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Research

Formulation And In-Vitro Evaluation Of Eprosartan Gelispheres

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Abstract

Eprosartan is an antihistamine agent used for the symptomatic relief of seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, lacrimation, and nasal congestion. The aim of present research is to develop Eprosartan gelispheres by using ionic gelation method. Eprosartan gelispheres were prepared using different ratios of polymers with alone and combination like HPMC K15M, Ethyl cellulose and carbapol as 1:1, 1:1.5, 1:2 Eprosartan gelispheres were evaluated for percentage yield, particle size. Surface morphology, flow properties, drug content and entrapment efficiency and were found to be within the acceptable range. Invitro dissolution studies of the gelispheres revealed that the formulation F9 containing drug and polymer ratio of Drug: carbapol, in 1:2. shows maximum drug release at the end of 12 hours, when compared with the other formulations. Drug release kinetics of the optimized formulation states that the formulation F9 follows zero order drug release with fickian diffusion mechanism.

Keywords: Eprosartan, HPMC K15M, Ethyl cellulose, carbapol

INTRODUCTION

The oral administration of pharmaceutical dosage forms is the more usual, convenient and comfortable route for active drug delivery to the body. Oral controlled release systems continue to be the most popular ones among all the drug delivery systems as it offers several advantages over the conventional systems like:

- Improve patient's compliance and convenience due to less frequent dosing of drug.
- Reduction in fluctuation of steady state plasma level and therefore helps in better control of disease condition.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care cost through improved therapy, shorter treatment period and less frequency of dosing.

There are various approaches in delivering a therapeutic substance to the target site in a controlled release fashion. One such approach is using microspheres as carriers for drugs. However, these formulations have to be injected either subcutaneously or intravenously, which in general is not acceptable. Hence, there is a need to develop an oral drug delivery system that is convenient for patients. Various natural polymers like Chitosan, Gelatin and Na CMC have been used to develop drug delivery systems for entrapping and delivering drugs orally.

CONTROLLED DRUG DELIVERY

One of essential issues of drug formulation is the controlled release of drugs, which can improve therapeutic efficacy by offering prolonged in vivo action, controlled blood concentration as well as tissue-targeted local release 4-6. A possible approach to the controlled and sustained release of drugs involves incorporation of drug molecules into the biodegradable polymer microspheres. Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant or cyclic

over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Controlled release refers to the use of a delivery device with the objective of releasing the drug into the patient body at a predetermined rate, or at specific rimes or with specific release profiles. This could revolutionize the manner of medication and offer following advantages along with some disadvantages.

Advantages	Disadvantages
Reduction in dosing frequency	High cost
Reduced fluctuations in circulatory drug levels	Unpredictable or poor in vitro – in vivo correlation
Avoidance of night patient compliance	Dose dumping
Increased patient compliance	Reduced potential for dosage adjustment
Mire uniform effect	Increased first pass clearance
Decreased side effects like reduced GI irritation	Poor systemic availability in general

Various characteristics of drug molecule that render it unsuitable for controlled release dosing

- Narrow therapeutic index
- Short/long elimination half life
- Poor absorption
- Active absorption large doses
- Low aqueous solubility
- Extensive first pass metabolism
- Incompatible pharmacological effects and
- Circulation time course
- Controlled-Release mechanisms

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale through pores in the polymer matrix or on a molecular level, by passing between polymer chains.

Biopharmaceutical aspects of regulatory requirement and new drug applications The controlled release formulation developed should aim to accomplish two important Objectives:

- It should allow a maximum possible percentage of the dose in the formulation to be absorbed in controlled manner.
- It should be capable of minimizing patient-to-patient variability.

Over the past three decades, considerable research interest has arisen worldwide in the development of new colloidal drug delivery systems. The ideal colloidal delivery system could transport the associated drug to its desired site of action and then release it at an optimum rate. The carrier itself should be non-toxic and able to be degraded in vivo so that it does not accumulate indefinitely in the tissues. The colloidal preparation also needs to be pharmaceutically acceptable with regards to stability and ease of administration12,13. Microencapsulation is a technology devoted to entrapping solids, liquids, or gases inside one or more polymeric coatings. Microencapsulation helps to separate a core material from its environment until it is released. It protects the unstable core from its environment, thereby improving its stability, extends the core's shelf life and provides a sustained and controlled release15, 16.

