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RESEARCH ARTICLE

Preparation and *In-Vitro* Study of Telmisartan Microspheres

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ABSTRACT

The aim of present work was preparation and *in vitro* study of telmisartan microspheres. Drug identification and drug interaction study was determined by FTIR spectroscopy. Microspheres prepared by emulsion solvent diffusion and evaporation method using different polymers ratio of HPMCK , ethyl cellulose and prepared different batch F1 to F6 which show different drug release profile in upper GI tract and provide prolong gastric retention for about 10hr. Microspheres enhance absorption and improve bioavailability and thereby patient compliance. This system decrease GIT toxic effect and drug frequency. Different evaluation parameters performed for prepared microspheres drug delivery system like particle size, bulk density, tapped density, angle of repose, compressibility index, flow rate, % entrapment efficiency, % yield, % buoyancy and drug release profile using different method. Formulation F4 show excellent drug release profile for about 8 hr. when use different polymer ratio cause fluctuation in % buoyancy and % entrapment efficiency.

KEYWORDS

Telmisartan, Microspheres, Solvent Diffusion and Evaporation, Buoyancy, Bioavailability

INTRODUCTION

A recent advance drug delivery system (RADDS) provide therapeutic substance in the body and improve its efficacy by controlling the releasing rate at site of action and control resistance of drug in the body. The present system is beneficial for drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half – lives are eliminated quickly from the systemic circulation frequent dosing of these drug is required to achieve suitable therapeutic activity. To avoid this drawback the development of oral sustained controlled release formulation is an attempt to release the drug slowly into the gastro intestinal tract (GIT) and maintain an appropriate drug concentration in systemic circulation for a long time without affecting stomatch activities.[1]

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After administration of this drug delivery system drug release in a control manner at specific site of action for a prolong period of time by decreasing drug solubility and increasing residence time of dosage form at the site of action. Such system design only those drug which action required in stomach only.[2-3]

RADDS including floating drug delivery system also known as hydrodynamically balanced system, polymeric bioadhesive system, welling and expending system, and the gastric emptying device.[4]

The design of oral controlled drug delivery system (ORDDS) should be primarily aimed to achieving more predictable and increase bioavailability. The most feasible method for achieving a prolong and predictable drug delivery in the GI tract is to control gastric residence time by gastro retentive sustained

dosage forms that have some benefits in safety and efficacy over normal release system[5].

Microspheres provides continuous (constant) and prolonged therapeutic effect, reduced the GI toxic effect and dosing frequency and thereby improve the patient compliance[6]. The drug telmisartan,2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazole-1 yl]methyl}phenyl)benzoic acid is poorly soluble, easily absorbed in GIT, have short half-life and eliminate quickly from blood circulation so that floating drug delivery system is beneficial for telmisartan because this drug have favorable properties which required for this system to make drug bioavailable, decrease GI tract toxicity affect and increase availability of drug at the site of action and improve patient compliance by controlling gastro residence time.

Microspheres of telmisartan prepared by emulsion solvent diffusion and evaporation method by using different polymers ratio (HPMCK and ethyl cellulose), solvents (acetone and dichloromethane) and emulsifying agent (polyvinyl alcohol and span 80) after preparation of microspheres drug release profile and *in- vitro* parameters performed by using different methods.

Mode of Action of Telmisartan

Telmisartan is an angiotensin 2 receptor blocker that shows higher affinity for the angiotensin 2 receptor type 1(AT1) with the binding affinity 3000 times greater for AT1than AT2. It has longer half life any ARB (24hr) and the target volume of distribution among ARB_s (500 ltr). Addition to blocking the RA_s (ranin angiotensin system), telmisartan act as a selective modulator gamma (PPAR-Y), central regulator of insulin and glucose metabolism.

Telmisartan have dual mode of action may provide protective benefits against the vascular and renal damage (CVD) [encyclopedia][7]

MATERIAL AND METHODS

Telmisartan as gifted sample from Arbro labs and HPMC, ethyl cellulose, poly vinyl alcohol (PVA), dichloromethane, acetone, span 80, and n-hexane purchased from central drug house (New Delhi).

Preparation of Microspheres

Microspheres formulated by emulsion solvent diffusion and evaporation method to create hollow inner core. The drug and polymer ratio was dissolve in 20 ml solvent mixture of acetone and dichloromethane of different ratio. The mixture was dropped in 200ml solution containing 0.4% PVA and 0.40% span 80.

