IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2022 Vol.:25, Issue:2

Formulation and Evaluation of Telmisartan Loaded Microsphere

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 21 August 2022
Accepted: 27 August 2022
Published: 30 September 2022

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Microspheres, Telmisartan, Solvent evaporation, Novel drug delivery system.

ABSTRACT

Microspheres are small spherical particles that are ranging from 1-1000 u. Microspheres are widely used in drug delivery system. The main applications are in the treatment of cancer, ophthalmic, diseases and diagnostic purposes, in this article discussion was made on drug Telmisartan which is prepared as microspheres by using solvent evaporation method. Where, drug-polymer ratio had a significant effect on each parameter like particle size, % in-vitro drug release and drug entrapment efficiency. It is observed that the drug-polymer ratio resulted in increase in particle size and % entrapment efficiency, here % drug release rate is decreased with increase in the concentration of the polymer. the drug release is 94% after 16 hours which is same as the market formulation release drug profile. As the study shows the respective formulation is more effective to show the impact on the disease.

INTRODUCTION

The drug content maintenance at the site of action is the primary concern of the drug formulation design. Some conventional drug dosage forms can lead to poor management of plasma drug concentration, drug level fluctuation can be due to frequent administration and variation in the absorption, distribution and metabolism can result in toxic effects or may drug ineffective. Such problems can be resolved by designing a new drug delivery system that can provide a steady state plasma concentration of the drug administration to the body. Recent studies and researches have shown the development of controlled released drug delivery systems. The advantage of controlled Release drug delivery system is to enhance of the commercial value of the product by increasing the patent life. These types of dosage forms are designed to release drug constantly over an extend period. [1,2]

Controlled drug delivery system is designed by in capsulating the drug content inside the polymeric carriers which made great progress in last decades as they enhance the drug release and reduce adverse events by drug localization and the site of action and to provide control on drug release, there for the entrapment inside polymers provides shield to sensitive drugs (like, proteins peptides) from enzymatic and chemical reactions or decomposition. Microspheres is designed by using biodegradable polymers which are widely used to achieve controlled release of drug the major advantage of using biodegradable polymers is after performing the function they break down in two biologically easy manner. There were many micro encapsulation techniques have been developed for the same purpose.[3] However, appropriateness of these techniques depends on the nature of the drug ingredients mainly polymer the most suitable microencapsulation techniques are phase separation, emulsion solvent evaporation, spray drying, polymerisation, etc. Where solvent evaporation method for microencapsulation of water-insoluble drugs using water-insoluble polymer.[4]

Telmisartan microspheres were successfully formulated and prepared by solvent evaporation method. Where drug polymer ratio had a significant role on various parameters like % entrapment efficiency, particle size and % invitro drug release.

MATERIAL AND METHOD

Selection of Drug and excipients

Telmisartan was obtained from Alembic Ltd., Vadodara, India. HPMC from Acros Organics, New Delhi, India. Eudragid from Himedia Laboratories Pvt. Ltd. Mumbai, India. Tween 80,

Dichloromethane and Ethanol from Merck India Ltd.Mumbai,India. All other chemicals and reagent were of analytical grade.

PREFORMULATION STUDY

It is the initial evaluation during preformulation studies which assess the color, odor and taste of the substance. The appearance was checked visually for color, homogeneity and transparency. The appearance was checked visually for color, homogeneity and transparency.[12]The basic purpose of the preformulation activity is to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product and to provide an ultimately basis for optimizing drug product quality, efficacy and performance. Preformulation Is defined as an investigation of physio-chemical properties of sustained release matrix dosage form substance alone and when combined with the excipient.

Organoleptic parameters

It is the initial evaluation during Preformulation studies which assess the color, odor and appearance of the drug.

Solubility

The most widely used techniques during preformulation analysis is solubility profile of a drug candidate. It is the backbone of study and efficacy stage that determines the performance of a developed dosage form or formulation. Solubility and permeability form the scientific basis of biopharmaceutics classification system (BCS), which can provide framework for designing type of drug delivery system. The solubility of a drug is the amount of the drug that dissolves in a given solvent to produce a saturated solution at constant temperature and pressure.[9]

Solubility is an important physical and chemical property of drug substance, that determines its systemic absorption and therapeutic efficacy. Solubility of drug was determined in various solvents.

Melting point

Melting point of a drug was determined by open capillary method.

