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Original Article

Formulation and Evaluation of Gastroretentive Drug delivery System of Telmisartan

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ABSTRACT

Purpose: The aim of the present study was to develop a gastro retentive system of telmisartan to prolong its gastric residence time and bioavailability. **Materials and Methods:** Non aqueous solvent evaporation method was used to prepare floating microspheres of telmisartan with kollidon SR. Total five formulations were made with varying concentration of kollidon SR. Prepared floating microspheres were subjected to various evaluation parameters, such as particle size determination, SEM, percent yield, entrapment efficiency, bulk and tapped density, compressibility index, angle repose, *In vitro* floatability, FT-IR study and *In vitro* drug release. **Results:** All the formulations displayed good flow properties. *In vitro* dissolution studies in HCl buffer pH 1.2 were performed to assess the release profile of prepared floating microsphere formulations. All the five formulation displayed sustained release of drug. FT-IR spectra of formulation F3 exhibited all the peaks as similar to the FT-IR spectra of pure drug, rejecting any doubts about the compatibility between drug and the excipients. **Conclusion:** We can conclude that kollidon SR can be successfully used to prepare floating microspheres of telmisartan to increase its gastric residence time and bioavailability.

Key words: Floating microsphere, Kollidon SR, Non aqueous solvent evaporation method, PEG 4000, Solid dispersion.

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INTRODUCTION

Among the various routes of drug administration, the oral route has gained the most attention. This is mainly because of the ease of administration as well as the fact that it offers more flexibility in dosage form designing than most other routes. Oral administration of a medication by means of a controlled drug delivery system should ideally produce the required plasma levels and maintain it at steady levels for a prolonged period of time. The development of oral drug delivery systems for a specific drug involves the optimization of the dosage form and characteristics of GI physiology.[1]

Oral sustained drug delivery may be complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in the stomach or the upper part of the small intestine.[2]

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolongation of gastric residence time (GRT) of a rate-controlled oral drug delivery system reduces inter-subject variability and the so-called "peak and valley" effect, leading to increased predictability and bioavailability of the dosage form, especially for molecules with a narrow absorption window. Moreover, the total gastrointestinal transit time is prolonged, thus, the number of dosage regimen can be reduced and solubility can be improved for drugs that are less soluble in a high pH environment.[3]

Most of the floating systems reported in literature are single-unit systems, which are generally unreliable and non-reproducible in prolonging the GRT, in virtue of their unpredictable all-or-nothing emptying process. On the other hand, multiple-unit dosage forms appear to be better suited, since they claim to reduce inter-subject variability in absorption and have a lower dose-dumping probability. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave way to the development of gastroretentive floating microspheres.

Floating microspheres are gastroretentive drug delivery systems based on a non-effervescent approach. Hollow microspheres, microballoons or floating microparticles are terms used synonymously for floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core. These are free flowing particles, with size ranging from 1 to 1000 μm. These gastrointestinal transit controlled preparation are designed to float on gastric juice with a specific density of less than one. This property results in delayed transit through the stomach. The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[3]

Telmisartan is a potent, long-lasting, nonpeptide antagonist of the angiotensin II type-1 (AT1) receptor that is indicated for the treatment of essential hypertension. It selectively and insurmountably inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. It is a white crystalline powder with a molecular weight of 514.6 and a melting point of 261 to 263°C. The solubility of telmisartan in aqueous solutions is strongly pH-dependent, with maximum solubility observed at high and low pH. In the range of pH 3–9 it is only poorly soluble.[4]

The objective of this work was to develop and characterize gastroretentive floating microspheres of telmisartan which, following oral administration, would exhibit prolonged gastric residence time and, hence increase the bioavailability of the drug.

MATERIALS AND METHODS

Telmisartan was obtained as a gift from Skymap Pharmaceuticals, Roorkee, India. Kollidon SR was a kind gift from BASF, Mumbai, India. All other chemicals were of analytical grade and were used as procured.

Preparation of Solid Dispersions

Telmisartan is practically insoluble in water, so we prepared its solid dispersion with PEG 4000 and PVP K-30 as hydrophilic carriers by solvent evaporation method.

