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Research Article

FORMULATION AND IN VITRO CHARACTERIZATION OF GASTRORETENTIVE MICROBALLOONS OF TELMISARTAN

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ABSTRACT

The main aim of the current study was to formulate and evaluate microballoons for Telmisartan which is having poor bioavailability. Telmisartan belongs to class II according to BCS classification of drugs,i.e. low solubility and high permeability. The Microballoons for Telmisartan were prepared by emulsion solvent evaporation method using different polymers and their ratios. The polymers include ethyl cellulose and HPMC. The obtained microballoons formulations were evaluated for percentage yield, particle size, buoyancy, drug content*, in-vitro* release studies. The bioavailability of Telmisartan can be increased by formulating it as gastroretentive drug delivery i.e. microballoons. Formulation F4 shows good results with good percentage yield, particle size and buoyancy. Microballoons prepared were spherical in size with smooth surfaces concluding it to be optimized formulations.

KEY WORDS: Telmisartan, Emulsion Solvent Evaporation Method, Buoyancy, Floating Drug Delivery, Gastro Retention.

INTRODUCTION

Microballoons, also called as hollow microspheres are gastro-retentive drug delivery systems which are spherical empty particles without core. These microspheres consists of proteins or synthetic polymers, characteristically free flowing powder having a size range of less than 200 µm. Floating microspheres are based on non-effervescent approach. Gastroretentive microballoons have sufficient buoyancy due to low density system so that they float over gastric contents for prolonged period of time. As the system floats over gastric contents, the gastric retention time is increased leading to desired drug release rate which results in increased gastric retention with reduced fluctuation in plasma drug concentration (Joshi and Jaimini. 2013). Increasing gastric retention time led to reduce in drug waste, improved bioavailability, and improving solubility of drugs that are less soluble in high or gastric pH environment. It also got application for local drug delivery to the stomach and proximal small intestine (Arora et al. 2005). Many approaches have been proposed to retain the dosage form in the stomach. These approaches include high- density systems, modified shape systems, mucoadhesive systems, swelling or expanding systems and other delayed gastric emptying devices (Vinod et al. 2010). Floating drug delivery systems are less dense than the gastric fluid. Floating single unit dosage form are also called hydrodynamically balanced systems

(HBS), have been studied. Floating single unit dosage forms have the disadvantage of a release all-or-nothing emptying process. However, the multiple unit particulate dosage forms release drug more uniformly, hence more reproducible drug absorption and reduce risk of local irritation than the use of single unit dosage form (Bhardwaj et al. 2010). In the cases of rate-controlled and time-controlled delivery systems, sustained drug absorption time is limited to the transit time of the dosage form through the absorption site because, thereafter, the released drug is not absorbed. Thus, when a drug possesses a narrow 'absorption window', design of the sustained release preparation requires both prolongation of gastrointestinal transit of the dosage form and controlled drug release. A dosage form targeting the gastrointestinal tract is designed to release a drug at a gastrointestinal site (Yadav et al. 2010). The main advantage of using microspheres as drugs delivery system is the controlled release of the drug content. This feature of microspheres made them suitable for carrying a particular drug which is frequently needed by the body in a small fixed amount (Kemala et al. 2012). The technique of emulsion solvent evaporation offers several advantages and is preferred over other preparation methods such as spray drying, sonication and homogenization, etc, as it requires only mild conditions such as ambient temperature and constant stirring (Mitra et al. 2011). Both natural and synthetic polymers have been used to prepare floating microspheres (Sharma et al. 2011). The current study includes preparation and evaluation of microballoons using emulsion solvent evaporation method. The study involves Telmisartan which is a 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 (Bansode et al. 2012).

MATERIALS AND METHODS

Telmisartan was obtained as a gift sample from Psychotropic India Limited, Haridwar and other ingredients like ethyl cellulose, HPMC, Acetone, Dichloromethane, n-hexane were obtained from Central Drug House Pvt. Ltd., New Delhi.

