ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology

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Indo-American Journal of Life Sciences and Biotechnology

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

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ABSTRACT

In this study, researchers attempted to create Telmisartan microballoons using the emulsion solvent diffusion technique. The goal was to use polymers like HPMC and Eudragit RS 100 to prolong the drug's release in the upper gastrointestinal tract (GIT) for approximately 12 hours. This could lead to better absorption and bioavailability. The optical micrometer was used to measure the particle size, which ranged from 189.5± 2.63 to 124.33± 2.14 on average. When compared to other formulations, Formulation F7, which had a combination of HPMC and Eudragit polymer, exhibited the highest floating ability at 91.26%. Scanning electron microscopy (SEM) revealed that the microballoons had a smooth outside and an inside hollow region. F7 was the best formulation since it achieved a 98.32% medication release rate in 12 hours while maintaining an optimum buoyancy.

Microballoons, buoyancy, bioavailability, emulsion solvent diffusion, telmisartan—these are the keywords.

INTRODUCTION

To improve predictability and bioavailability, oral control drug delivery systems (ORDDS) need mainly be designed. Controlling the stomach residence duration using gastro retentive and sustained release dosage forms, which provide certain advantages in safety and effectiveness compared to regular release methods, is the most practical way to achieve a longer and predictable drug administration throughout the GI tract. Drugs that are just weakly soluble or completely insoluble may be delivered more effectively with this application approach. We all know that when a medication's solubility drops, the amount of time it takes for it to dissolve falls as well. when a result, for pharmaceuticals with reduced solubility, transit time becomes a major factor influencing drug absorption. [1] The technical definition of a hollow microsphere (microballoon) is a spherical, empty particle devoid of a core. These microscopic particles, which are usually protein or synthetic polymer powders with a size of less than 200 μm, are known to be free-flowing. Since microballoons are less dense than stomach fluids, they float in the stomach for a long time without slowing the emptying pace of the stomach. The medicine is released from the system at a controlled pace as it floats on stomach contents. The stomach is cleared of the residual system once the medicine is released. The end effect is a longer stomach retention duration and more stable plasma medication concentrations. References 2-3 Angiotensin II receptor antagonists that are not peptides are telmisartan. Telmisartan lowers arterial blood pressure by blocking the actions of angiotensin II on the AT1 receptor in several tissues, including vascular

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smooth muscle and the adrenal gland. This action reduces vasoconstriction and the secretion of aldosterone. One of the factors that went into choosing Telmisartan was its low bioavailability (40-58%), which may be improved by extending the time it stays in the stomach. It was previously shown that floating microspheres might increase the bioavailability of Telmisartan. four to five] Microballoons made of hollow telmisartan microspheres were created using the emulsion solvent diffusion technique for sustained delivery. Polymers such as Hydroxy Propyl Methyl Cellulose (HPMC) and Eudragit RS 100 were used to extend the drug release for approximately 12 hours in the upper gastrointestinal tract (GIT). This extended release time may lead to improved absorption and bioavailability.

MATERIALS AND METHODS

Chandra labs Pvt., Ltd. of Hyderabad provided the telmisartan, while S.D. Fine chemicals Ltd. of Mumbai supplied the hydroxypropylmethylcellulose (HPMC), eudragit RS100, dichloro methane, ethanol, and poly vinyl alcohol (PVA).

Methods

Making Microballoons, or Hollow Microspheres

Using the emulsion solvent diffusion approach, floating microballoons containing telmisartan were created. The medication to polymer ratios used to create the various formulations ranged from 1:1 to 1:5. A solution of dichloromethane (DCM) and ethanol (in a ratio of 1:1 to 2:1) was used to dissolve the drug polymer combination. A propeller-type agitator was used to swirl the mixture for 1 hour at different temperatures and speeds after it had been put into a 200 ml solution of 0.75% polyvinyl alcohol. Table 1 shows the process of screening, washing, and drying the floating microballoons in desiccators at room temperature. [6-7]

Microballoons: A characterization

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

The drug-polymer interaction was examined using FT-IR. The FT-IR spectra of several substances were acquired using a Shimadzu 8700 FTIR spectrophotometer. These substances included Pure Drug, Eudragit RS 100, HPMC,, and floating microballoons (F7). [8] Characterization of the microballoons was carried out to determine their micromeritic qualities. These attributes included particle size, bulk density, tapped density, compressibility index, and flow characteristics. [9]

