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Preparation and *In-vitro* Evaluation of Microballoon Drug Delivery System of Telmisartan

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ABSTRACT

In present study an attempt was made to prepare hollow microspheres (microballoons) of Telmisartan by emulsion solvent diffusion technique for sustained delivery by using polymers like Hydroxy Propyl Methyl Cellulose (HPMC) and Eudragit RS 100 in order to extend the drug release for about 12 h in the upper GIT, which may result in enhanced absorption and there by improved bioavailability. The particle size was determined by optical micrometer and average particle size was found to be in range of189.5± 2.63 to 124.33± 2.14. Formulation F7 containing HPMC and Eudragit polymer blend showed the best floating ability (91.26%) as compared with other formulations. From Scanning Electron Microscopy (SEM) it was observed that, microballoons were found to be spherical in shape with smooth surface texture with a hollow space within. Among all formulations, F7 showed appropriate balance between buoyancy and drug release rate of 98.32% in 12 h, which is considered as the best formulation.

Keywords: Telmisartan, Microballoons, Emulsion solvent diffusion technique, Buoyancy, Bioavailability.

INTRODUCTION

The design of oral control drug delivery systems (ORDDS) should be primarily aimed to achieve more predictable and increased bioavailability. The most feasible method for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by gastro retentive and sustained release dosage forms that have some benefits in safety and efficacy over normal release systems. This method of application is especially helpful in delivery of sparingly soluble and insoluble drugs. It is acknowledged that, the time available for drug dissolution becomes less adequate, the solubility of a drug decreases, and so the transit time becomes an important factor affecting drug absorption in drugs with lower solubility. [1] Hollow microspheres (microballoons) are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200µm. Microballoons have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. [2-3] Telmisartan is a non-peptide angiotensin II receptor antagonist. Telmisartan blocks the vasoconstriction and aldosterone secreting effects of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, leading to a reduction in arterial blood pressure. The poor bioavailability of Telmisartan (40-58%) was the criteria which caused the selection of drug, which could be increased by prolonging the gastric retention time. A previous approach for increasing the bioavailability of Telmisartan by floating microspheres was reported. [4-5] Hollow microspheres (microballoons) of Telmisartan were prepared by emulsion solvent diffusion technique for sustained delivery by using polymers like Hydroxy Propyl Methyl Cellulose (HPMC) and Eudragit RS 100 in order to extend the drug release for about 12 h in the upper GIT, which may result in enhanced absorption and there by improved bioavailability.

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MATERIALS AND METHODS

Telmisartan was obtained from Chandra labs Pvt., Ltd. (Hyderabad), Hydroxy Propyl Methyl Cellulose (HPMC), Eudragit RS100, Dichloro methane, Ethanol, Poly Vinyl Alcohol (PVA) were procured from S.D Fine chemicals Ltd (Mumbai).

Methods

Preparation of hollow microspheres (Microballoons)

Floating microballoons containing Telmisartan were prepared using Emulsion solvent diffusion technique. The drug to polymer ratio used to prepare the different formulations were 1:1 to 1:5. The drug polymer mixture was dissolved in a mixture of dichloromethane (DCM) and ethanol (1:1 to 2:1). The mixture was dropped in to 0.75% polyvinyl alcohol solution (200 ml) and the resulting solution was stirred with a propeller-type agitator at 1300 rpm and various temperature ranges for 1h. The floating microballoons formed were screened, washed with water and dried at room temperature in desiccators (Table 1). [6-7]

Characterization of microballoons

Fourier Transform Infra-red Spectroscopy (FT-IR) analysis

The FT-IR analysis was done for the analysis of drug polymer interaction. FT-IR spectra of Pure Drug, Eudragit RS 100, HPMC and floating microballoons (F7) were recorded using Shimadzu 8700 FTIR spectrophotometer. [8]

Micromeritic properties

The prepared microballoons were characterized for micromeritic properties, such as particle size, bulk density, tapped density, compressibility index and flow properties. [9]