Solid dispersions of telmisartan were prepared by solvent evaporation method according to the composition given in Table 1. PEG 4000 & PVP K-30 were used as the carriers to formulate solid dispersions. Carriers were separately dissolved in ethanol in different petri-dishes and then the drug was added in each petri-dish slowly with continuous stirring. The mixture was heated on water bath until the solvent evaporated. After scraping the prepared solid dispersions, they were screened with the help of sieve no. 60 and were stored in desiccators.[5]

Solubility study of drug and solid dispersions

Solubility study of drug and solid dispersions was carried out by shake flask method. In this method excess amount of drug and solid dispersions was taken in 10 ml medium (distilled water) in a separate 25 mL volumetric flasks. The samples were then placed for 48 h in a rotatory shaker at 37°C. After 48 h, the samples was removed, filtered and after appropriate dilutions analyzed by UV-visible spectrophotometer (Jasco V-630, Japan) at 298 nm.[6]

Preparation of floating microspheres

Form the result of solubility study of solid dispersions; it was found that the solid dispersion SD6 exhibited most increase in solubility. Therefore, we selected it to formulate floating microspheres. The non aqueous solvent evaporation method was used to prepare floating microspheres.

The composition of the floating microsphere formulations is given in Table 2. Light liquid paraffin (LLP) containing 1% span 80 was taken in a beaker which worked as the continuous phase. Kollidon SR (KSR) and drug loaded solid dispersion formulation SD6 were dissolved in methanol and a clear solution was made with the help of a magnetic stirrer which was considered as the dispersed phase. Dispersed phase was then dispersed inside the continuous phase with the help of a high speed stirrer (Jyoti Scientific Industries, India). After 2 hours of stirring, microspheres were formed. Microspheres were then filtered and washed with petroleum ether several times and were kept in desiccator until further study.[7]

Particle size determination

Particle size determination was done by optical microscopy. A small quantity of microspheres was dispersed on the slide with the help of capillary tube and diameters were sized using a suitable objective (×10 and ×40). The sizes of around 100 particles were measured and their average particle size was determined.[8,9]

Table 1: Batches of solid dispersion of telmisartan with PEG 4000 and PVP K-30

Solid dispersion formulations	Drug (g)	Carriers (g)	
		PEG 4000	PVP K-30
SD1	1	1	1
SD2	1	2	1
SD3	1	3	1
SD4	1	1	2
SD5	1	2	2
SD6	1	3	2
SD7	1	1	3
SD8	1	2	3
SD9	1	3	3

Table 2: Formulation batches of floating microspheres

Formulation	SD6 (g)	Polymer (g)
F1	1	1
F2	1	2
F3	1	3
F4	1	4
F5	1	5

Scanning electron microscopy (SEM)

To determine shape and surface morphology of prepared floating microspheres, we used scanning electron microscope (LEO-435VP, Leo Co. Ltd). The sample was prepared by sprinkling the formulation on a double-adhesive tape stuck to an aluminum stub. The stuck were then coated with gold to a thickness of ~300 A° under an argon atmosphere. The coated sample was then randomly scanned and photomicrographs were taken with SEM.[8,9]

Percent yields of microspheres

The practical yield of microspheres of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres. Yields were calculated by the formula given below.[10]

$$\% \ Yield = (Practical\ yield/Theoretical\ yield) \times 100$$

Entrapment efficiency of microspheres

Predetermined amount of microspheres (25 mg) containing drug was dissolved in methanol (25 ml) by ultrasonication (Jyoti Scientific Industries, India). The solution was filtered through 0.45 µm Whatman filter paper and 0.5 ml was transferred to 10 ml volumetric flask. The volume was made up to the mark with methanol. The sample was analyzed for drug content spectrophotometricaly at 298 nm.[10]

The percentage entrapment efficiency (%EE) was calculated by the equation given below.

$$\% \ EE = (calculated\ drug\ concentration/theoretical\ drug\ content) \times 100$$

Bulk density

It is the ratio of total mass of floating microspheres to the bulk volume of floating microspheres. It was measured by pouring the weighed floating microspheres into a graduated cylinder and the volume was noted. It is expressed in gm/mL and is determined by following formula.[8]

$$Bulk\ density = mass\ of\ floating\ microspheres/bulk\ volume$$

Tapped density

Tapped density was determined by using graduated cylinder. An accurately weighed sample of floating microspheres was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.[8]

$$Tapped\ density = mass\ of\ floating\ microspheres/tapped\ volume$$

It is expressed in gm/ml.

