution studies**

Eprosartan mesylate is insoluble in water and solubility is pH dependent, increasing with phosphate buffer (pH 7.4) which is used for in vitro release to stimulate gastric condition and allows the better discrimination of our processing effects. The aim of improving the Eprosartan mesylate dissolution rate in microspheres was achieved.At the end of the 12th hour, only 36.64 percent of Eprosartan mesylate was released in phosphate buffer.

Eprosartan mesylate release from the microsphere was studied for 12 hrs the drug released at constant rate in all these formulations drug and polymer ratios (F1,1:1), (F2,1:3) and (F3,1:5) showed that 91.34 % (F1), 96.82 % (F2) and 81.86 % (F3) (in phosphate buffer) drug was released with increasing carrier proportion at the end of 12 hours [21]. As drug:polymer ratio 1:3 (F2) was, with the consequent increases 96.82% for formulation sustained release at pH 7.4 it is shown in the **Fig. 7**.

The results showed that the more sustained effect with increasing the concentration of Eudragit RL 100. The *in-vitro* profiles of microspheres are designed to assist in predicting the ultimate behavior of the Eprosartan mesylate.

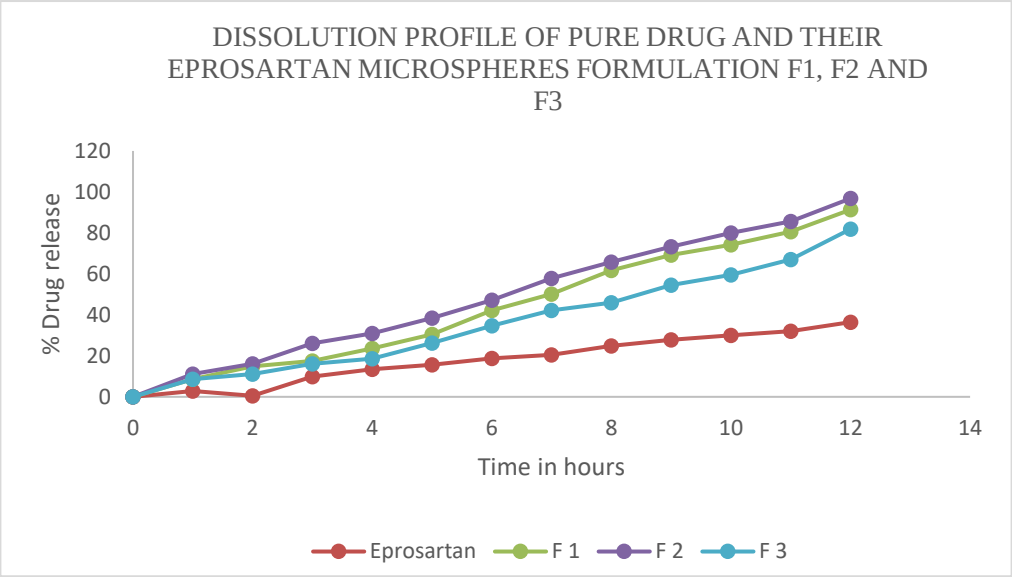

Figure 7

Dissolution profile of pure drug and their Eprosartan microspheres formulation F1, F2 and F3

Conclusion

Polymeric microsphere of Eprosartan mesylatewas successfully prepared using the solvent evaporation technique using Eudragit RL100. The particle size was significantly reduced with increasing polymer proportion due to increase in relative viscosity. The investigation of Eudragit RL 100 polymer was found to have a sustained effect on the release of Eprosartan mesylate from their microspheres in this study. It retarded the release rate of drug in an increasing manner with the increase of the polymer content. As a result, Eudragit RL100 can be utilized for better sustained effect on drug release.

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Reference

1.Pharmacopoeia I, Volume II. Published by the controller of Publication. Vol. I, New Delhi. 2007:655.
2. Jain NK, Sharma SN. A textbook of professional pharmacy. New Delhi: Vallabh Prakashan. 1998;4:83-9.
3.James S, Encyclopedia of Pharmaceutical Technology Third Edition, New York: informa healthcare, 2007; 1: 1325-1333.