Determination of percentage yield and Entrapment Efficiency

Entrapment efficiency was determined by taking 20 mg of hollow microballoons which were thoroughly triturated and dissolved with 10 ml ethanol in 100ml volumetric flask and volume was made up with 0.1 N HCl. The resulting solution is then filtered (Whatmann filter paper No. 44), suitably diluted and the absorbance was measured at 296nm against 0.1N HCI as blank. The percentage drug entrapment was calculated as follows. [10]

$$\text{Percentage Entrapment} = \frac{\text{Calculated drug Concentration}}{\text{Theoritical drug concentration}} \times 100$$

$$\text{Percentage yield} = \frac{\text{Total weight of hollow microspheres}}{\text{Total weight of all non volatile component}} \times 100$$

Morphology

The dried microballoons were coated with gold film under vacuum using a sputter coater. The surface part of microballoons was observed under scanning electron microscopy (Jeol JSM-1600, Tokyo, Japan).

Floating behaviour

Fifty milligrams of the floating microballoons were placed in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v% Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 6h, the floating and the settled portion of microballoons were recovered separately by filtration. The microballoons were dried and weighed. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. [11]

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

Where W_f and W_s are the weights of floating and settled micro particles respectively, all the determinations were made in triplicate.

In vitro release studies

The drug release rate from microballoons was determined using USP XXIII basket type dissolution apparatus. A weighed amount of hollow microspheres equivalent to 20 mg drug was filled into a capsule (# 3) and placed in the basket. Simulated gastric fluid (SGF, pH-1.2) (900 ml) containing Tween 20 (0.02 w/v %) was used as the dissolution medium and maintained at 37± 0.5° C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release studies. 5ml sample was withdrawn at each 1h interval, passed through a 0.5µm membrane filter (Millipore) and analysed Spectrophotometrically at 296 nm to determine the concentration of drug present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were conducted in triplicate. [11]

Stability study

From the prepared floating microballoons, best formulation was selected on basis of buoyancy and the percentage drug released. The selected formulation was placed in borosilicate screw capped glass containers and stored at different temperatures (27±2°C), oven temperature (40±2°C) and in the refrigerator (5-8°C) for a period of 90 days. The samples were assayed for drug content (Drug entrapment) at regular intervals. [7]

RESULTS AND DISCUSSION

Hollow microspheres of Telmisartan in different ratios were designed and prepared by Emulsion solvent diffusion technique. Drug-polymer compatibility studies were carried out using FTIR spectroscopy to establish any possible interaction of Telmisartan with the polymer used in the formulation. Thus results indicate that the characteristic absorption peak due to pure Telmisartan have appeared in the formulated microspheres without any significant change in their position indicating no chemical interaction between Telmisartan and polymers (Fig. 1-4).

Optimization of Process Variables

Effect of solvent composition

Solvent composition was found to be a vital factor in the formulation process governing the yield of microballoons. When the amount of dichloromethane was increased the production yield and entrapment efficiency of microballoons decreased as some polymer aggregated on the shaft. Such result was attributed to the fact that as ethanol diffused into the aqueous phase, dichloromethane became major constituent of the internal organic phase. The polymer being insoluble at the dichloromethane and aqueous interface, started to solidify because of rapid evaporation of dichloromethane polymer aggregated on the shaft. Best results were obtained when the ratio of ethanol: dichloromethane was 2:1. With increasing the ethanol volume, it took more time for ethanol to diffuse in the external aqueous phase, forming stable emulsion droplets and preventing the aggregation of embryonic microsphere droplets, thus increasing the yield of Microballoons (Table 2).