Partition Coefficient

Partition coefficient (Log P) value is defined as ratio of an unionized drug distributed between the aqueous and the organic phase. Oil-water partition coefficient gives an idea about drug's

ability to cross the lipid membrane. Lipophilic or hydrophilic balance is one of the most important factors for optimum drug absorption and delivery of drug. Due to lipidic nature of biological membrane, the amount of a drug absorbed which depends heavily on its lipophilicity. It is an unionized form of a molecule that has better lipophilicity and therefore, it has received a major importance.[15]

The partition coefficient of drug was examined in n-Octanol: water system. It was determined by taking 5mg of drug in separating funnel containing 5ml of n-Octanol and water. The separating funnel was shaken for 2 hours in a wrist action shaker for equilibrium. Two phases were separated and the amount of drug in the aqueous phase was analyzed spectrophotometrically at 270 nm after appropriate dilution with buffer.

$$\text{Partition Coefficient} = \frac{\text{Concentration of drug in oil phase}}{\text{Concentration of drug in aqueous phase}}$$

If the value of Log P is 0, then it indicated that drug has equal distribution in water and in partition solvent. Value of Log P less than 1 is indicative of higher water solubility and value greater than 1 is indicative of higher lipidic solubility. For the optimum solubility and absorption, a proper hydrophilic and lipophilic balance is necessary.

Determination of absorption maximum (λ_{max})

0.2 ml of stock solution (100 µg/ml) was taken in 5ml volumetric flask and volume was made up to 5 ml with solutions of methanol (4 ug/ ml) and scanned on a double beam spectrophotometer against the respective media blanks. Where, the absorption maximum (λ max) of 293 nm was obtained. This λ max was selected for the preparation of standard curve of telmisartan in different media.[10]

Standard calibration curve

From the stock solution (100µg/ml) aliquots of 5, 15, 20-, 25-, 30-, and 35-ml solution were taken and diluted with methanol to obtain concentrations from 5 to 35µg/ml. The absorbance of solutions was determined at λ max 293 nm against methanol as blank. The experiment was repeated and the calibration curve was plotted from the mean value.

Compatibility Study of drug and excipient

Drug excipient compatibility was determining by the FTIR. In this work we are using FTIR for compatibility studies.

FTIR

Fourier transform infrared (FTIR) spectral analysis, the pure drug telmisartan and polymers used in this experimental work were studied for compatibility studies. We carried out these studies by taking 2 mg of sample in 200mg of potassium bromide (Perkin Elmer, Spectrum100, Japan). The range of scanning was 400-4000 cm-1 and the resolution was 1 cm^{-1}.

Composition of microsphere

Table 1: Composition of microsphere

S.No.	Formulation	HPMC (mg)	Eudragit (mg)	DCM+Ethanol (ml) (1:3)	Drug (mg)	Aqueous phase containing 1% Tween 80 (ml)
1.	F1	800	100	20	40	150
2.	F2	700	200	20	40	150
3.	F3	600	300	20	40	150
4.	F4	500	400	20	40	150
5.	F5	400	500	20	40	150
6.	F6	300	600	20	40	150
7.	F7	200	700	20	40	150

Characterization of microspheres Percentage yield

The percentage yield of microspheres was calculated using the following formula,

$$Percentage\ Yield = \frac{Practical\ Yield}{Theoritical\ Yield} \times 100$$

Drug entrapment efficiency

Aliquots of microsphere dispersion were subjected to centrifugation using cooling ultracentrifuge at 12000rpm. The clear supernatant was siphoned off carefully to separate the unentrapped drug and the absorbance was recorded at λmax 293nm using UV/Vis spectrophotometer. Sediment was treated with 1ml of 0.1% Triton X 100 to lyse the vesicles and then diluted to 100 ml with ethanol and absorbance was taken at 293 nm. Amount of telmisartan in supernatant and sediment gave a total amount of drug in 1 ml dispersion. The

percent entrapment was calculated using the formula,

$$\%\ entrapment = \frac{Amount\ of\ drug\ in\ sediment}{Amount\ of\ drug\ added} \times 100$$

Vesicle size by Zeta Potential

Size and size distribution was determined by dynamic light scattering (DLS) and using a computerized inspection system (Malvern Zeta master ZEM 5002, Malvern).

SEM

Scanning electron microscopy (SEM) was also conducted to characterize the surface morphology of the microsphere for which a drop of microsphere system was mounted on clear glass stub, air dried and coated with Polaron E 5100 Sputter coater (Polaron,) and visualized under Scanning Electron Microscope (SEM Leo 430,).