Finding the Entrapment Efficiency and Percentage Yield

Twenty milligrams of hollow microballoons were mixed with ten milliliters of ethanol in a one hundred milliliter volumetric flask, and then the remaining volume was filled with 0.1 N hydrochloric acid to evaluate the entrapment effectiveness. After that, the solution is filtered using Whatmann filter paper No. 44. It is then diluted to the appropriate concentration and its absorbance is measured at 296 nm with 0.1N HCI used as a blank. What follows is the formula for determining the percentage of drug entrapment. [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 microballoons were vacuum-coated with a gold film using a sputter coater once they had dried. Microballoons' surface features were studied using a scanning electron microscope (Jeol JSM-1600, Tokyo, Japan).

Symptoms of levitation

The simulated stomach fluid (pH 1.2, 100 ml) with 0.02 w/v% Tween 20 was mixed with 50 milligrams of the floating microballoons. I used a magnetic stirrer to combine the ingredients at 100 revolutions per minute. Separate filtration was used to collect the microballoons' floating and settled portions after 6 hours. We weighed and dried the microballoons. By comparing the mass of floating particles to that of both floating and sinking particles, the buoyancy was calculated for each proportion of microspheres. the eleventh

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

The weights of the microparticles that floated and those that settled were measured three times each.

Experiments on release in vitro

An apparatus of the USP XXIII basket type was used to ascertain the rate of drug release from microballoons. A capsule (#3) containing 20 mg of the medication was filled with a measured quantity of hollow microspheres and placed in the basket. The solution was prepared using 900 ml of simulated gastric fluid (SGF, pH-1.2) with 0.02 weight percent Tween 20 and kept at 37±0.5° C with a spin speed of 100 rpm. Throughout the drug release trials, ideal sink conditions were maintained. At each hourly interval, 5 ml of the dissolving liquid was removed, filtered using a Millipore 0.5 µm membrane, and then analyzed spectrophotometrically at 296 nm to ascertain the drug concentration. Each time 5 ml of new dissolving fluid was added after each withdrawal, the starting volume of the fluid was maintained.

Assessment of stability

Based on buoyancy and the proportion of medicine released, the optimal formulation was chosen from the manufactured floating microballoons. For 90 days, the chosen mixture was kept in borosilicate screw-capped glass containers at various temperatures (27±2°C), in an oven at 40±2°C, and in the fridge at 5-8°C. At certain intervals, the samples were tested for drug entrapment, a measure of drug content. [7]

RESULTS AND DISCUSSION

Using the emulsion solvent diffusion approach, we created Telmisartan microspheres with varying ratios of the drug. In order to determine if the polymer used in the formulation may interact with Telmisartan, drug-polymer compatibility experiments were conducted using Fourier transform infrared spectroscopy. Thus, the findings show that the formed microspheres contain the distinctive absorption peak of pure Telmisartan, but there has been no noticeable change in their location, suggesting that there is no chemical interaction between the two (Fig. 1-4).

Eliminating Wasteful Variables in the Process

The impact of solvent type

The formulation process that controls the microballoon yield is heavily influenced by the solvent composition. Due to polymer aggregation on the shaft, microballoon manufacturing yield and entrapment efficiency declined when dichloromethane concentration was raised. The main reason for this outcome was that dichloromethane formed a significant component of the internal organic phase when ethanol diffused into the water phase. Since the polymer was insoluble at the interface between dichloromethane and water, it began to harden as a result of the fast evaporation of the polymer aggregated on the shaft. A 2:1 ratio of ethanol to dichloromethane produced the best outcomes. Table 2 shows that the yield of microballoons increased as the amount of ethanol increased. This is because it took longer for the ethanol to diffuse in the external aqueous phase, generating stable emulsion droplets and inhibiting the aggregation of embryonic microsphere droplets.

Table 1: Telmisartan Microballoon Formulas for Various Lots

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	17.84±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	78.24	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	78.85	0.726±0.034	1.02± 0.04	14.28±0.8	19.68±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	19.35±0.16	Good

Mean± SD (n=3) S.D standard deviation

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

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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

Because it regulates the solvent evaporation rate, dispersing medium temperature played a significant role in microballoon production. Temperature also has an effect on the floating characteristics of microballoons. The produced microballoons yielded very little when heated to temperatures below 20°C. Faster dichloromethane evaporation at higher temperatures causes the prompt creation of a porous structure after the diffusion of ethanol, leading to an excellent floating percentage. Microballoons worked best when formed between 35 and 40 degrees Celsius. A high buoyancy percentage and hollow interior characterized microballoons made at 40°C. On the other hand, microballoons made at 50°C settled to the bottom after being heated, which reduced their buoyancy (Table 4).