MICROSPHERES

There are various approaches in delivering a therapeutic substance to the target site in a controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 m17. Microsphere based drug delivery have received considerable attention in recent years. The most important characteristic of microspheres is the micro phase separation morphology which endows it with a controllable variability in degradation rate and also drug release. Biodegradable microspheres can be prepared from certain synthetic as well as natural polymers. An important requirement of such polymers is that the degradation products should be non-toxic because such products eventually enter circulation or result in tissue deposition. Biodegradability carrier matrices can be designed to deliver the therapeutic agent for periods ranging from a few days to a few years. Methods of preparation Preparation of microspheres should satisfy certain criteria The ability to incorporate reasonably high concentrations of the drug.

- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagents with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and
- Susceptibility to chemical modification.
- Some of the important methods used for the preparation of microspheres are:
- Single emulsion technique

The micro particulate carriers of natural polymers i.e., those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, diacid chloride etc. Heat denaturation is not suitable for thermo labile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation.

Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the Poly Vinyl Alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. a number of hydrophilic drugs like Luteinizing Hormone Releasing Hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction.

Polymerization techniques

Polymerization techniques conventionally used for the preparation of microspheres are mainly classified as:

- Normal polymerization
- Interfacial polymerization
- Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be molded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization.

Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion.

MATERIALS

Eprosartan-Pharma grade-Glenmark Pharmaceuticals LTD, HPMC K 15M-LR-Spectrum pharmalabs Hyderabad, EC-LR-Spectrum pharmalabs Hyderabad, Carbopol 940-LR-Shreeji chemicals, Mumbai, NAHCO3-LR-S D fine chemical Ltd, Mumbai, Calcium Chloride-LR-S D fine chemical Ltd, Mumbai, Sodium Alginate-LR-S D Fine chemical Ltd, Mumbai.

METHODOLOGY

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the ratio development of dosage form.

1. Solubility

Solubility of Eprosartan was determined in pH 1.2 and pH 7.4 and 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Eprosartan in beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analyzed by spectrophotometrically.

Identification of Eprosartan

2. Determination of UV spectrum of Eprosartan:

10 mg of Eprosartan was dissolved in 10 ml of 7.4 pH buffers so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 100 µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10 µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

3. Calibration curve

II. Preparation of Standard Calibration Curve of Eprosartan in pH 7.4:

Preparation of Stock Solution

10mg of Eprosartan was dissolved in 10ml of pH 7.4 buffer so as to get a stock solution of 1000µg/ml concentration

Preparation Standard Solution

1ml of stock solution was diluted to 10ml with pH 7.4 buffer in 10ml volumetric flask this gives a concentration of 10µg/ml.

Aliquot of standard drug solutions were prepared and transferred in to 10ml volumetric flask and were diluted up to the mark with pH 7.4 buffer. This gives the final concentration of 0.5, 1, 1.5, 2.0, 2.5, 3.0 µg/ml µg/ml of Eprosartan respectively. The absorbances of the solution were measured against pH 7.4 as blank using UV visible spectrophotometer. The absorbance values at 233 nm were plotted against concentration (µg/ml) to obtain the standard calibration curve.

4. Drug-Excipient Compatibility Studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information.

FT-IR Studies

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

FORMULATION DESIGN

Preparation of Eprosartan gelispheres

Method used: Ionic Gelation Technique

Gelispheres of Eprosartan were prepared by ionotropic gelation method using Sodium alginate, HPMC K15M, EC, Carbopol 940 and calcium chloride. Weighed quantity of drug and polymer were added to sodium alginate solution with stirring at about 800 rpm. Add NAHCO3 to the solution. The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 60 minutes. The obtained gelispheres were filtered and washed with purified water and then dried for 12 hours at 40°C. Preparation of gelispheres was optimized based on entrapment efficiency and release data.