***In vitro* drug release from the formulation**

The release of telmisartan from optimized microsphere was determined by membrane diffusion technique using Franz diffusion cell. The microsphere equivalent to 5%w/w of microsphere was taken in donor compartment. The donor and receptor compartment were separated by synthetic cellophane membrane. The synthetic cellophane membrane was mounted between donor and receptor compartment of cell. The receptor medium was filled with the phosphate buffer pH 7.4. The assembly was stirred at 200 rpm and receptor compartment was replenished with equal volume of phosphate buffer. Aliquots each of 1 ml was withdrawn periodically at an interval of 2, 4, 6, 8, 10, 12 and 24 hrs and replaced by an equal volume of receptor medium. The aliquots were suitably diluted with receptor medium and analysed by UV visible spectrophotometer.

Release kinetics

To analyse the in vitro release data various kinetic models were use to describe the release kinetics. The zero-order rate Eq. (2) describes the systems where, the drug release rate is directly independent on its concentration. The first order Eq. (3) describes the drug release from system where, the release rate is truly concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time-dependent process based on Fiskian diffusion. The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment.[18]

Zero - order kinetic model – Cumulative % drug released versus time.

First – order kinetic model – Log cumulative percent drug remaining versus time.

Higuchi's model – Cumulative percent drug released versus square root of time.

Zero order kinetics

$$A_t = A_0 - K_0 t$$

Zero order release would be predicted by the following equation: Where,

At=Drug release at time 't'

A0=Initial drug concentration.

K0=Zero-order rate constant(hr^{-1})

When the data is plotted as a cumulative percent drug release versus time, so, if the plot is linear then the data obeys Zero– order kinetics and its slope is equal to Zero order release constant K_0.

$$\log C = \log C_0 - Kt/2.303$$

First order kinetics

First-order release could be predicted by the following equation: Where,

C=Amount of drug remained at time 't'

C0=Initial amount of drug.

K=First-order rate constant (hr^{-1}).

When the data plotted as log cumulative percent drug remaining versus time, yields astraight line, indicating that the release follow first order kinetics. The constant 'K1'can be obtained When the data plotted as log cumulative percent drug remaining versus time, yields a straight line, indicating that the release follow first order kinetics. The constant 'K1' can be obtained by multiplying 2.303 with the slope value.[18]

Higuchi's Model

Drug release from the matrix devices by diffusion has been described by following Higuchi's

classical diffusion equation:

$$Q=[D\epsilon/\tau(2A-\epsilon Cs)Cst]^{1/2.}$$

Where,

Q=Amount of drug release at time‘t’

D=Diffusion coefficient of the drug in the matrix.

A=Total amount of drug in unit volume of matrix.

Cs=Solubility of drug in the matrix

Є=Porosity of the matrix.

τ=Tortuosity.

t=Time (hrs at which q amount of drug is released)

Above equation can be simplified as if we assume, that ‘D’, ‘Cs’ and ‘A’are constant. Then equation: becomes

$$Q=Kt^{1/2}$$

Preparation of Microsphere

Microspheres containing telmisartan as a core material were prepared by Solvent Evaporation method. Telmisartan, Hydroxy Propyl Methyl Cellulose (HPMC) and eudragid were dissolved in a mixture of ethanol and dichloromethane (3:1) at room temperature (As in table I). This was poured into 250mL water containing 1% Tween-80 maintained at a temperature of 30–40 °C and subsequently stirred at 300rpm agitation speed for 45 minutes to allow the volatile solvent to evaporate. The microspheres are formed and filtered, then washed with water and dried in oven at 37°C.

RESULT AND DISCUSSION

Zero order kinetic model refers to the process of constant drug release from a drug delivery device independent of the concentration. The zero-order graph of F4 formulation showed the constant drug release from the microsphere, the results of the zero-order model was found to be y = 5.637x + 1.150, R^2= 0.988. The first order kinetic model describes the release from system where release rate is concentration-dependent. The results of first order kinetic model

were found to be y = -0.052x + 2.097, R^2= 0.964. The Higuchi model is used to describe the limits for transport and drug release. The Higuchi model of patches was found to be, 21.02x - 10.44 R^2= 0.954. Sustained drug release in this study indicates, the hydrophobic matrix microspheres of stavudine, prepared using EC, and successfully prepared by the emulsion solvent diffusion technique.