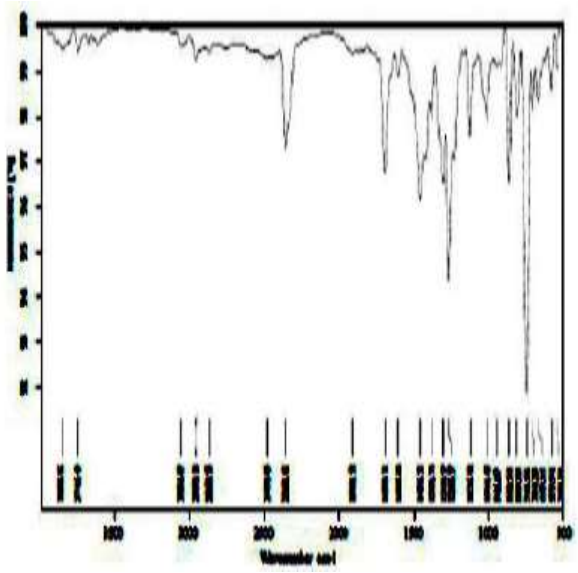
Polymers' Impact

By combining various amounts of HPMC with Eudragit RS100, nine distinct formulations (F1–F9) were created to control the rate of drug release from the Microballoons. As the ratio of HPMC increased, the percentage of entrapment dropped. From F8 and F9, the buoyancy reduced as the ratio of the polymer mix (HPMC and Eudragit RS 100) increased. This may be because HPMC has a gelling effect when mixed with a dissolving liquid (Table 3).

Yield percentage and micromeritic characteristic

There was no correlation between the percentage yield of microballoons and the rising polymer content, as all nine formulations (F1–F9) demonstrated good yields ranging from 72.42 to 80.25%. Formulations' bulk density values ranged from 0.962±0.053 to 0.642±0.14 g/cm3. Between 1.28 ± 0.09 and 1.09 ± 0.04 g/cm3 were the density values that were tapped. The presence of low-density Telmisartan particles in the microballoons might be the reason of this notable disparity in densities. When measured in terms of angle of repose (<40°), all of the formulations demonstrated exceptional flow capabilities. Floating microballoons made do not agglomerate, as their superior flow quality proves.

The results show that microballoons are easy to work with while processing.



ISSN 2347-2243 www.iajlb.com
Vol.19 , Issue.3, July 2022

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Fig. 1: FTIR Spectrum of pure drug – Telmisartan