Table 1: Formulation design for Eprosartan gelispheres using different ratios of drug and polymers

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eprosartan	400	400	400	400	400	400	400	400	**400**
HPMC K15M	400	600	800	--	--	--	--	--	**--**
Ethyl cellulose	--	--	--	400	600	800	--	--	**--**
Carbopol 940	--	--	--	--	--	--	400	600	**800**
Drug : Polymer (Ratio)	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	**1:2**
Sodium alginate	400	400	400	400	400	400	400	400	400
Calcium chloride(%)	2	2	2	2	2	2	2	2	2

RESULTS AND DISCUSSION

Solubility studies

Table 2: Solubility studies of Eprosartan:

Solvent	% Solubility
1.2 pH buffer	0.321±0.16
7.4 pH buffer	0.895±0.14
6.8 pH buffer	0.754±0.18

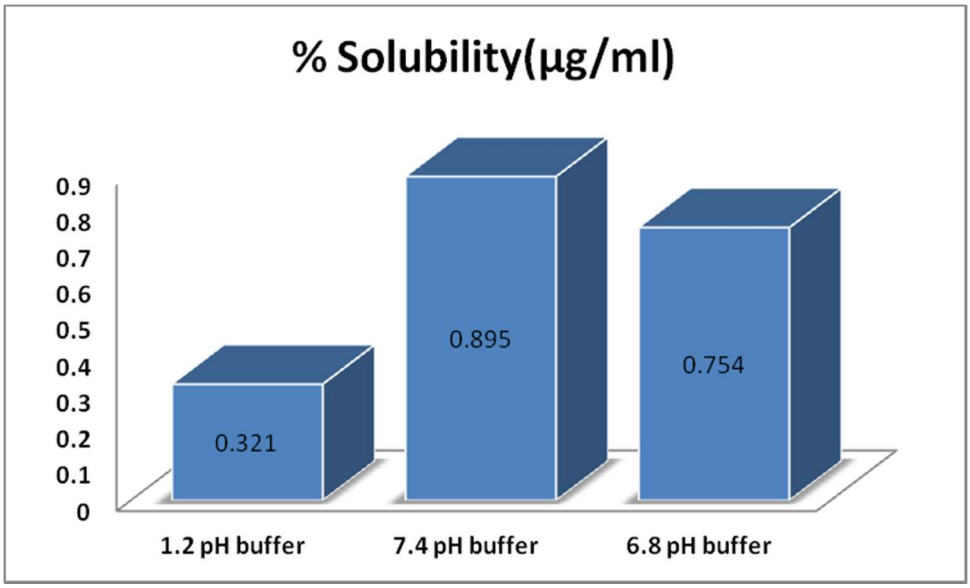

Fig 1: Solubility studies of Eprosartan

From the solubility studies it was observed that 7.4 pH buffer has more solubility than the other buffers.

Melting Point

Melting point of Eprosartan was determined by capillary method. The melting point of Eprosartan was found to be in the range 248°C and 250°C which compiled with BP standards, indicating purity of the drug sample.

UV Determination

The maximum absorbance of the Eprosartan in pH 7.4 buffer was found to be 233 nm as shown in Fig.

Calibration Curve of Eprosartan in pH 7.4

Table 3: Standard Calibration Curve of Eprosartan in pH 7.4

Concentration(µg/ml)	Absorbance
0	0
0.5	0.128
1	0.246
1.5	0.361
2	0.488
2.5	0.597
3	0.722

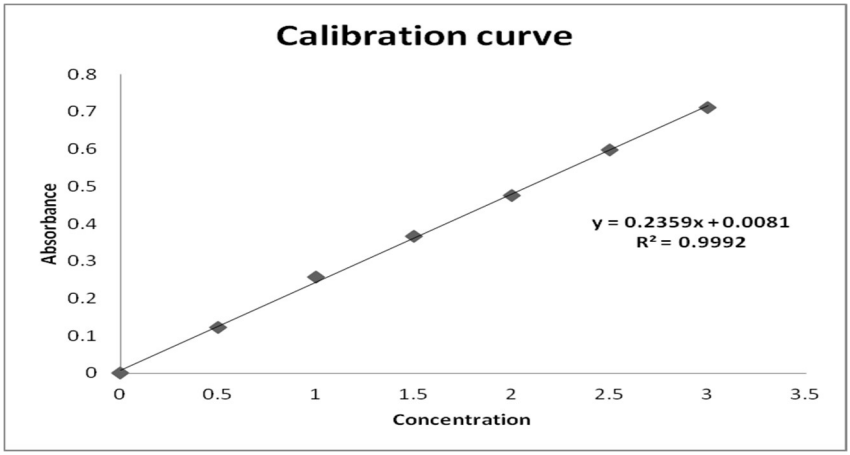

Fig 2: standard calibration curve Eprosartan in pH 7.4

the developed UV method for estimation of Eprosartan, the calibration curve data is presented in Table. The linearity range was found to be 0.5-3 µg/ml. Goodness of fit of regression equation was supported by highly significant value of 'r' (0.999).