The purpose of this study was to formulate telmisartan against microsphere. Several characteristics such as entrapment efficiency, zeta potential, SEM, drug release study, kinetic and stability studies were investigated. The preformulation studies such as organoleptic characters of the drug were performed and the results were found to be colour, odour, and appearance of the drug are white to slightly yellowish in colour, odourless and solid in appearance. The solubility of the telmisartan was found to be is freely soluble in ethanol, methanol, soluble in Dichloromethane and chloroform, and sparingly soluble in water. Partition coefficient is calculated by the ratio of equilibrium concentration of a dissolved substance in a two-phase system they are n-octanol and buffer at Ph 7.4. The partition coefficient of Telmisartan was found out to be 3.2. The UV absorbance of telmisartan standard solution in the range of 5-35 µg/ml of drug in methanol showed linearity at λ max 293nm. The linearity was plotted for absorbance against concentration with R^2 value 0.985 and with the slope equation y=.0.023x + 0.137. The compatibility between the drug and the selected lipid and other Excipients was evaluated using FTIR peak matching method. As results in no appearance or disappearance of peaks in the drug lipid mixtures, which has confirmed the absence of any interaction between the drug, lipid and other chemicals. Formulation of the microsphere was performed with varying the quantity of HPMC and Eudragid in ethanol+DCM (1:3). Microspheres were subjected to characterization by calculating percentage yield, entrapment efficiency SEM, particle size and in-vitro drug release. The entrapment efficiency of the drug was investigated by ultra-centrifugation and among all formulations F4 formulation showed better entrapment (78.5%).

The best formulation was selected based on percentage yield and entrapment efficiency and the best formulation was subjected to SEM and particle size analysis. The in-vitro drug release of telmisartan-containing microsphere were determined. Among all the formulations F4 formulation was found to release maximum (94%) drug within 16 hours.

Pre-formulation Studies

It is the initial evaluation during preformulation studies which assess the colour, odour, melting point, solubility and determination of lamda max of the substance.

Organoleptic parameters

It is the initial evaluation during Pre-formulation studies which assess the color, odor and appearance of the drug.

Table 2: Organoleptic properties of Telmisartan

Drug	Organoleptic properties	Observation
Telmisartan	Color	White to slightly yellowish
	Odor	Odorless
	Physical state	Solid

From the above table it is depicted that the drug telmisartan is white to slightly yellowish in colour, odourless and solid in appearance.

Melting point determination

Melting point of drug was determined by Open capillary method.

Melting point of Telmisartan

Table 3: Melting point of Telmisartan

Drugs	Observed	Reference
Telmisartan	263°C	261-263° C

The melting point of Telmisartan was found to be 263^{o} C.

Solubility study of Telmisartan

Solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy. Solubility of drug was determined in different solvents.

Solubility of Telmisartan

Table 4: Solubility of Telmisartan

Drug	Solvents	Observation/Inference
Telmisartan	Methanol	Freely soluble
	Ethanol	Freely soluble
	Water	Sparingly soluble
	Dichloromethan	Soluble
	Chloroform	Soluble

The above table shows that the drug Telmisartan is freely soluble in ethanol, methanol, soluble in Dichloromethane and chloroform, and sparingly soluble in water.

Partition Coefficient

Table 5: Partition coefficient of telmisartan.

S. No.	Drug	solvent	Result
1	telmisartan	n-octanol-buffer at pH 7.4	3.2

Partition coefficient is calculated by the ratio of the equilibrium concentration of a dissolved substance in a two-phase system they are n-octanol and water. The partition coefficient of Telmisartan was found out to be 3.2.

Determination of λ max

Solution was scanned under UV-Vis Spectrophotometer and λ max was determined. It was found to be as per the monograph.

