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Formulation and evaluation of telmisartan microspheres by emulsion solvent evaporation technique

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ABSTRACT

Microspheres are multi-component system provide constant and prolonged drug release. Furthermore their floating abilities increase gastric residence time. These properties reduce the gastrointestinal toxic effects and dosing frequency and thereby improve the patient compliance. The present study aimed to formulate and evaluate telmisartan microspheres. Emulsion solvent evaporation (ESE) technique was employed for microsphere preparation using different ratios of ethyl cellulose polymer and drug. Prepared microspheres were evaluated for drug entrapment efficiency, micromeritic characters, floating behaviour and in vitro drug release. This revealed polymer drug ratio has influence on drug release.

INTRODUCTION

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time (Ma *et al.*, 2008). Novel drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system (Vasir *et al.,* 2003, Gaba *et al.,* 2011). However problem frequently encountered with controlled release dosage forms is the inability to increase residence time of the dosage at the site of absorption (Santus *et al.* 1997). Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation (Jain *et al.,* 2005). Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. Various attempts have been made to prolong the retention time of the dosage form in the stomach (Goyal and Mehta, 2011). These include floating drug delivery systems, also known as hydrodynamically balanced systems, polymeric bioadhesive systems, swelling and expanding systems, high-density systems, modified-shape systems, and other delayed gastric emptying devices (Bordonnet *et al.,* 2006). Microencapsulation is used to modify and retard drug release. In pharmaceutical sustained release preparations, the uniqueness of microcapsules lies in the wide distribution throughout the gastrointestinal tract (Amperiadou and Georgarakis, 1995). Microspheres provide constant and prolonged therapeutic effect, reduced the GI toxic effects and dosing frequency and thereby improve the patient compliance (Chella *et al.,* 2010). The drugs which are poorly soluble and unstable in intestinal fluids these systems are useful (Tejaswi *et al.,* 2011). One of the most common approaches for the preparation of microparticles is based on emulsification solvent evaporation. The emulsification solvent evaporation technique involves a three step processes. In the first step, a combination of polymer and drug solution (internal phase) is emulsified into the continuous phase. Then the solvent evaporates through the emulsion/air interface resulting in polymer precipitation and particle hardening. In the last step, microparticles are separated from the continuous phase by filtration and then they are

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washed by an appropriate solvent (Nilkumhang and Basit, 2009). Telmisartan, 4-((2-n-propyl-4-methyl-6-(1- methylbenzimidazol – 2 – yl) – benzimidazol – 1 - yl) methyl) biphenyl-2- Carboxylic acid, blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland (Tatane, 2011). The present work proposed to study influence of drug polymer ratio on telmisartan microspheres prepared by emulsion solvent evaporation technique. Prepared microspheres were evaluated for drug entrapment efficiency, micromeritics characters, floating behaviour and in vitro drug release.

MATERIALS AND METHODS

Materials

Telmisartan obtained from Mylan Labs, Hyderabad, India, as free gift sample. Ethylcellulose, dichloromethane, ethanol, polyvinyl alcohol and tween-80 purchased from Loba Chemie, India.

Preparation of microspheres

Emulsion solvent diffusion technique was employed for formulation of microsphere (Liu *et al.,* 2011). The polymer and drug were dissolved in a solvent mixture of dichloromethane and ethanol (1:1). Then, the dispersion solution was added drop-by-drop into 1.5% PVA solution containing 0.3% Tween-80. Resultant emulsion was stirred at 500 rpm using a propeller-type agitator for 2 hour. The microspheres were separated by filtration, washed with water and dried at room temperature in a desiccator for 24 hour. (Goyal and Mehta, 2011).

Evaluation of microspheres

Micromeritic properties

The microspheres were characterized by their micromeritic properties, such as particle size, tapped density, compressibility index and flow properties.

Size and Size distribution

The particle size of microspheres was determined using an optical microscopy method (Chella *et al.,* 2010). The size was measured using an optical microscope, and the mean particle size was calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer.

Tapped density

Tapped density of the microspheres was calculated as the ratio between the mass of the microsphere sample (g) and its volume (ml) after 100 tapping (Liu *et al.,* 2011).

Compressibility index

% Compressibility index= $[1- V/V_o] X 100$

Here V and V_o are the volumes of the sample after and before the standard tapping, respectively.

Angle of repose

Angle of repose of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method and calculated as

$$\tan \theta = 2H/D$$

where H and D are standing height and diameter of the microspheres heap formed on a graph paper after making the microspheres flow from the glass funnel.