Method

Preparation of microballoons : Accurately weighed amount of drug and polymer was mixed with 15 ml of acetone and dichloromethane in a beaker. The solution was stirred for 5 minutes. This solution was poured drop wise drop to 0.5% w/v of PVA solution. Add 0.5 % span 80 to the solution. The resultant solution was kept under a mechanical stirrer at a constant speed of 500 rpm for 4 hours. After 3 hours, add 10 ml n- hexane to the solution. The prepared microballoons were washed, filtered, collected and dried (Table 1).

Table 1: Formulation Chart of Microballoons

S.No.	Formulation	Polymer	Drug:Polymer Ratio
1	F1	EC	1:1
2	F2	EC	1:2
3	F3	EC	1:3
4	F4	HPMC:EC	1:1:1
5	F5	HPMC:EC	1:1:2
6	F6	HPMC:EC	1:1:3
7	F7	HPMC:EC	1:2:1
8	F8	HPMC:EC	1:3:1

Evaluation Parameters:

1. **Drug-Excipients Compatibility Studies:**

Drug excipients compatibility studies were carried using FTIR. The study was carried out using pure drug alone and pure drug with the excipients used in the study.

2. Yield of microspheres:

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

% yield = (weight of dried microballoons)/total polymer weight+weight of drug taken) x100 (Jagtap et al. 2012)

3. Particle Size Analysis:

Scanning Electron Microscopy was done to determine the size and shape of microballoons after gold coating of Microballoons. As the polymer concentration increases, viscosity increments influenced the interaction between disperse phase and dispersion medium that affected the size distribution of particle. Increased EC or HPMC in a fixed volume of solvent increases the viscosity of the medium which might have diminished the shearing efficiency leading to increased droplet size and hence microsphere size (Raut et al. 2013).

4. **Buoyancy Studies:**

Accurately weighed 50 mg of microballoons were placed in a beaker containing 100 ml of SGF (pH 1.2) and placed in a magnetic stirrer at a speed of 100 rpm. Percentage buoyancy was calculated by

% buoyancy = weight of floating microballoons/weight of floating +weight of settled microballoons *100 (Jain et al. 2006)

5. Drug Content:

100 mg of accurately weighed microballoons were crushed in glass mortar. It was then kept in a solution of 0.1 N HCl for 6 hours. Solution was then filtered and absorbance was noted at 295 nm (Patel et al. 2000).

6. *In Vitro* diffusion studies:

50 mg of microballoons was filled in hard gelatin (No. 0). The study was carried out at a temp. of 37 $\pm 1^0$ C in a USP apparatus (basket type) containing 900 ml of simulated gastric fluid (pH 1.2) at a rotation speed of 100 rpm. Perfect sink condition was maintained during the study.5 ml of sample was withdrawn at each1 hr interval and analysed spectrophotometrically at a range of 295 nm to determine the drug concentration 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 (Singh et al. 2000, Dinarvand et al. 2002, Abral et al. 2004).

7. *In vitro* drug release kinetic kinetics:

The release data obtained were treated according to zero order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug release versus root time) and korsmeyer- peppas (log cumulative percentage of drug released versus log time) equation models.

RESULT

As Telmisartan is a poorly water soluble drug so the poor bioavailability of Telmisartan was the criteria which caused the selection of drug, which could be increased by prolonging the gastric retention time. Microballoons were prepared by using emulsion solvent evaporation and solvent evaporation diffusion method but it was conferred that emulsion solvent evaporation method produces smooth, uniform and spherical particles. Telmisartan was incorporated with different

polymer like ethyl cellulose, HPMC and their combination. It was found that combination of polymers in appropriate ratio were best for preparation of microballoons. When drug and polymer are introduced into the aqueous solution containing PVA, an oil in water emulsion is formed. Agitation provided by stirrer breaks the poured solution into droplets in which drug and polymers are in organic phase and PVA in aqueous phase of the emulsion. As the stirring continues, acetone starts to diffuse out leaving drug and polymer at the emulsion interface leaving DCM at the hollow cavity (Pachuau et al. 2009). n- Hexane is added as a hardening agent for the quick precipitation of polymer leaving a porous surface.