Table 1: Formulae of Different Batches of Telmisartan Microballoons

Formulation code	Drug (mg)	HPMC (mg)	Eudragit RS 100 (mg)	Ethanol : DCM	Temp (°C)
F1	20	10	10	1:1	20
F2	20	15	15	1:1	20
F3	20	20	20	1:1	25
F4	20	25	25	1:2	25
F5	20	30	30	1:2	30
F6	20	35	35	1:2	35
F7	20	40	40	2:1	40
F8	20	45	45	2:1	45
F9	20	50	50	2:1	50

Table 2: Percentage Yield and Micromeritic properties of Hollow microspheres (F1 to F9)

Formulation code	Percentage Yield (%)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Angle of repose(θ)	Flow properties
F1	72.42	0.962±0.053	1.14± 0.09	18.20±0.2	28.6± 0.31	Good
F2	78.26	0.817±0.04	1.16± 0.07	17.94±0.6	27.58±0.15	Good
F3	76.84	0.859±0.165	1.246± 0.09	17.58±0.8	25± 0.11	Good
F4	74.6	1.008±0.024	1.15± 0.04	15.16±0.1	26.36±0.13	Good
F5	79.24	0.860±0.032	1.12± 0.01	15.09±0.6	25.52±0.19	Good
F6	74.63	0.882±0.045	1.28± 0.04	14.48±0.8	20.32±0.19	Good
F7	79.85	0.726±0.034	1.02± 0.04	14.28±0.8	19.69±0.19	Good
F8	74.93	0.642±0.14	1.09±0.04	13.20±0.1	18.36±0.23	Good
F9	80.25	0.872±0.52	1.15±0.42	12.24±0.8	19.33±0.16	Good

Mean± SD (n=3) S.D standard deviation

Table 3: Particle Size and Percentage Entrapment (F1 to F9)

Formulation code	Particle size(µm)	%Entrapment efficiency
F1	189.5±2.63	82.26±0.19
F2	176.33±2.14	83.2.6±2.35
F3	163.68±1.69	79.6±0.19
F4	158.63±2.52	77.24±2.14
F5	146.38±2.69	78.26±1.34
F6	141.66±1.58	76.63±1.68
F7	137.26±1.97	78.3±2.47
F8	124.33±2.14	75.66±2.69
F9	142.35±2.08	74.3±1.68

Mean± SD (n=3) S.D standard deviation

Table 4: Percentage Buoyancy of microballoons at different time intervals

Formulation code	1hr	2hr	4hr	6hr
F1	98.26%	97.15%	80.85%	85.64%
F2	92.42%	87.16%	82.15%	78.69%
F3	96.14%	89.29%	83.46%	79.14%
F4	95.28%	93.59%	90.14%	88.19%
F5	96.19%	90.59%	88.65%	82.41%
F6	92.18%	90.28%	87.96%	84.65%
F7	**98.42%**	**95.58%**	**93.69%**	**91.26%**
F8	97.65%	95.19%	88.82%	82.14%
F9	93.15%	85.19%	80.54%	77.26%

Table 5: Data for Stability of F7 Formulation

S. No	Days	% Entrapment efficiency (5-8±2°C)	% Entrapment efficiency (27±2°C)	% Entrapment efficiency (42±2°C)
1	0	78.14±1.4	79.92±1.6	79.14±0.58
2	30	78.06±0.28	78.35±0.29	78.22±1.24
3	45	78.29±0.19	78.27±0.98	78.32±1.85
4	90	78.03±0.29	78.15±1.42	77.15±1.62

Effect of temperature

The temperature of the dispersing medium was an important factor in the formation of microballoons, because it controls the evaporation rate of the solvents. Floating properties of microballoons were also affected with variation in temperature. At lower temperatures (20°C), prepared microballoons had low yield. At higher temperature, faster evaporation of dichloromethane leads to the formation of porous structure immediately after diffusion of ethanol resulting in good floating percentage. The optimum temperature to form good microballoons was in the range of 35-40°C. Microballoons prepared at 40°C were hollow and buoyancy percentage was high. In contrast, microballoons prepared at 50°C had poor buoyancy because higher temperature resulted in settling of particles (Table 4).