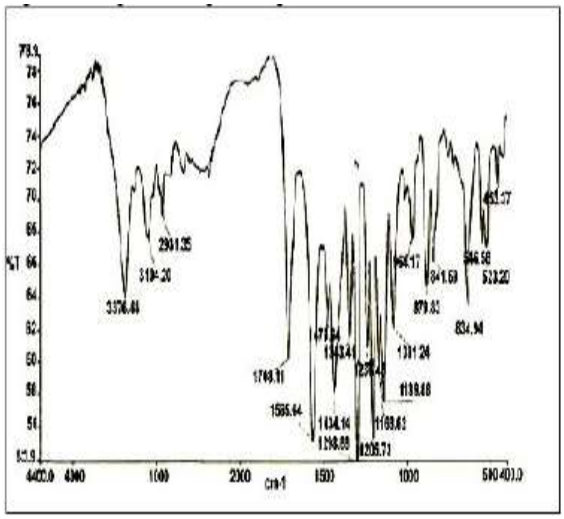

Fig. 2: FTIR Spectrum of HPMCK4M

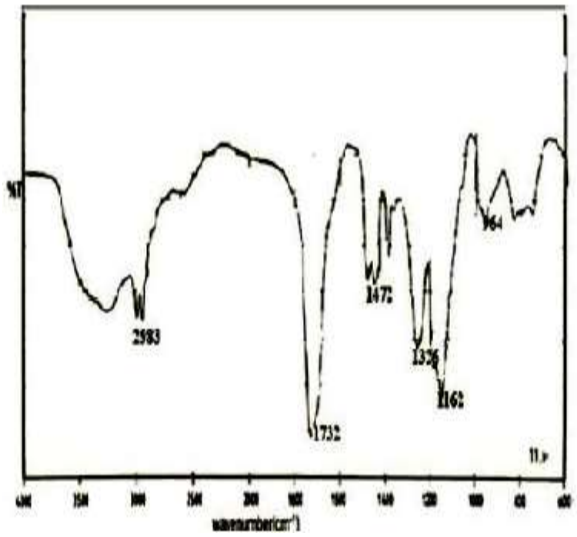

Fig.3: FTIR Spectra of Eudragit RS 100

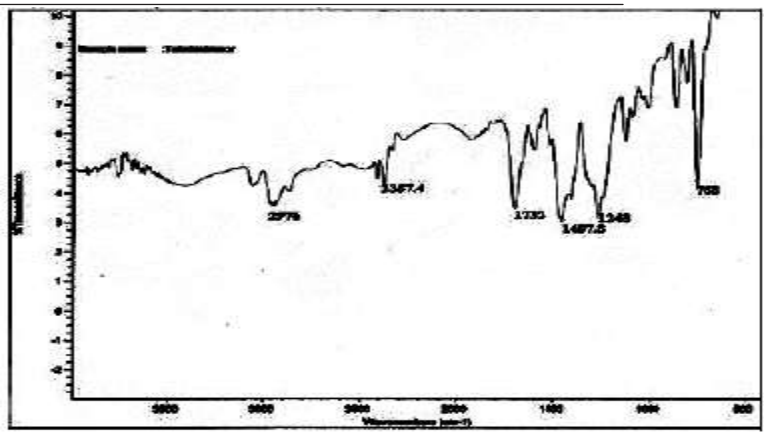

Fig. 4: FTIR Spectra of Drug with HPMC and Eudragit RS 100 (F7)

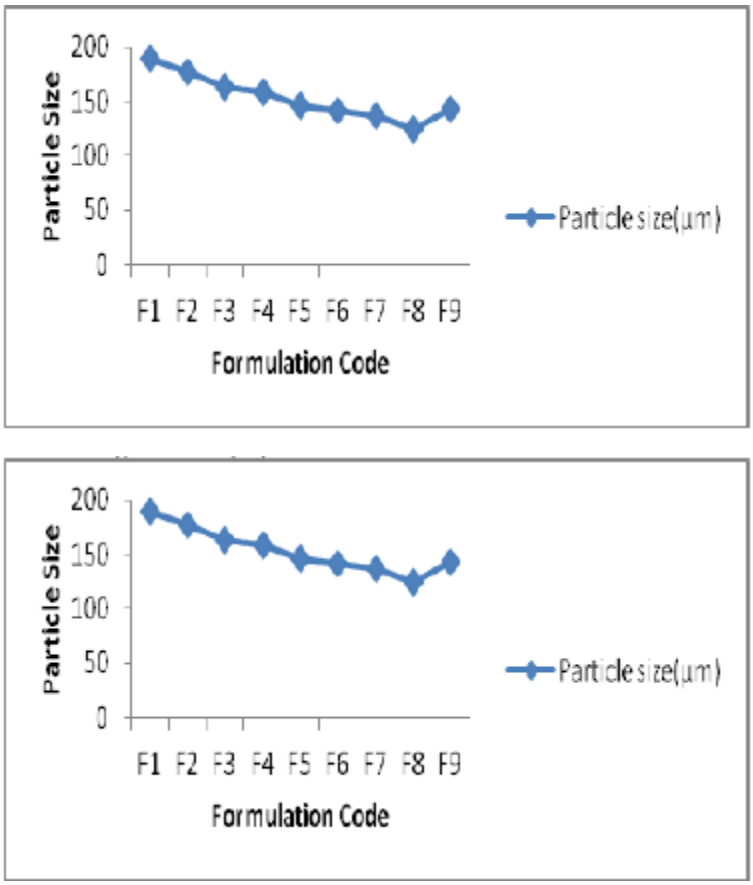

Fig. 5: Particle Size Distribution Curve of Formulations F1 to F9

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Vol.19 , Issue.3, July 2022

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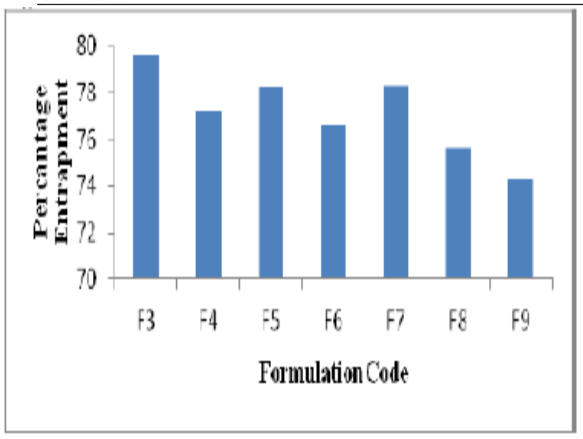