A significant decrease in the release was seen when the solvent composition was changed. As the solvent increases the release rate also decreases.

Particle size analysis

The formed microballoons showed that they were spherical in size with smooth surfaces. All microballoons prepared from different ratio of polymers lie in the micro size. Microballoons were prepared using ethyl cellulose alone and with its combination with HPMC. The mean particle size of microballoons increase with increase in EC concentration Fig. 1(a) and 1(b). At higher concentration, the viscosity of medium also increases, hence, greater particle size. Smaller microballoons were prepared at lower polymer concentration alone and in combination. Span 80 is oil and produces a stable emulsion when the dispersion medium is oil (Phutane et al. 2010). Agitation speed is also a major factor in determination of microballoons. On increasing the agitation speed, the mean particle size decreases due to frothing and adhesion to the wall. Spherical microspheres were obtained using span 80 (Jelvehgiri et al. 2010). Temperature plays an important role in formation of microballoons. The optimum temperature for formation is 35-40ºC at room temperature. At low temperature, the yield was low and at higher temperature, the buoyancy of microballoons decreases. As the size of microballoons increased, the release rate decreases due to decrease in surface area.

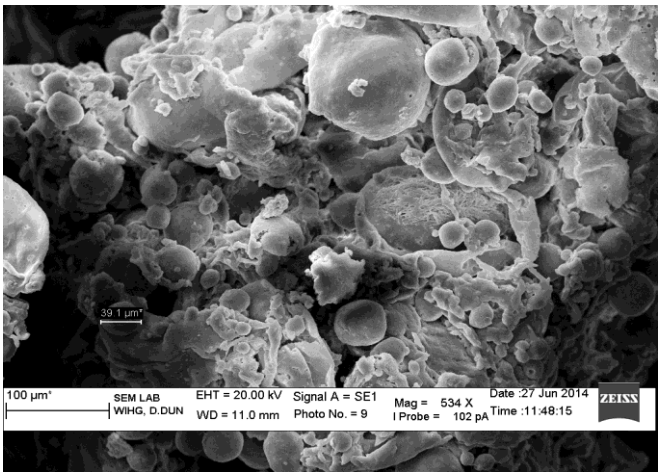

Fig. 1(a): SEM image of formulation F4

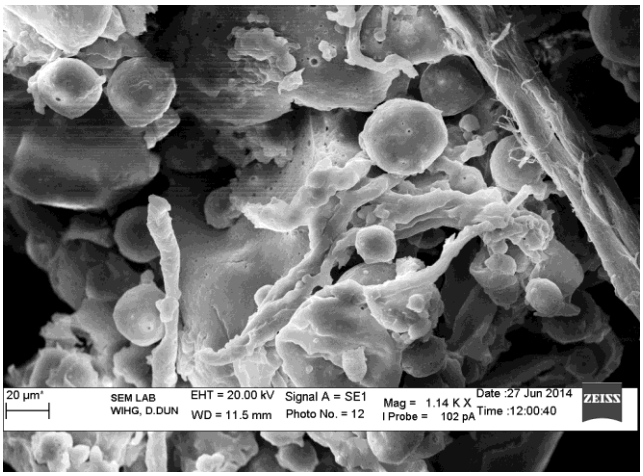

Fig. 1(b): SEM image of formulation F5

Buoyancy

With increase in EC concentration, buoyancy increases when EC was used alone (from 67.943 to 73.384). The buoyancy decreases when concentration of HPMC increases (from 75.384 to 57.142). Larger the particle size, longer will be the floating time.

All the results of evaluation are given in Table no 2 as shown below.