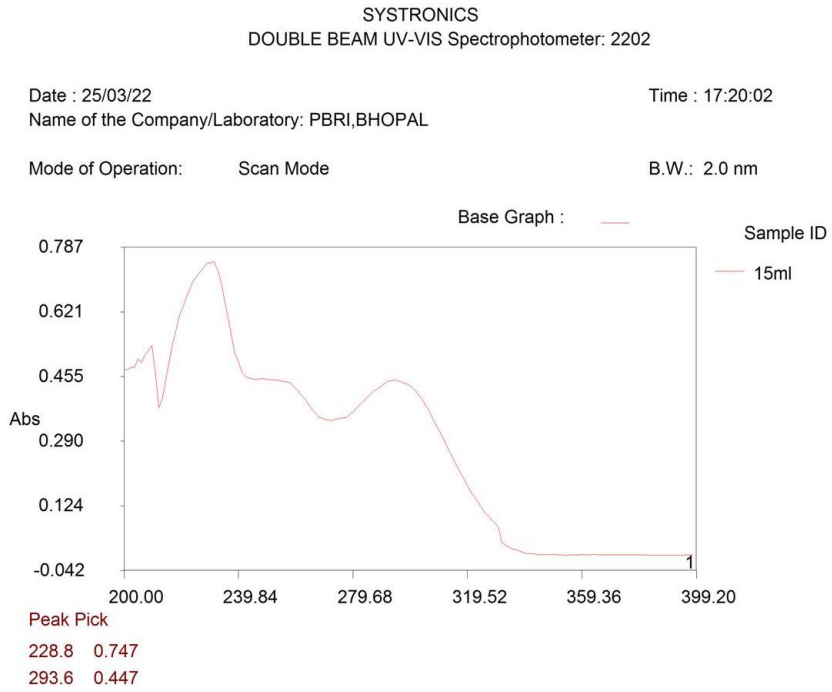

Figure 1: λmax of Telmisartan

Standard Calibration Curve of Telmisartan

All dilutions and measurements were made in methanol and the absorbance was taken at λ_{max} 293 nm against a reagent blank. The standard curve was plotted between absorbance and concentration.

Table 6: Calibration Curve of telmisartan

S.NO.	Concentration (µg/ml)	Absorbance (293nm)
1.	5	0.284
2.	10	0.344
3.	15	0.467
4.	20	0.608
5.	25	0.761
6.	30	0.881
7.	35	0.932