Compressibility index %

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by the following formula.[8]

$$I = (D_t\text{-}D_b/D_t) \times 100$$

Where, D_t is the tapped density of the powder, D_b is the bulk density of the powder.

Angle of repose

The angle of repose was determined by funnel method suggested by Newman. Angle of repose is determined by following formula.

$$\theta = tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height of the cone, r = radius of heap.

A funnel was fixed at a height of approximately of 2-4 cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder.[8]

In vitro floatability

Microparticles (0.3 g) were spread over the surface of a USP dissolution apparatus (type II) filled with 900 ml of HCl buffer pH 1.2, containing 0.01% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portion of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres. Buoyancy (floatability) was calculated from the following formula.[9]

$$Buoyancy\ (\%) = Q_f / (Q_f + Q_s) \times 100$$

Where Q_f and Q_s are the weights of the floating and the settled microspheres, respectively.

FTIR spectroscopy

To detect any possible interaction between the drug and various excipients, we performed FT-IR spectroscopy on drug and formulation F3. Interaction between drug and excipients was studied by infrared spectroscopy using FTIR spectrometer (FTIR-4100, Jasco, Japan). Sample preparation involved potassium bromide (KBr) pallet technique. The spectrum was scanned over a frequency range 4000-400 cm^{-1}.[9]

In vitro release studies

The USP paddle type dissolution rate test apparatus was used for all the *in vitro* release studies. A weighed quantity of the microspheres was suspended in 900 mL of HCl buffer pH 1.2. The dissolution medium was stirred at 100 rpm and maintained at constant temperature (37±0.5 °C). At preset time intervals 5 ml aliquots were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium maintaining sink condition throughout the experiment. After suitable dilution, the samples were analyzed for drug quantification at 298 nm by a UV Visible spectrophotometer (Jasco V-630, Japan).[11]

RESULTS AND DISCUSSION

Solubility study of solid dispersions

Solubility study was performed for all the 5 formulations. Results are presented in Table 3. Solid dispersion formulation SD6 exhibited the maximum solubility enhancement.

Particle size determination

The particle size of floating microspheres of all the formulations ranged from 429 to 781 μm (Table 4). It was observed that, on increasing the concentration of kollidon SR, the average size of floating microspheres was also increased. This may be due to diminished shearing efficiency at higher concentration of the polymer (higher viscosity).[8]

Scanning electron microscopy (SEM)

SEM photomicrograph indicated that the prepared floating microspheres were spherical in nature and have rough surface (Figure 1).

Percent yields and entrapment efficiency of floating microspheres

The percentage yield of microspheres was found to be in the range of 62.40 to 86.45. The entrapment efficiency of formulation F1 to F5 was also determined and found to be in the range 61.07 to 81.70. Results are presented in Table 4.

Table 3: Solubility of drug and various solid dispersion formulations in distilled water

Solid dispersion formulations	Solubility (mg/ml)
Drug	0.02
SD1	40.2 ± 3.4
SD2	45.3 ± 2.1
SD3	50.8 ± 4.3
SD4	49.9 ± 1.7
SD5	55.4 ± 3.1
SD6	87.2 ± 2.4
SD7	60.1 ± 4.5
SD8	62.4 ± 2.8
SD9	78.6 ± 3.7

Table 4: Average particle size, percent yield and entrapment efficiency of floating microspheres

Formulations	Average particle size (μm)	Percent yield	Entrapment efficiency (%)
F1	429 ± 2.1	62.40 ± 3.2	61.07 ± 2.4
F2	516 ± 3.5	76.13 ± 2.4	81.70 ± 1.6
F3	634 ± 1.9	86.45 ± 1.7	79.94 ± 3.7
F4	709 ± 2.6	85.26 ± 3.1	81.07 ± 2.4
F5	781 ± 4.1	84.08 ± 2.8	79.03 ± 2.9