Resultant emulsion was stirred with mechanical stirrer at a constant speed 1000 rpm at various temperature range for 2 hr. After 1.30hr add 10 ml n-hexane and continuously stirrer.

After that prepared microspheres were washed with water, filtered and dried at room temperature.[8-9]

Evaluation of Microspheres

Micromeritic Properties

Microspheres evaluated by micromeritic properties such as particle size, bulk density, tapped density, angle of repose, flow properties, compressibility index etc[10].

Particle Size

Scanning electron microscopy was used to determine the size and shape of microspheres after gold coating.

Dry microspheres place on a electron microscope brass stub a coated with gold in an ion sputter then picture of microscope were taken by spectro random scanning of the stub. The microspheres were viewed at an accelerating voltage of 20kv.

Bulk Density

Weight accurately a quantity of microspheres and poured into the measuring cylinder and note the volume consumed by microspheres without tapping then calculate by formula.

Bulk density = weight of microspheres in gm/volume in ml consumed by microspheres

Tapped Density

After determination of bulk density, tapped graduate measuring cylinder 100 time and note

tapped volume and determined tapped density by formula.

Tapped density = weight of microspheres in gm/volume in ml after tapping

Flow Properties

The flow properties of the material result from many forces. Solid particles attract one another and force acting between particles when they in contact. The acting force between solid particles is

1. Frictional forces
2. Surface tension force
3. Mechanical force cause by interlocking of particles of irregular shape
4. Electrostatic force
5. Cohesive and vanderwaals forces
6. All of these force affecting the flow properties of solid.

Angle of Repose

Angle of repose measured the flow properties of powder and granules. Defined as the base angle of the cone formed when a powder or granular material falls freely on a flat surface through an orifice.

Formula used to determine angle of repose.

$$\text{Tan } \Theta = 2H/D$$

Where, H = standing height

D = diameter of the microspheres heap formed on a graph paper

Flow Rate (Compressibility Index)

Flow rate of microspheres determine by compressibility index (I) equation

$$I = [1\text{-}V/V_O] \times 100$$

Where, V = volume occupied by sample after tapping

V_O = volume before tapping

When value of I below than 15% show good flow properties and when value of I above 25% show poor flow properties.

Percentage Entrapment

Take microspheres equivalent to 30 mg telmisartan were crushed in glass mortar. Then crushed microspheres transferred into 100ml volumetric flask and make up the volume up to 100ml with 0.1 N HCl mix well and left the solution for 8hr. After 8hr filter the resultant solution and dilute according to need. The solution was analyzed by using UV spectrometer at 295nm wavelength against 0.1 N HCl as blank. The percentage (%) entrapment calculated as[11]

$$\% \text{ entrapment} = \frac{Calculated drug concentration by uv assay}{Theortical drug concentration} \times 100$$

Percentage Yield

The yield of microspheres can be calculated by weighing the final weight of microspheres after drying to the initial weigh of polymer and drug. It can be calculated using the formula[12]

$$\% \text{ yield} = \frac{Weight of dried microspheres}{Total polymer weight + Weight of drug taken} \times 100$$

Buoyancy Studies

Take 50 mg floating microspheres in a beaker which contain 100 ml simulated gastric fluid (SGF) of 1.2 pH with 0.02% W/V span 80. The mixture was stirred with magnetic stirrer at 100 rpm for 6hr. After 6 hr the floating and settled microspheres were separate by filtration, dried in oven, weight and calculate % buoyancy as[13]

$$\% \text{ buoyancy} = W_f / (W_f + W_s) \times 100$$

Where, W_f = floating microspheres

W_s = Settled microspheres

In Vitro Dissolution Study

In vitro dissolution study was performed using USP basket type dissolution apparatus. Take microspheres equivalent to 30 mg active drug filled in hard gelatin capsule. Simulated gastric fluid (SGF) of pH 1.2 used as dissolution medium fill in basket apparatus up to 900 ml set temperature at 37±0.5^{O}C and rotation speed 60 rpm for 8 hr. Drug release profile determined by withdrawing of 5 ml solution after each 1 hr interval and replace by fresh 5 ml dissolution medium, withdrawal solution filtered by filter paper, dilute according to need and drug release

profile of microspheres analysed by UV spectroscopy at 295 nm wavelength[14,15].