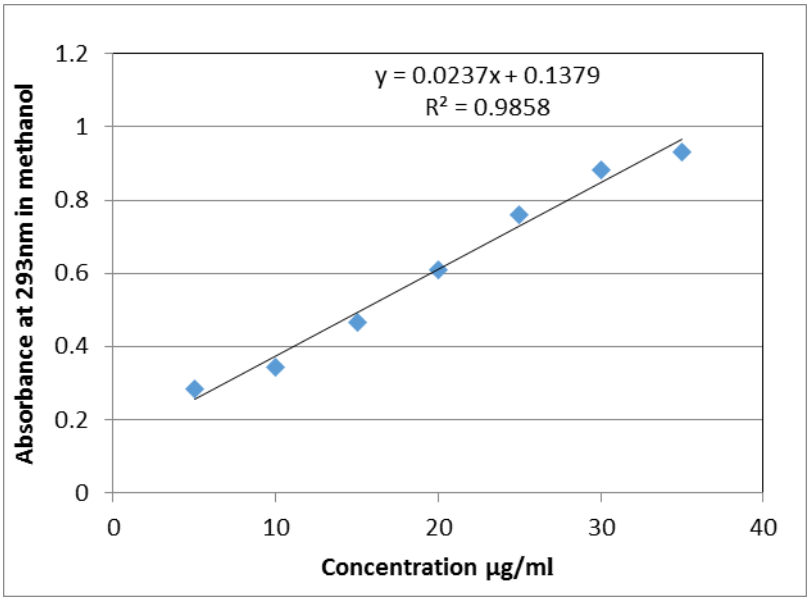

Figure 2: Calibration Curve of Telmisartan

Compatibility studies by FTIR

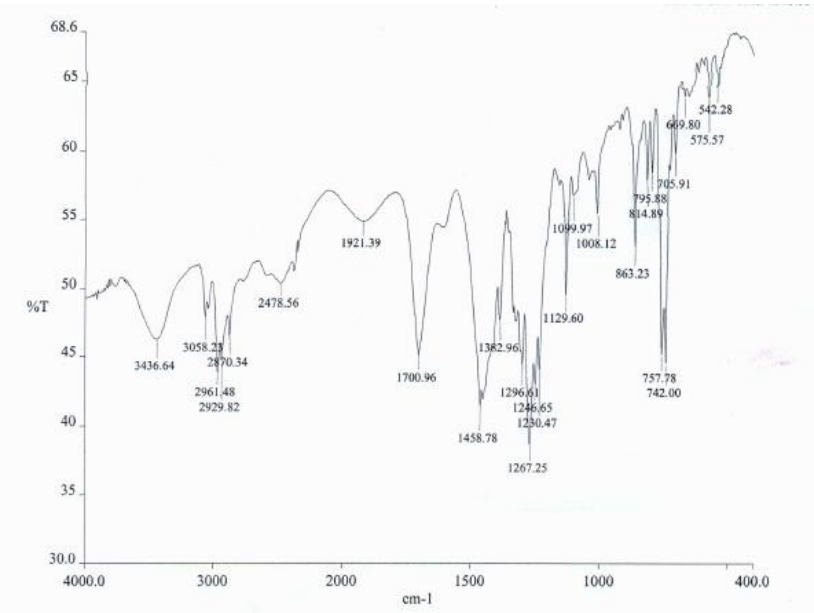

Figure 3: FTIR of Telmisartan

Interpretation of FTIR of telmisartan

Table 7: Interpretation of FTIR of telmisartan

S. No.	Wave number	Functional group
1	3436.64	N–H stretching
2	3058.23	C–H stretching (aromatic)
3	2929.82	C–H stretching (alkane)
4	2478.56	O–H stretching
5	1921.39	C≡C stretch
6	1700.96	C=O stretch
7	1458.78	C–C stretch (aromatic)
8	1267.25	C–N stretch

Characterization of microsphere

Percentage yield

Percentage yield of all the formulations were calculated and results are showing below:

Table 8: Percentage yield of microshpere formulations

S.No.	Formulation	%yield
1	F1	54.65
2	F2	59.34
3	F3	62.21
4	F4	58.11
5	F5	49.72
6	F6	51.23

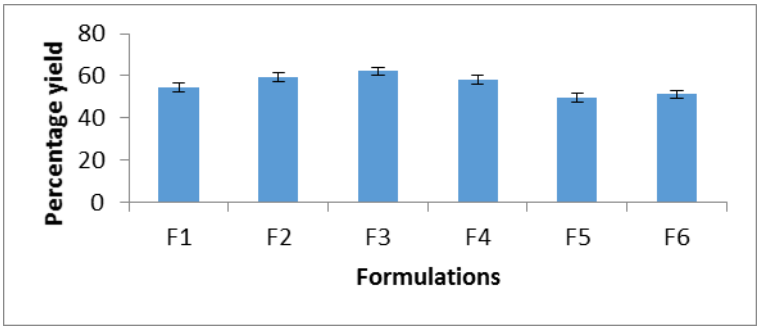

Figure 4: Percentage yield of all formulations

Drug entrapment efficiency

Once the presence of bilayer vesicles was confirmed in the microsphere system, the ability of vesicles for entrapment of drug was investigated by ultra-centrifugation. Ultracentrifugation was the method used to separate the microsphere vesicles containing drug and un-entrapped or free drug, to find out the entrapment efficiency.

Table 9: Drug entrapment efficiency of microsphere formulation

S.No.	Formulation	% Entrapped drug
1	F1	72.5
2	F2	62.2
3	F3	75.7
4	F4	78.5
5	F5	50.4
6	F6	48.4

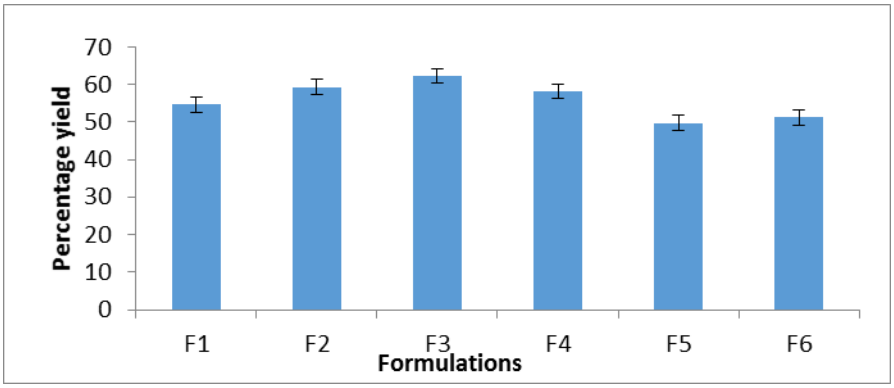

Figure 5

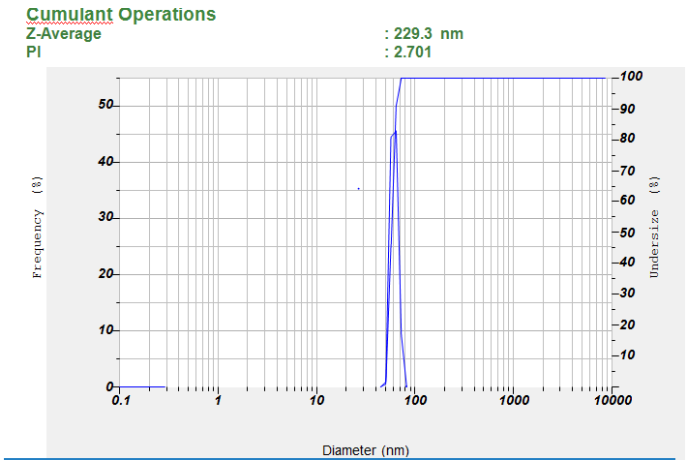

Figure 6: Zeta potential of prepared F4 formulation

Scanning Electron Microscopy

Scanning Electron Microscope (SEM) is also used to characterize the surface morphology of the microsphere. One drop of ethosomal is mounted on a clear glass tube, it is air dried and visualized under Scanning electron microscope.