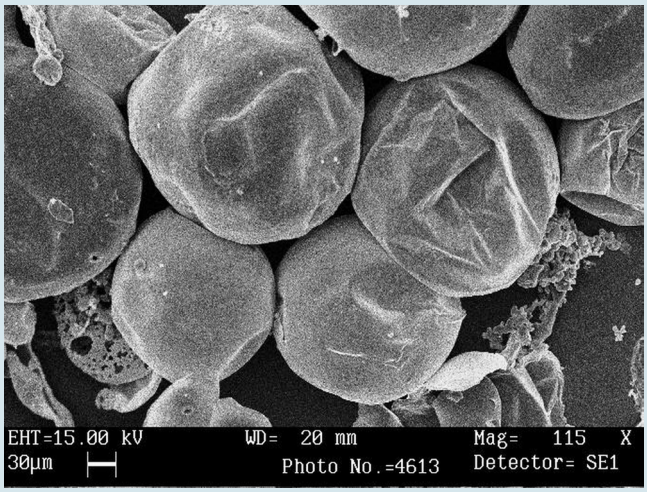

Figure 1: Scaning electron micrograph of floating microspheres (formulation F3)

Bulk density, tapped density, compressibility index and angle of repose

To determine their flow property, all the formulations were evaluated for bulk density, tapped density, compressibility index and angle of repose. Results are presented in Table 5.

In vitro floatability/buoyancy

Prepared floating microspheres were also subjected to buoyancy test to assess their floatability. Results are presented in Table 5.

FTIR spectroscopy

To assess the drug-excipients compatibility, we obtained the FT-IR spectra of formulation F3 and compared it with the FT-IR spectra of pure drug. FT-IR spectra of drug and formulation F3 can be seen in Figure 2 and 3, respectively. As we can see in Figure 2 and 3, there are no consid-

Table 5: Results of bulk density, tapped density, compressibility index, angle of repose and % buoyancy

Bulk density (g/ml)	Tapped density (g/ml)	compressibility index	angle of repose	% Buoyancy
0.622 ± 0.06	0.692 ± 0.05	10.11 ± 0.4	16.48 ± 0.9	61.26 ± 1.6
0.632 ± 0.02	0.684 ± 0.04	7.60 ± 0.2	22.73 ± 1.1	63.19 ± 2.5
0.674 ± 0.09	0.725 ± 0.09	7.56 ± 0.2	20.02 ± 1.3	67.81 ± 1.4
0.591 ± 0.03	0.652 ± 0.08	9.35 ± 0.7	21.02 ± 0.7	68.21 ± 2.1
0.658 ± 0.02	0.707 ± 0.07	6.93 ± 0.3	25.23 ± 1.6	74.02 ± 1.3