Stability Study

The optimum formulation of prepared microspores was selected on the basis of % entrapment, % drug release profile and % buoyancy. The selected formulation expose at two temperature 5-10^{O}C and 40-45^{O}C. Take 100-100 gm microspheres in two dishes and put one dish at 5-10^{O}C and other dish at 40-45^{O}C after 12 hr put those both dishes at room temperature for next 12 hr, these procedure continue for 30 days and formulation again evaluate for % buoyancy and % entrapment[7].

In Vitro Drug Release Kinetics

The obtained drug release data calculated according to Zero order (cumulative amount of drug versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi equation (cumulative percentage of drug release versus root time), korsmayer peppas equation models (log cumulative percentage of drug released versus log time)[16,17].

RESULTS AND DISCUSSION

Table 1: Different Batch Formulation of Telmisartan Microspheres

Batch code	Drug (mg)	HPMC (mg)	Ethyl cellulose(mg)	Acetone : DCM	Temperature (^{O}C)
F1	30	10	10	1:1	25
F2	30	20	20	1:2	30
F3	30	30	30	1:3	35
F4	30	40	40	3:1	40
F5	30	50	50	2:1	45
F6	30	60	60	1:1	50

Table 2: Micromeritic Properties of Microspheres (F1-F6)

Batch code	Particle size (µm)	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (ɵ)	Flow rate (compressibility index)
F1	173.4	0.6917	1.0346	25.64	Good
F2	158.7	0.7861	1.1768	19.86	Good
F3	152.4	0.7983	1.1924	21.73	Good
F4	139.3	0.8671	1.2378	20.51	Good
F5	161.7	0.7437	1.1362	26.23	Good
F6	131.8	0.8924	1.2764	23.64	Good

Table 3: % Entrapment, % Buoyancy and % Yield of Microspheres

Batch code	% entrapment	% buoyancy	% yield
F1	85.21	77.64	75.68
F2	82.35	83.96	79.57
F3	85.62	86.24	88.39
F4	87.34	90.57	86.81
F5	86.45	87.59	83.87
F6	83.69	75.64	72.53

Table 4: Stability Data of F4 Formulation

S.no	Days	% Entrapment		% Buoyancy	
		At 5-10 ^{O}C	At 40-45^{O}C	At 5-10^{O}C	At 40-45^{O}C
1	0	87.34	87.34	90.57	90.57
2	30	87.25	87.29	90.54	90.46

Effect of Excipients on Formulation

Effect of Solvent

- When dichloromethane ratio increased in the formulation of microspheres of telmisartan cause increased of % yield and decreased entrapment efficiency.
- When acetone ratio increased in formulation of microspheres of telmisartan cause increased % yield.

Effect of Polymers

- When HPMC ratio increased in formulation this caused decreased % entrapment efficiency.
- When combination of HPMC and ethyl cellulose increased this cause decreased % buoyancy

Effect of Temperature

- A 20-30^{O}C % yield of microspheres of telmisartan decreased.
- At 35-40^{O}C % yield of microspheres of telmisartan decreased.
- At 45-50^{O}C % buoyancy of microspheres decrease due to settling of particles at high temperature.

Micromeritic Properties of Microspheres (F1-F6)

Particle size of microspheres depend upon using of different type of polymers, solvents, temperature range and stirring.

When particle size decreased surface area for absorption of drug increased. Particle size of microspheres of telmisartan obtained in a range from 131.8 µm to 173.4µm.

Bulk density depend upon particle shape as the more spherical in shape bulk density is increase, as granules size increase bulk density decrease[22]. The obtained bulk density of microspheres range from 0.6917g/mi to 0.8924g/ml and tapped density range from 1-0346g/ml to 1.2764g/ml. The value of angle of repose ≤30^{O} usually indicate a free flowing material and angle of repose ≥40^{O} suggest the poorly flowing materials and the obtained angle of repose of microspheres range from 19.96^{O} to 26.23^{O} which indicate a good flow properties.

% Entrapment Efficiency, % Buoyancy and % Yield (F1-F6)

The % entrapment efficiency found in range of 82.35% to 87.34% of F1 to F6 batches of telmisartan microspheres. The % buoyancy of microspheres found in range 83.96% to 90.57% so that excellent % buoyancy obtained of microspheres due to density (0.6417g/ml-0.8924g/ml) of formulated microspheres lower than gastric fluid (1.004g/cm^{3}).on the basis of higher % buoyancy we selected a excellent formulation from F1to F6 batches. The F4 formulation carried higher % buoyancy 90.57% so F4 selected as an optimum formulation. % yield of microspheres found in arrange 72.5% to 88.39%.