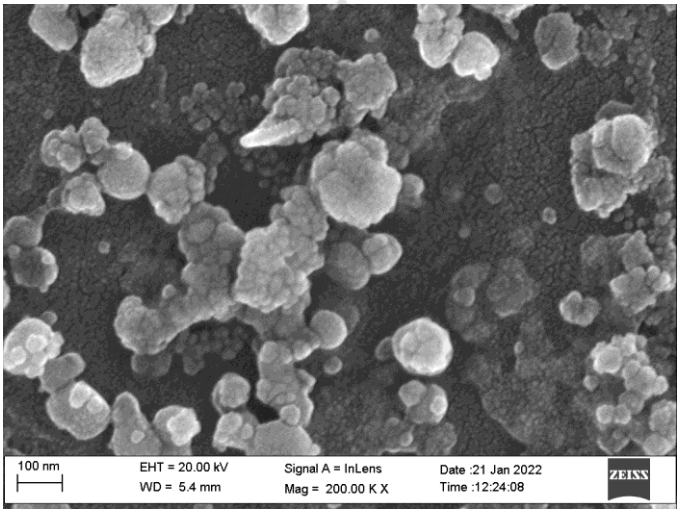

Figure 7: SEM image of F4 formulation

In vitro Drug release study

The in vitro release study of prepared formulations was determined. The drug release was carried out for a period of 24 hrs in 7.4 pH phosphate buffer. The cumulative percent drug release in all formulations was plotted against time. The Maximum percent of drug release was found in F4 formulation which contains maximum drug release.

Table 10: % cumulative drug release of formulation

Time (hrs)	F1	F2	F3	F4	F5	F6
2	13.65	10.64	11.74	15.84	11.64	16.84
4	22.866	19.65	25.94	22.37	25.85	24.37
6	30.76	26.02	32.47	36.38	31.84	38.64
8	41.85	35.68	48.72	44.84	46.83	46.48
10	58.56	48.38	52.73	51.83	52.46	62.74
12	68.63	55.84	66.62	68.37	64.37	70.43
14	80.73	71.64	83.84	80.74	79.64	81.74
16	91.47	88.65	92.73	94.74	90.74	90.47

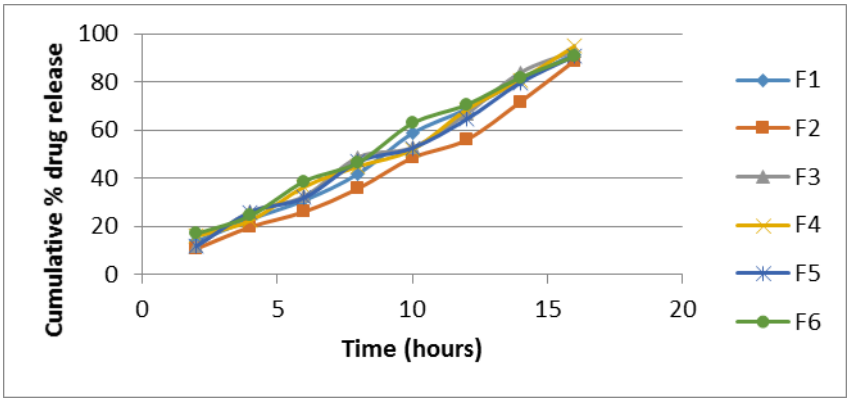

Figure 8: Cumulative % drug release

Release kinetics

Since formulation F4 showed highest drug release so it was selected for the kinetic modelling.

Table 11. Release kinetics study of F4 formulation.