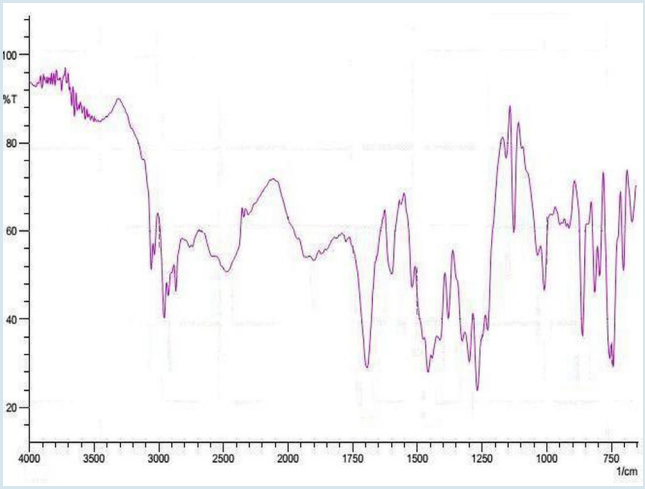

Figure 2: FT-IR spectrum of telmisartan

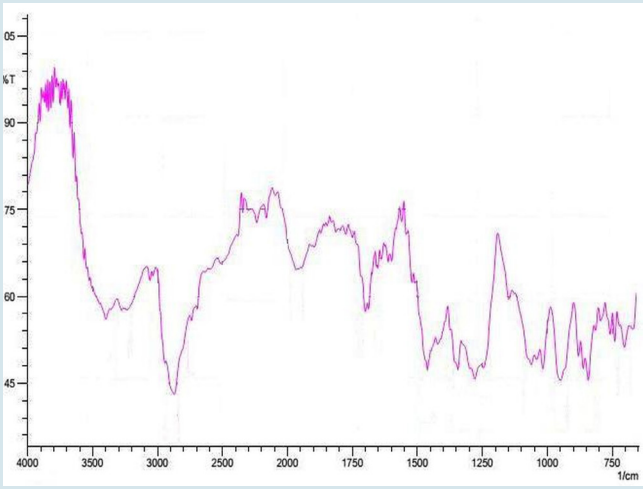

Figure 3: FT-IR spectrum of formulation F3

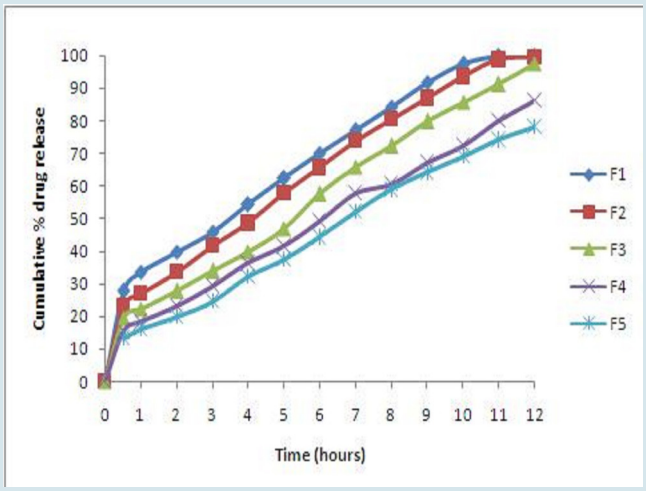

Figure 4: Comparison of *In vitro* drug release from different formulations

erable changes in the peaks of functional groups available in telmisartan in formulation F3 when compared to the pure drug.

In vitro release studies

In vitro release study was performed on all the five floating microsphere formulations in HCl buffer (pH 1.2), over a period of 12 hours. An USP paddle type dissolution rate test apparatus (Jyoti Scientific Industries, India) was used for this purpose. Cumulative % drug release was found to be 99.71, 99.54, 97.68, 86.09 and 78.19 for formulations F1, F2, F3, F4 and F5, respectively. These results show that the cumulative % drug release was decreased with the increase in concentration of kollidon SR. This may due to the increased density of the polymer matrix at higher concentration which ultimately results in an increased diffusion path length and therefore slower drug release.[8,11] The release pattern from various floating microsphere formulations is presented in Figure 4.

CONCLUSION

Floating microspheres of telmisartan were successfully prepared by non aqueous solvent evaporation method. Entrapment efficiency of all the formulations was found to be satisfactory. The practical yield of microspheres production was also found to be good, particularly at higher concentrations of kollidon SR. All the formulations exhibited good flow properties. *In vitro* buoyancy was also found to be satisfactory. FT-IR study suggested that there were no interaction present between the drug and excipients. Drug release form all the formulation was satisfactory, especially from microspheres having higher ratio of kollidon SR. We can conclude that the floating microspheres formulations of telmisartan can be developed that can effectively sustain the drug release for a desired period. Among the formulations examined F3 was found to be the best controlled/sustained release floating formulation for 12 h. Further, potential of the floating microspheres of telmisartan to improve telmisartan bioavailability in humans need to be investigated.

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CONFLICT OF INTEREST

The authors declares no conflict of interest.

ABBREVIATION USED

GI: Gastrointestinal physiology; **GRT:** Gastric Residence Time; **AT1:** Angiotensin II type-1; **PEG:** Polyethylene Glycol; **PVP:** Polyvinylpyrrolidone; **UV:** Ultra Violet; **SD:** Solid Dispersion; **LLP:** Light Liquid Paraffin; **KSR:** Kollidon SR; **SEM:** Scanning Electron Microscope; **%EE:** %Entrapment Efficiency; **USP:** United State Pharmacopoeia; **FT-IR:** Fourier Transform Infrared Spectroscopy.

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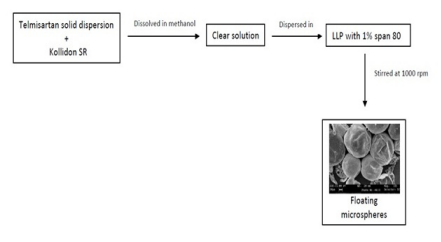
PICTORIAL ABSTRACT



SUMMARY

- The practical yield of microspheres production was found to be good, particularly at higher concentrations of kollidon SR.
- It was observed that, on increasing the concentration of kollidon SR, the average size of floating microspheres was also increased.
- Prepared floating microspheres were spherical in nature and have rough surface.
- Drug release form all the formulation was satisfactory, especially from microspheres having higher ratio of kollidon SR. Results show that the cumulative % drug release was decreased with the increase in concentration of kollidon SR.

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