4.Tamizharasi S, Rathi V, Rathi JC. Floating Drug Delivery System. Systematic Reviews in Pharmacy. 2011 Jan 1;2(1).
5.Chandana OS, Kumar DS, Babu RR. Method development and validation of eprosartan mesylate and its impurities using reverse phase high-performance liquid chromatography. Int J Curr Pharm Res. 2016;8(4):49-53..
6.Rao ME, Swain S, Patra CN, Mund SP. Formulation design, optimization and characterization of eprosartan mesylate nanoparticles. Nanoscience & Nanotechnology-Asia. 2018 Apr 1;8(1):130-43.
7.Rewar S, Bansal BK, Singh CJ, Sharma AK. Approach for quantitative estimation of Eprosartan mesylate by UV spectrophotometer. International Journal of Research and Development in Pharmacy & Life Sciences. 2014 Nov 15;3(6):1288-91..
8.Bansode SS, Banarjee SK, Gaikwad DD, Jadhav SL, Thorat RM. Microencapsulation: a review. International journal of pharmaceutical sciences review and research. 2010 Mar;1(2):38-43.
9.Chung TW, Huang YY, Liu YZ. Effects of the rate of solvent evaporation on the characteristics of drug loaded PLLA and PDLLA microspheres. International journal of pharmaceutics. 2001 Jan 16;212(2):161-9.
10.Berkland C, King M, Cox A, Kim KK, Pack DW. Precise control of PLG microsphere size provides enhanced control of drug release rate. Journal of controlled release. 2002 Jul 18;82(1):137-47.
11. Li M, Rouaud O, Poncelet D. Microencapsulation by solvent evaporation: State of the art for process engineering approaches. International Journal of pharmaceutics. 2008 Nov 3;363(1-2):26-39.
12.Igartua M, Hernández RM, Rosas JE, Patarroyo ME, Pedraz JL. γ-Irradiation effects on biopharmaceutical properties of PLGA microspheres loaded with SPf66 synthetic vaccine. European journal of pharmaceutics and biopharmaceutics. 2008 Jun 1;69(2):519-26
13.Ye M, Kim S, Park K. Issues in long-term protein delivery using biodegradable microparticles. Journal of Controlled Release. 2010 Sep 1;146(2):241-60.
14.Angadi SC, Manjeshwar LS, Aminabhavi TM. Stearic acid-coated chitosan-based interpenetrating polymer network microspheres: controlled release characteristics. Industrial & Engineering Chemistry Research. 2011 Apr 20;50 (8):4504-14.
15. Chaturvedi K, Kulkarni AR, Aminabhavi TM. Blend microspheres of poly (3-hydroxybutyrate) and cellulose acetate phthalate for colon delivery of 5-fluorouracil. Industrial & engineering chemistry research. 2011 Sep 21;50 (18):10414-23.
16.Oh YJ, Lee J, Seo JY, Rhim T, Kim SH, Yoon HJ, Lee KY. Preparation of budesonide-loaded porous PLGA microparticles and their therapeutic efficacy in a murine asthma model. Journal of controlled release. 2011 Feb 28;150(1):56-62..
17.Balpande HM, Raut NS, Umekar MJ, Kotagale NR. Compatibility study of metformin with pharmaceutical excipients. Int. J. Chem. Tech. Res. 2013;5(1684):e1693.
18.Tamizharasi, S.,Sivakumar, T.,Chandra, R.JFormulation and evaluation of floating drug delivery system of aceclofenac. International journal of drug development and research 2011;3(3)242-251.
19.Sagar B, Singh S K and Jalwal P: Formulation and evaluation of gastro-retentive floating microspheres bearing metformin HCl for treatment of diabetes mellitus. The Pharma Innovation Journal 2017; 6(10): 173-80.

20.Chung TW, Huang YY, Liu YZ. Effects of the rate of solvent evaporation on the characteristics of drug loaded PLLA and PDLLA microspheres. International journal of pharmaceutics. 2001 Jan 16;212(2):161-9..

21.Tamizharasi, S.,Rathi, J.C.Rathi, V. Preparation and in vitro evaluation of Eudragit microspheres containing cephalexin.Asian journal of chemistry 2008;2(20):845-848.