Fig. 6: Histogram showing entrapment efficiencies of formulations F1to F9

Particle Size and Entrapment Efficiency

Table 3 shows that all of the formulations exhibited good entrapment efficiencies ranging from 82.26±0.19 to 74.3±1.68%. As the percentage of HPMC and Eudragit RS100 polymer mix increased, the efficiency marginally dropped. The size distribution of microballoon particles was affected by the loading extent; with high loading, there was a high proportion of larger particles formed, with 82.5±0.19% drug entrapment; and the majority of the particles fell within the oral administration-suitable size range of 189.5±2.63 to 124.33±2.14.

Study on Buoyancy

All of the formulations showed excellent buoyancy, since their density values were lower than stomach fluid's (1.004 g/cm3). The microballoon compositions all showed good in vitro percentage buoyancy. Figure 7, Table 4. In both cases, the low bulk density value before and after tapping is likely responsible for these traits. Out of all the microballoon formulations tested, the one with the highest floating ability (91.26%) was F7, which had a combination of HPMC and Eudragit polymer. As far as the developed formulas are concerned, the microballoons' capacity to float for 6 hours is adequate. The microballoons' excellent floating quality may have been due to their ability to stay buoyant for an extended period of time across the dissolving medium's surface, since they did not seem to gel.

An SEM analysis of the improved formulation F7 revealed that the hollow microballoons had a smooth surface, a spherical shape, and an internal hollow region (Fig. 8-10).

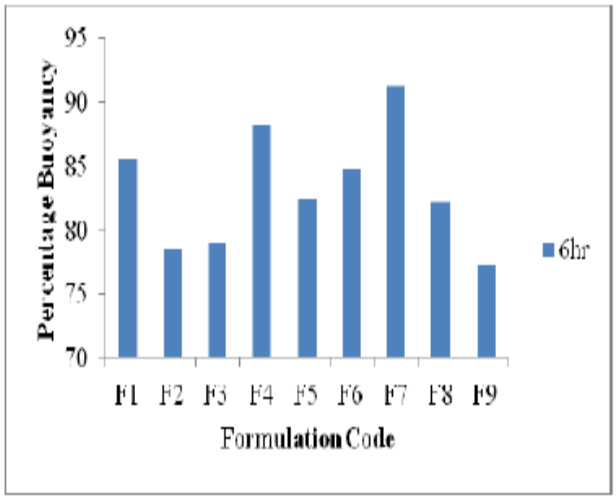

Fig. 7: Histogram Showing Percentage buoyancy study for formulations F1 to F9

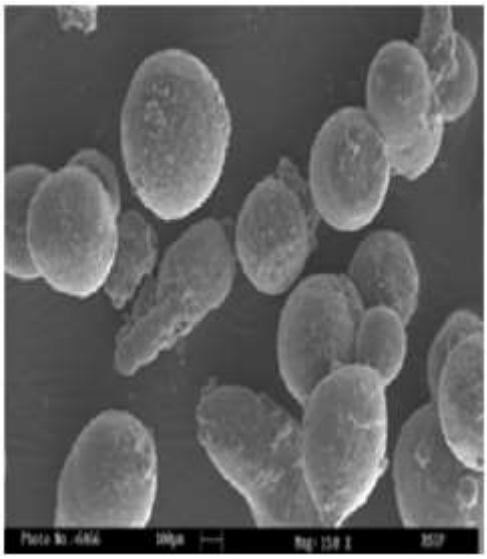

Fig. 8: Scanning Electron Microscopic (SEM) images showing size range of Microballoons