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

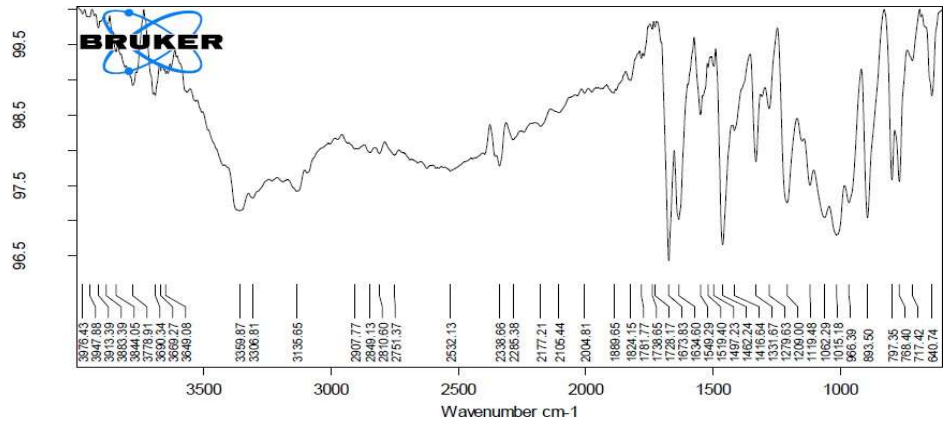

Fig 3: FTIR Spectrum of pure Eprosartan

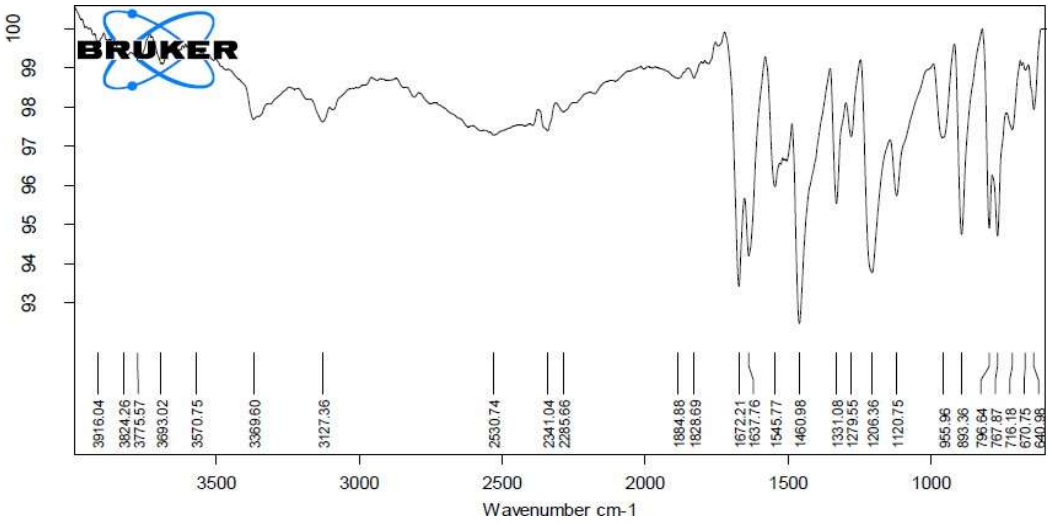

Fig 4: FTIR Spectrum of Eprosartan best formulation

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Eprosartan) and optimized formulation (Eprosartan + excipients) which indicates there are no physical changes.