Formulation	Model	Kinetic parameter values
F4	Zero Order	$y = 0.109x + 33.48$ $R^2 = 0.683$
	First Order	$y = -0.000x + 1.853$ $R^2 = 0.936$
	Higuchi	$y = 19.97x + 14.80$ $R^2 = 0.869$

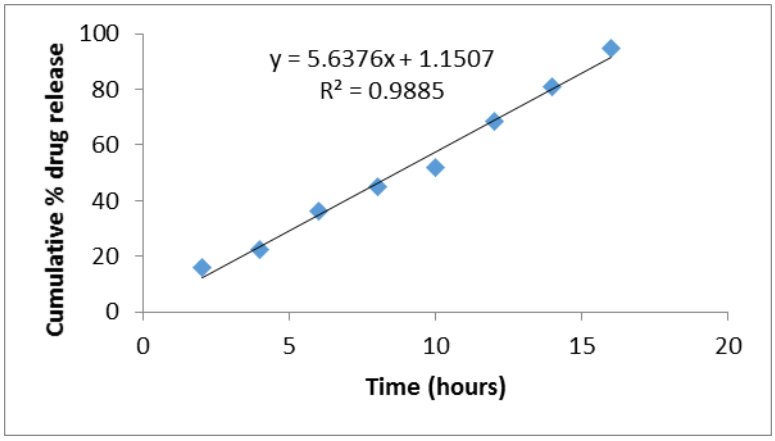

Figure 9: Zero order kinetic model

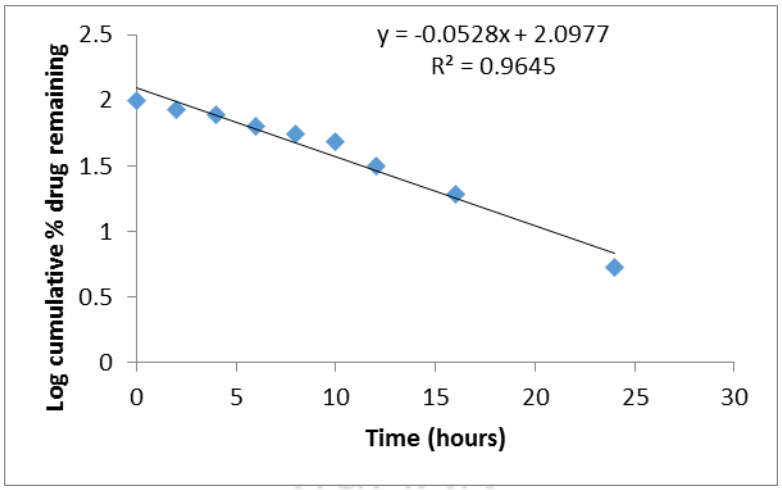

Figure 10: First Order kinetic model

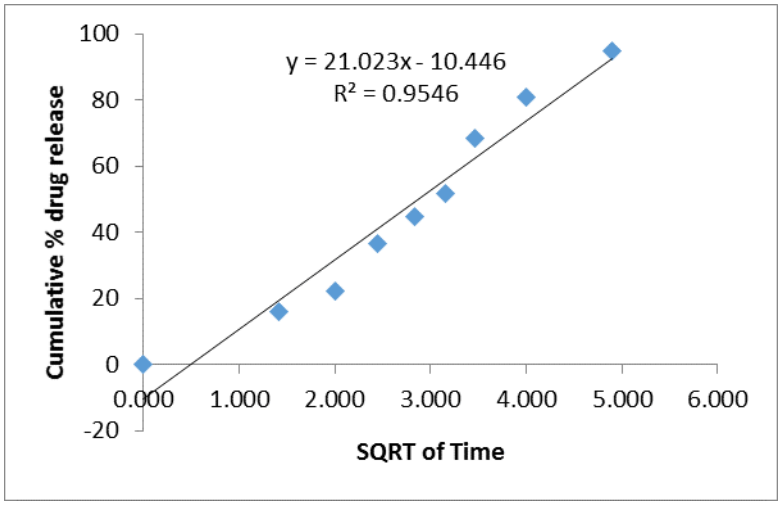

Figure 11: Higuchi mode

CONCLUSION

In this paper, Microspheres are the potential drug delivery carrier systems in the segment of novel drug delivery systems and are prepared with assorted polymers. Telmisartan microspheres were formulated and prepared successfully by solvent evaporation method. Drug polymer ratio played a significant effect on different parameters like % entrapment efficiency, particle size, and % *in vitro* drug release. It was observed, that increase in the drug-polymer ratio increased in particle size and % entrapment efficiency. Therefore, % drug release rate is decreased with increasing the concentration of the polymer. The batch F4 shows the drug release 94% after 16 hours, which was matched with the market formulation release profile. From the SEM study, it was observed that the microspheres were spherical and fairly smooth surface in appearance.

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