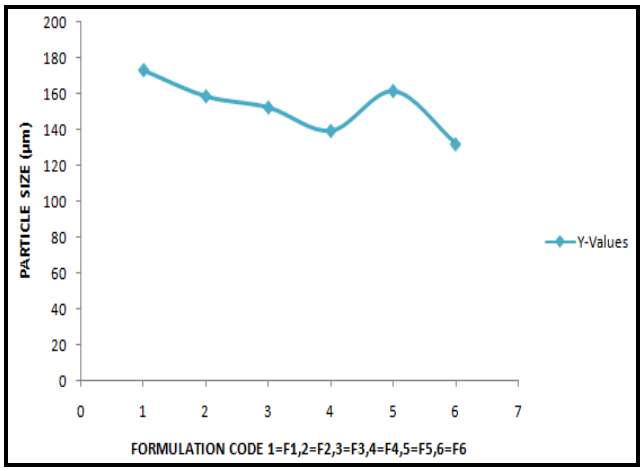

Figure 1: Curve of Particle Size Distribution of Formulation F1 to F6

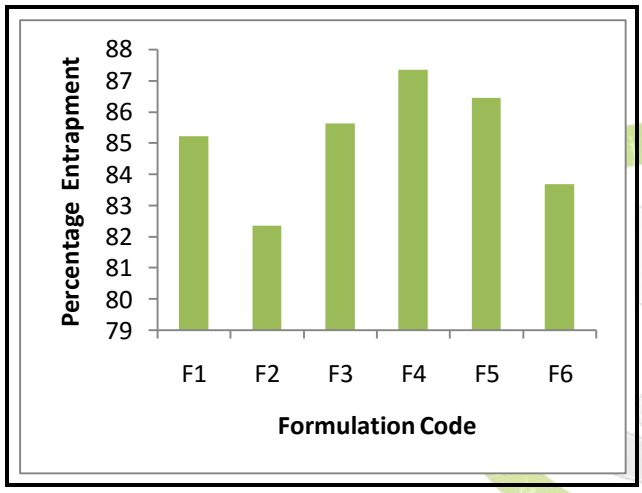

Figure 2: Histogram of Percentage Entrapment Efficiency of Formulation F1 to F6

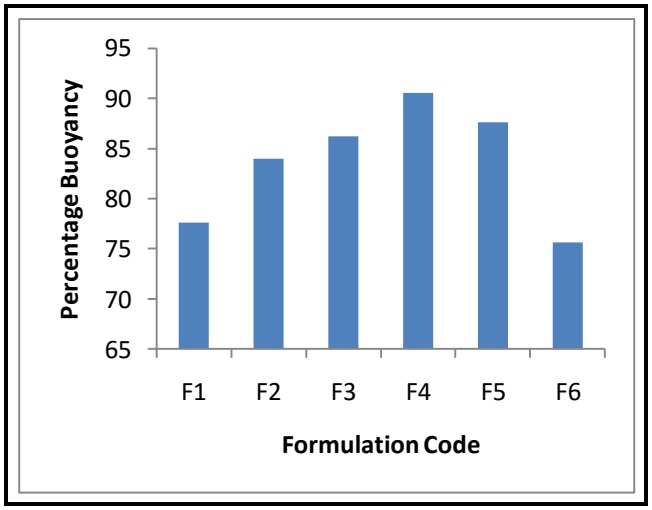

Figure 3: Histogram of Percentage Buoyancy of Formulation F1 to F6

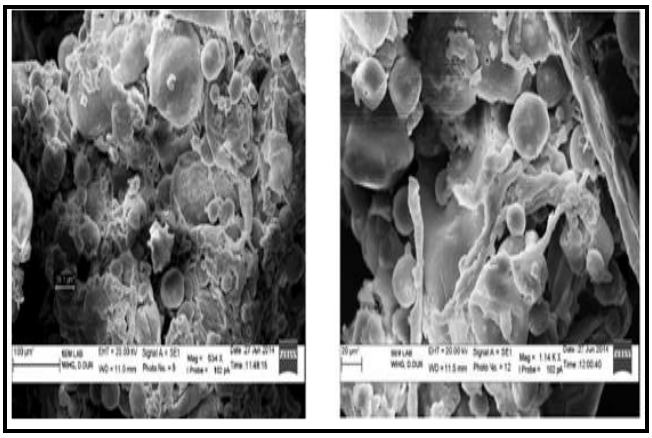

Figure 4: Scanning Electron Microscopy (SEM) of Microspheres

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