Drug entrapment efficiency

To assess drug content, 20 mg of microspheres were weighed and dissolved in 0.1N HCl solution under ultrasonication. After filtration through a whattmann filter paper and the resulting solution further diluted and telmisartan content was determined spectrophotometricaly (UV 1800 Shimadzu, Japan) at 296 nm. In the concentration range of 1–8 µg/ml, the absorbance of telmisartan (Y) correlated well with its concentration (X): $Y = 0.1411X$ ($r^2 = 0.9997$, n = 3).

The percentage drug entrapment and yield of microsphere were calculated as follows (Jain *et al.,* 2005):

% Drug entrapment = [Experimental drug content / Theoretical drug content] X 100

% Yield = [Total weight of microsphere / Total weight of drug and polymer used] X 100

Drug loading efficiency

Percent drug loading was calculated as follow (Singh *et al.,* 2011):

% Drug loading = [Weight of drug loaded in the microspheres / Total weight of powdered microspheres] X 100

Morphological characterization

The dried samples were coated with gold film under a vacuum using a sputter coater. The surface part of the microspheres was observed under scanning electron microscopy (SEM; Hitachi S-3000, Tokyo, Japan).

In-vitro buoyancy studies

50mg of microparticles were containing 0.02 w/v% tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 8 h, the layer of buoyant microparticles was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight. 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 (Jain *et al.,* 2005).

$$\% \text{ Buoyancy} = [W_f / (W_f + W_s)] X 100$$

where W_f and W_s are the weights of the floating and settled microparticles, respectively. All the determinations were made in duplicate.

In-vitro drug release study

The in-vitro release study of the microsphere was carried out using USP rotating basket method. A weighted amount of microspheres was placed in the basket, and then put into the 500 ml dissolution medium (SGF, pH 1.2, HCl)) at 37 ± 0.5 ◦C with a paddle rotation speed of 50 rpm. At 1, 2, 3, 4, 6, 8 and 10 h, 5 ml samples were withdrawn, passed through a whattman filter, and analyzed using a Shimadzu 1800 UV spectrophotometer at 296 nm to determine the concentration of telmisartan. Simultaneously, 5 ml of fresh dissolution fluid was added to the dissolution medium after each withdrawal.

Release kinetics

Data obtained from *in-vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from the ethyl cellulose microsphere. The kinetic models used were (Nath *et al.,* 2010, Chella *et al.,* 2010):

$Q_t = K_0 t$ (zero-order equation)

$\ln Q_t = \ln Q_0 - K_1 t$ (first-order equation)

$Q_t = K_h t^{1/2}$ (Higuchi equation)

where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the microsphere, and K_0 , K_1 , and K_h are rate constants of zero order, first order and Higuchi equations, respectively. Further to confirm the mechanism of drug release, the first 60% of drug release was fitted in Korsemeyer-Peppas model (power law) (Das and Rao, 2007).

$M_t / M_\infty = k t_n$

where M_t is the amount of drug release at time t and M_∞ is the amount release at time t = ∞, thus M_t / M_∞ is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent which can be used to characterize both mechanism for both solvent penetration and drug release.

The rate constants for respective models were calculated from slope. Determining the correlation coefficient assessed fitness of the data into various kinetic models.

RESULT AND DISCUSSION

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit forms has relative merits compared to a single unit preparation (Goyal and Mehta, 2011). Multiple-unit particulate dosage forms (e.g. microspheres) have the advantages of passing through the GIT uniformly, which not only avoid the vagaries of gastric emptying but also provide an adjustable release, and reduced inter-subject variability in absorption and risk of local irritation were achieved consequently (Ma *et al.,* 2008). The floating microspheres were prepared by emulsion solvent diffusion technique. Ethanol and dichloromethane were used as the primary solvent and PVA solution as continuous phase. When ethanol alone is used as a solvent along with processing medium, it does not ensure the formation of primary emulsion of the aqueous phase in the polymer solution. Immediately on mixing, the water miscibility of ethanol brought about the precipitation of the polymer (ethylcellulose). Hence, a non-polar solvent, namely dichloromethane was included with ethanol to decrease the polarity of the polymer solution. The optimal proportion of dichloromethane and ethanol was found to be 1:1, which enable emulsion formation and yield good free flowing microspheres (Chella *et al.,* 2010).