Effect of Polymers

In order to modulate the drug release rate from the Microballoons different formulations (F1 to F9) were prepared by mixing in different proportions of HPMC with Eudragit RS100. Percentage entrapment decreased on increasing the ratio of HPMC. The buoyancy decreased with increasing the ratio of polymer blend (HPMC and Eudragit RS 100) from the formulations F8 and F9. It could be due to gelling property of HPMC in dissolution medium (Table 3).

Percentage yield and Micromeritic Properties

The percentage yield of formulations F1 to F9 were found in the range of 72.42 to 80.25%, all the formulations show satisfactory yield indicating that increasing polymer concentration had no impact on percentage yield of microballoons. The bulk density values of formulations were found in the range 0.962±0.053to 0.642±0.14 g/cm^3. The tapped density values ranged from 1.28 ± 0.09 to 1.09 ± 0.04 g/cm^3. This significant difference in the densities may be caused by the presence of low-density of Telmisartan particles in the microballoons. All formulations showed excellent flow ability as expressed in terms of angle of repose (<40°). The better flow property of microballoons indicates that the floating microballoons produced are non-aggregated. It indicates that microballoons can be handled easily during processing.

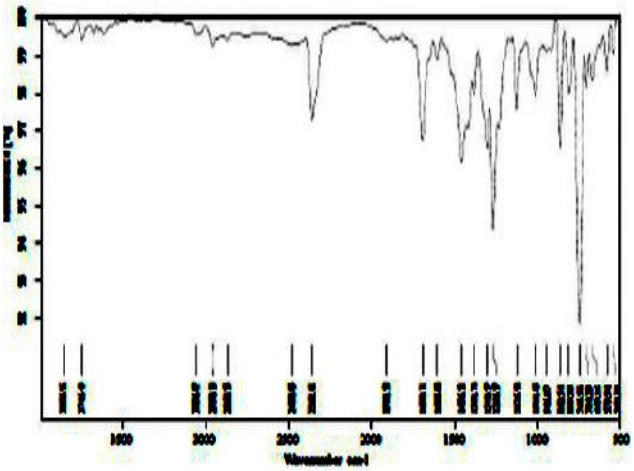

Fig. 1: FTIR Spectrum of pure drug – Telmisartan

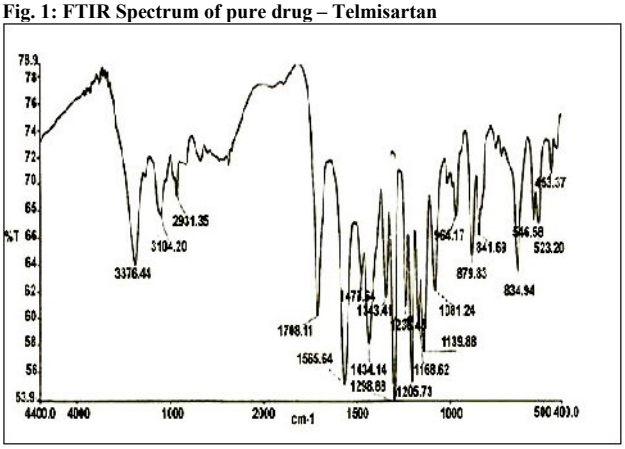

Fig. 2: FTIR Spectrum of HPMCK4M

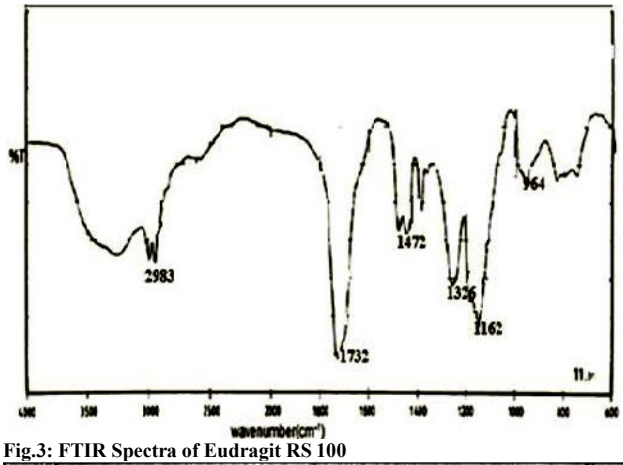

Fig.3: FTIR Spectra of Eudragit RS 100

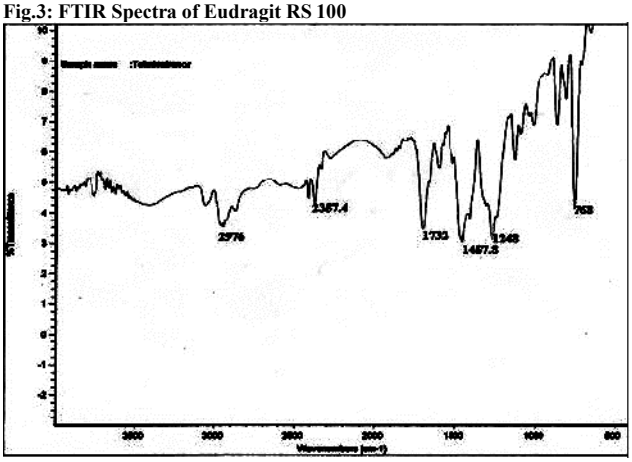

Fig. 4: FTIR Spectra of Drug with HPMC and Eudragit RS 100 (F7)

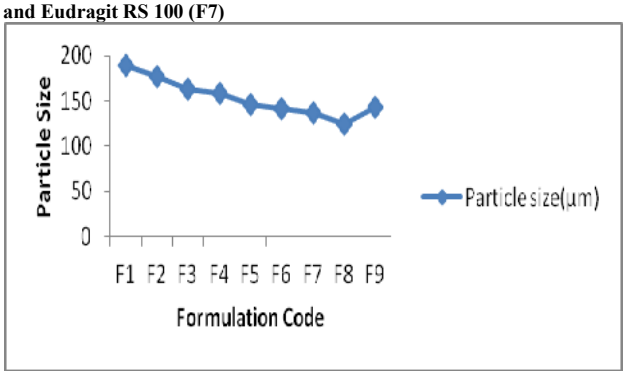

Fig. 5: Particle Size Distribution Curve of Formulations F1 to F9

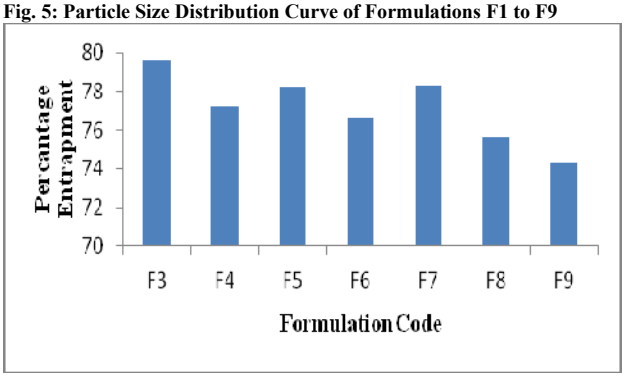

Fig. 6: Histogram showing entrapment efficiencies of formulations F1to F9

Particle Size and Entrapment Efficiency

All the formulations showed satisfactory entrapment efficiency ranging in 82.26±0.19 to 74.3±1.68% (Table 3) and its efficiency slightly decreased with increasing the HPMC and Eudragit RS100 polymer blend. The extent of loading influenced the particle size distribution of microballoons when the loading was high the proportion of larger particles formed was also high with 82.5±0.19% drug entrapment, most of the particles were in the size range of 189.5± 2.63 to 124.33± 2.14 which is suitable for oral administration.