Evaluation Parameters

Flow Properties

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.478±0.04	0.521±0.02	21.18±0.24	15.48±1.47	1.48±0.02
F2	0.462±0.01	0.534±0.04	25.45±0.39	19.52±1.24	1.75±0.06
F3	0.428±0.012	0.567±0.06	28.34±0.18	18.23±1.12	1.34±0.05
F4	0.398±0.02	0.498±0.18	27.75±0.25	20.11±1.26	1.45±0.02
F5	0.423±0.06	0.485±0.06	36.16±0.35	18.61±1.12	1.51±0.03
F6	0.456±0.05	0.524±0.08	29.25±0.36	16.86±3.18	1.62±0.14

F7	0.419±0.04	0.541±0.02	32.34±0.16	18.22±1.46	1.54±0.02
F8	0.465±0.16	0.536±0.14	33.36±0.24	15.22±1.24	1.69±0.05
F9	0.485±0.04	0.545±0.22	35.19±0.19	21.68±1.78	1.89±0.04

Inference

The angle of repose of all formulations (GF1-GF9) was ≤ 34.44 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.36g/cm3 - 0.41g/cm3. +Tapped density was found between 0.44g/cm3 to 0.48g/cm3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.12-17.02and Hausner's ratio from 1.12-1.20 which reveals that the blend has good flow character.

Percentage drug entrapment efficiency, drug content, percentage yield

S.no	Formulation Code	Percentage yield	Drug content (%)	Entrapment efficiency (%)
1	**F1**	74.64	92.10	94.16
2	**F2**	76.42	94.62	93.22
3	**F3**	84.19	96.62	96.78
4	**F4**	86.41	98.96	95.26
5	**F5**	89.46	95.82	97.82
6	**F6**	85.62	97.83	96.68
7	**F7**	86.72	95.16	93.62
8	**F8**	88.74	97.72	95.29
9	**F9**	95.92	98.29	97.28

Surface morphology - Scanning Electron Microscopy (SEM)

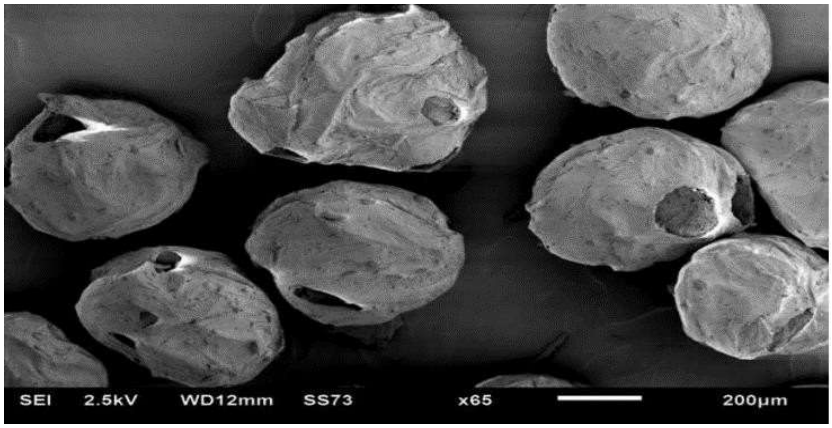

Fig 5. SEM photographs of floating gelispheres using sodium alginate and guar gum

From the results of SEM analysis it was observed that the surface area of Gelispheres was spherical and found to be rigid in nature, due to the higher polymer concentration, and the viscosity of the guar gum.

Determination of Average particle size

Table 4: Average diameter of Eprosartan gelispheres

Formulation code	Average size (µm)
F1	612
F2	524
F3	446
F4	320
F5	260
F6	100
F7	700
F8	600
F9	560

As the ratio of polymer was increased, the mean particle size of Eprosartan gelispheres had also. The significant decrease may be due to the increase in the viscosity of the droplets. Eprosartan spheres having a size range of 100 to 700 micrometer with normal frequency distribution was obtained.

In Vitro Dissolution Studies

Table 5: In Vitro Release Data of Eprosartan Gelispheres

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	29.48	21.25	25.48	26.82	32.27	29.54	18.26	28.56	16.24
2	38.25	34.19	37.52	39.26	41.81	36.27	26.48	37.71	25.61
3	46.65	48.26	48.62	51.84	53.19	48.19	39.85	45.81	38.38
4	55.29	57.28	58.19	56.86	59.25	56.28	45.66	52.87	45.75
5	68.34	65.42	68.46	68.92	68.74	62.65	52.98	59.82	52.15
6	73.19	78.16	79.28	83.86	86.81	69.76	59.85	68.46	59.26
7	82.28	85.28	85.47	89.76	92.26	76.12	66.76	76.84	68.39
8	89.34	91.36	89.76	93.01	96.36	88.24	75.68	88.76	74.16
9	98.16	95.29	97.19	98.75	98.19	93.12	83.84	93.92	83.75
10		98.15				99.28	89.26	98.28	90.18
11							98.84		95.26
12									99.75