Telmisartan microspheres were prepared using drug polymer (ethyl cellulose) ratio 1:1, 1:2, 1:5 and analyzed for drug entrapment, drug loading, yield and buoyancy (table 1). The floating test was carried out to investigate the buoyancy of the prepared microspheres. Increase in polymer concentration showed increase in entrapment efficiency, yield and buoyancy but decrease in loading efficiency. The micromeritic properties of microspheres were characterized in terms of mean diameter, angle of repose, tapped density, bulk density and compressibility and angle of repose (table 2). All formulation excellent flowability as expressed in term of angle of repose ($< 40^0$). All microspheres further subjected to *in vitro* drug release study (figure 1) and data obtained was fitted in different kinetic model for determination of release properties (table 3). Microsphere with drug polymer ratio 1:1 and 1:2 showed maximum correlation of regression for first order drug release and microsphere with drug polymer ratio 1:5 showed maximum correlation of regression for higuchi model. Korsemeyer-peppas model's n value found between 0.4957 to 0.5601 (table 3) for various drug polymer ratio indicating drug release from microsphere was diffusion controlled.

Table. 1: Physicochemical properties of telmisartan floating microsphere.

Drug/ polymer ratio	Entrapment efficiency (%)	Loading efficiency (%)		(%) Yield	Buoyancy (%)
		Theoretical	Practical		
1:1	63.23±1.27	50.00	31.62	83.34±1.11	82.58±0.76
1:2	74.08±1.68	33.33	24.69	87.58±1.32	90.86±0.93
1:5	81.69±1.74	16.67	13.62	91.69±1.81	94.36±1.26

Values are average of three readings± standard deviation

Table. 2: Micromeritic properties of telmisartan floating microsphere.

Drug/ polymer ratio	Mean diameter (µm)	Tapped density (gm/ml)	Bulk density (gm/ml)	Compressibility (%)	Angle of repose (^{o})
1:1	84.73	0.375	0.273	27.27	11.48
1:2	97.46	0.429	0.231	46.15	22.73
1:5	92.81	0.500	0.200	60.00	16.99

Table 3: *In vitro* drug release kinetic parameter of telmisartan floating microsphere

Drug/ polymer ratio	Zero order		First order		Higuchi model		Korsemeyer-peppas model	
	R^2	K_0	R^2	K_1	R^2	K_h	R^2	n
1:1	0.8086	7.4323	0.8789	0.4645	0.9615	29.5692	0.8752	0.5601
1:2	0.8509	7.6183	0.9739	0.3463	0.9768	29.7809	0.8536	0.4957
1:5	0.8712	7.5808	0.9887	0.2686	0.9839	29.3931	0.8996	0.5238

R^2 is the coefficient of correlation, K_0, K_1 and K_h are the release rate constant of zero-order, first-order and higuchi model respectively; and n is the release exponent of korsemeyer-peppas model.

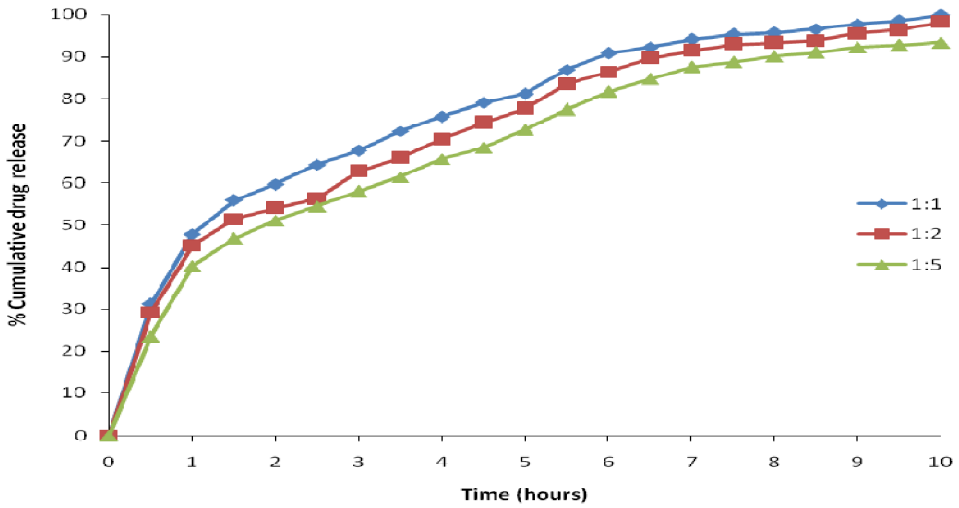

Fig. 1: *In-vitro* drug release profile of telmisartan microsphere at various drug polymer ratios.

CONCLUSION

Emulsion solvent evaporation can be used as suitable technique for preparation of hollow microsphere. Polymer concentration influences drug loading and drug release from microsphere. Generally drug entrapment increases with increasing concentration of polymer.

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