Buoyancy Study

Density values for all formulations were less than that of gastric fluid (1.004 g/cm^3), suggesting that they exhibit good buoyancy. Good *in vitro* percentage buoyancy was observed for all the microballoons formulations. (Table 4, Fig. 7). These characteristics may be attributed to its low bulk density value obtained before and after tapping respectively. Microballoons formulation F7 containing HPMC and Eudragit polymer blend showed the best floating ability (91.26%) as compared with other formulations. The floating ability of microballoons for 6h may be considered a satisfactory performance of the prepared formulations. The microballoons remained buoyant for prolonged time over the surface of the dissolution medium without any apparent gelation, which might be responsible for good floating property.

Scanning Electron Microscopy

SEM study for optimized formulation F7 suggested that hollow microballoons were found to be spherical in shape with smooth surface texture with a hollow space within (Fig. 8-10).

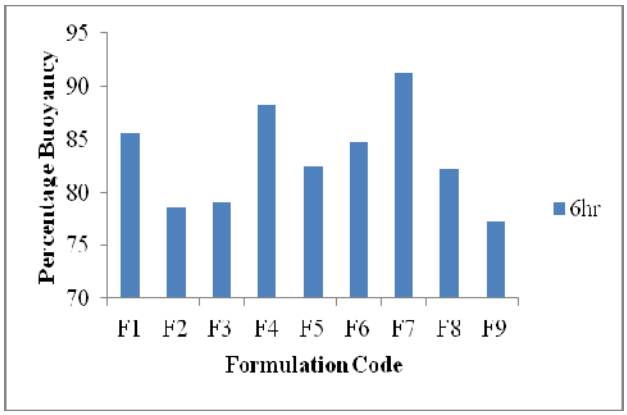

Fig. 7: Histogram Showing Percentage buoyancy study for formulations F1 to F9

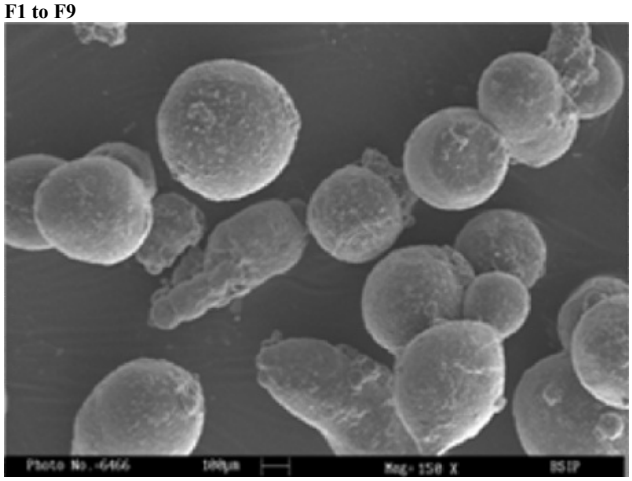

Fig. 8: Scanning Electron Microscopic (SEM) images showing size range of Microballoons