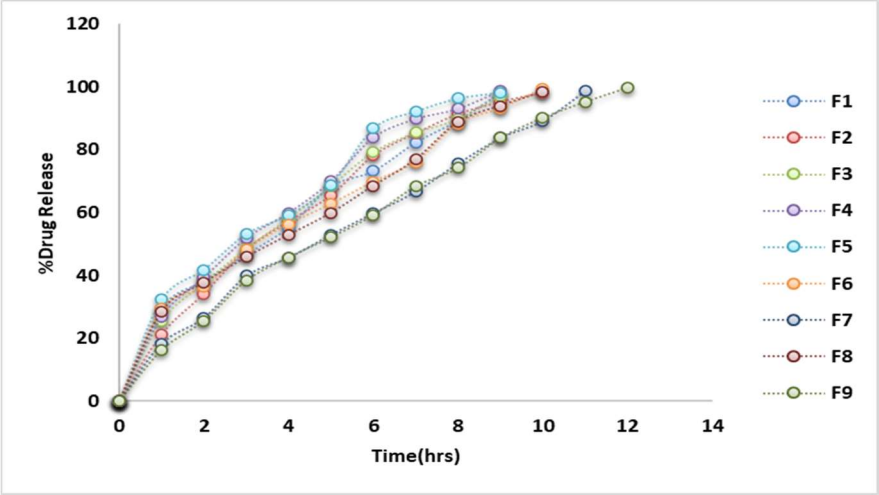

Fig 6: % CDR profile of Eprosartan gelispheres F1-F9

By comparing the above dissolution studies of formulations F1-F9. Maximum drug release was found in F9 formulation containing Drug: Carbopol 940 in 1:2 ratio. So F9 formulation was taken as the optimized formulation, and drug release kinetics were performed for F9 formulation.

Drug Release Kinetics Studies

Table 6: Regression co-efficient (r2) values Eprosartan gelispheres

Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				r^2 value	'n' value
F9	0.983	0.717	0.971	0.723	1.224

The optimized formulation F9 has coefficient of determination (R2) values of 0.983 0.717 0.971 and 0.723 for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the First order, indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation

which showed linearity with n value of 1.224 for optimized formulation. Thus n value indicates the Non -Fickian diffusion. Thus, the release kinetics of the optimized formulation was best fitted into Zero order with Non -Fickian diffusion.

SUMMARY & CONCLUSION

Goal of present work is to provide a therapeutic amount of (Eprosartan) to the proper site in the body and also to achieve and maintain the desired Eprosartan concentration. An attempt was made to prepare gelispheres of Eprosartan ionic gelation techniques by using polymers like HPMC K15M, carbopol and EC achieve an oral controlled release of the Eprosartan. In the present study nine formulations were formulated by using HPMC K15 M, Carbopol and EC in various concentrations with individual and combination with different ratios. In preformulation study, estimation of Eprosartan was carried out by Shimadzu UV spectrophotometer at λ max 233nm using 7.4 pH Phosphate buffer as buffer, which had a good reproducibility and this method was used in entire study. All the formulations were subjected for evaluation. Results of preformulation studies, FTIR, % yield, drug content, and entrapment efficiency, in vitro dissolution and release kinetics shown satisfactory results. The FTIR Spectra revealed that, there was no interaction between polymers and Eprosartan. Entrapment efficiency was increased with increased polymer concentration. From the results it can be inferred that there was a proper distribution of Eprosartan in the gelispheres and the deviation was within the acceptable limits. On the basis of release data and graphical analysis formulation F9 showed a good Sustained release profile with maximum entrapment efficiency because of high polymer concentration. The co-efficient of determination indicated that the release data was best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism. The diffusion exponent 'n' values of Korsemeyer-Peppas model was found to be in the range of more than 1 for the Eprosartan gelispheres prepared with drug and Carbopol 940 indicating super case II transport diffusion mechanism of drug through Eprosartan gelispheres.

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