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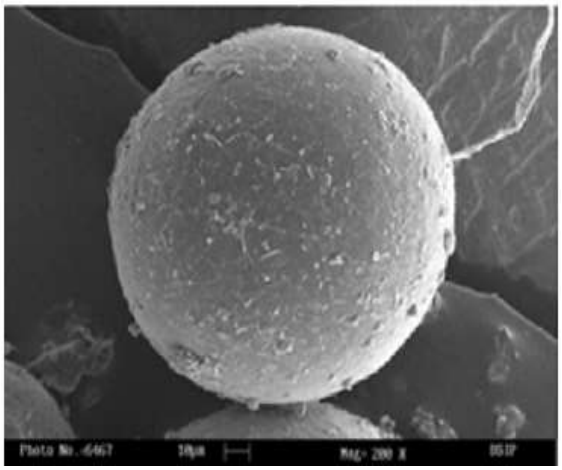

Fig. 9: SEM images showing Smooth texture of Microballoons

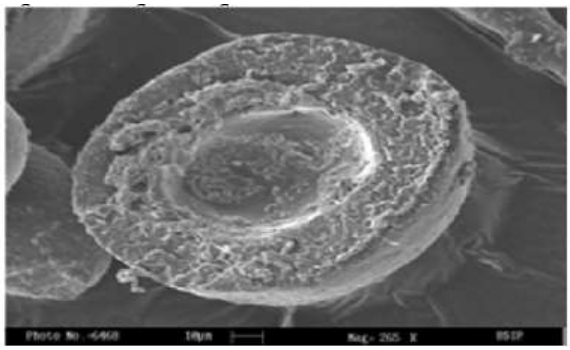

Fig. 10: SEM images showing Hollow structure of microballoons

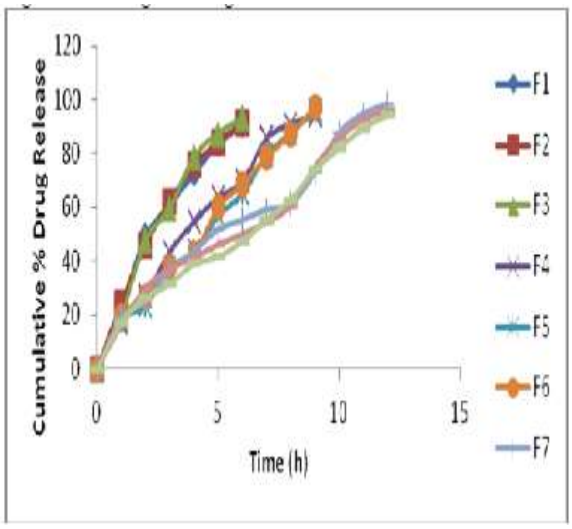

Fig. 11: Dissolution Profile for Formulations F1 to F9

***In-vitro* drug release study**

In a simulated stomach fluid (pH 1.2), hollow microspheres should have great buoyancy and adequate medication release as their ideal properties. A 12-hour in vitro release study was conducted in 0.1 N HCl. As a whole, the drug release rates of the various formulations tested were determined to be as follows: F1> F2> F3> F4> F5> F6> F7> F8> F9. Formulations F1–F3 demonstrated a rapid release rate of 90.86%, 91.43%, and 92.84% in 6 hours, respectively. The rapid drug release observed in experiments F4–F6 (94.42%, 96.33%, 97.12%) after 9 hours and in experiments F7–F9 (96.24%, 94.12%) after 12 hours may be attributable to the fact that smaller hollow microspheres (microballoons) are created at a lower polymer concentration and have a large surface area exposed to the dissolution medium. If this trend holds, we may infer that microballoon drug release is affected by the ratio of polymer blends, with a larger ratio resulting in lesser drug release. Diffusional path-length also increases as concentrations rise due to the dense polymer matrix. As a result, the polymer matrix may not release drugs as uniformly. While F8 and F9 exhibited a high release rate in 12 hours with little buoyancy, the optimal formulation, F7, demonstrated a compromise between buoyancy and drug release rate of 98.32% in 12 hours (Fig. 11).

Research on Stability

After 90 days of storage at different temperatures, the F7 formulation showed no significant changes in content, according to the stability analysis. The F7 formulation was subjected to temperatures of 5-8°C, 27±2°C, and 40±2°C for a duration of three months in order to conduct a stability study. At regular intervals, the sample was tested for drug content. Table 5 shows that over the 90 days of storage at different temperatures, the content of the F7 formulation did not vary noticeably.

Soluble in stomach fluid, the microballoons will release Telmisartan gradually as they float. Based on the results of in vitro investigations, microballoons have the potential to be a better bioavailability delivery mechanism for Telmisartan than the current standard of care.

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