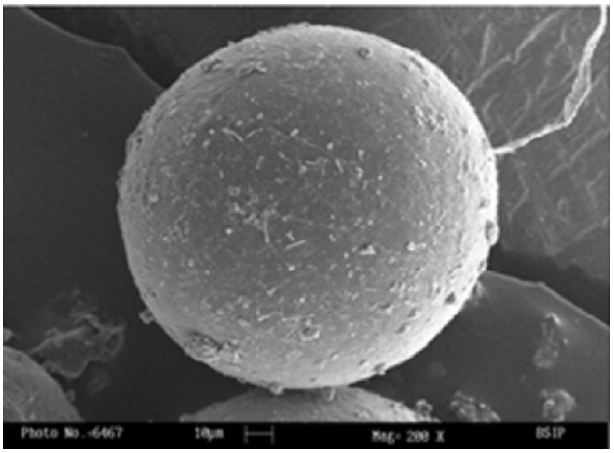

Fig. 9: SEM images showing Smooth texture of Microballoons

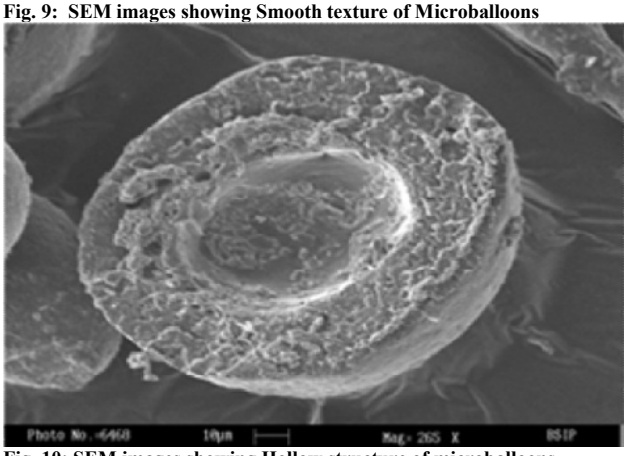

Fig. 10: SEM images showing Hollow structure of microballoons

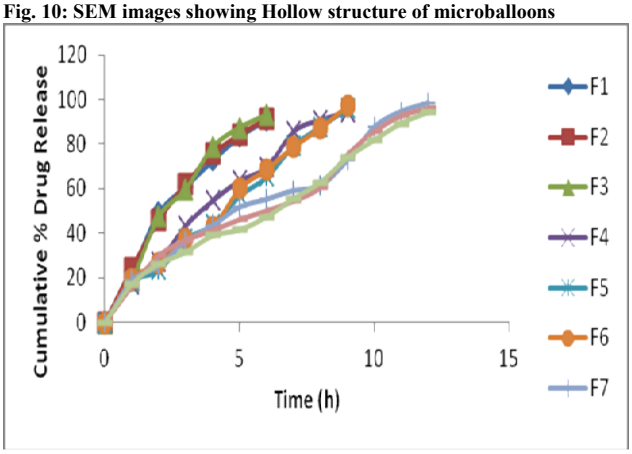

Fig. 11: Dissolution Profile for Formulations F1 to F9

In-vitro drug release study

Ideal property of hollow microspheres includes high buoyancy and sufficient release of drug in simulated gastric fluid (pH 1.2). *In vitro* release studies were performed in 0.1 N HCl for12h. The cumulative Percentage of drug release rate of prepared formulations was found to be in the following order: F1> F2> F3> F4> F5> F6> F7> F8> F9. Formulations F1 to F3 showed high release rate (90.86%, 91.43% and 92.84%) in 6h. This could be due to, smaller hollow microspheres (microballoons) are formed at a lower polymer concentration and have a large surface area exposed to dissolution medium, giving rise to faster drug release and F4 toF6 showed the release rate (94.42%, 96.33%, 97.12%) in 9 h and F7 to F9 showed the drug release (98.32%, 96.24% and 94.12%) in 12 h respectively. This pattern may provide an idea about the effect of drug release from the microballoons i.e., the higher the ratio of polymer blends, lower the drug release. And also the increased density of the polymer matrix at higher concentrations results in an increased diffusional path-length. This may decrease the overall drug release pattern from the polymer matrix. However F8 , F9 showed high release rate in 12h with less buoyancy and F7 formulation showed appropriate balance between buoyancy and drug release rate of 98.32% in 12 h, which is considered as the best formulation (Fig. 11).

Stability Studies

In stability study, there was no remarkable change in content of F7 formulation during 90 days in which it was stored at various temperatures. Stability study was carried out for the F7 formulation by exposing it to 5-8°C, 27±2°C and 40±2°C for 3 months. The sample was analyzed for drug content at regular intervals. There was no remarkable change in content of F7 formulation during 90 days in which it was stored at various temperatures (Table 5).

The microballoons so prepared will remain buoyant on surface of gastric fluid releasing Telmisartan in sustained fashion. Inferences drawn from *in vitro* studies suggest that microballoons may prove as potential delivery system for Telmisartan by improving bioavailability in comparison to conventional dosage forms.

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