S. No	Formulation	Percentage yield	% Drug release	% Buoyancy	Drug content
1	F1	56.6	79.330	67.943	88.632
2	F2	64.9	70.620	72.222	82.917
3	F3	68.6	62.201	73.384	84.072
4	F4	73.7	78.362	75.169	88.932
5	F5	70	73.959	65.551	85.874
6	F6	71.5	60.024	70.437	83.711
7	F7	68.8	74.879	60.140	81.962
8	F8	63.4	71.927	57.142	79.783

Table 2: Results of Various evaluation parameters

A significant decrease in the release was seen when the solvent composition was changed. As the solvent increases the release rate also decreases.

As the concentration of polymer increases, the release rate also increases (fig. 2).

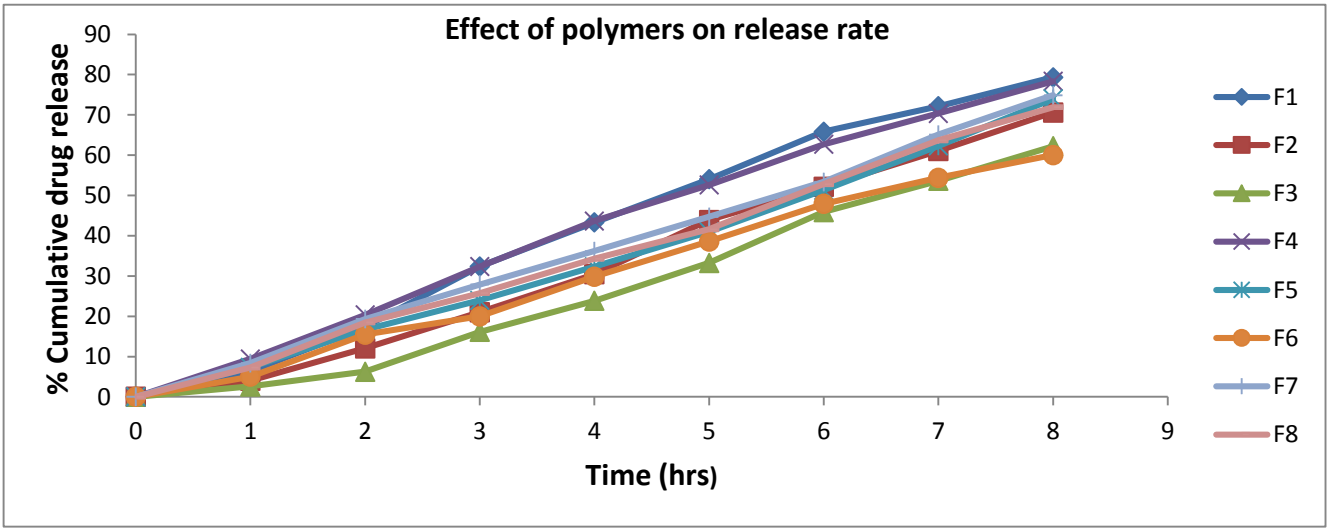

Fig. 2: *In-vitro* drug release profile of Telmisartan microballoons using various polymer concentration.

Agitation speed is also a major factor in determination of formation of microballoons. When agitation speed was increased, due to frothing and adhesion to the wall the mean particle size also decreases. Using Span 80, spherical microspheres were obtained (Jelvehgari et al. 2010). Temperature plays an important role in formation of microballoons. The optimum temperature for formation is 35-40 ºC at room temperature. At low temperature, the yield was low and at higher temperature, the buoyancy

of microballoons decreases. As the size of microballoons increased, the release rate decreases due to decrease in surface area.

CONCLUSION

The results obtained from *in vitro* data revealed that the prepared microballoons were having good buoyancy and better drug release. It was further concluded that with the variation in concentration of polymer, microballoons of different size, buoyancy and drug content can be obtained. Microballoons were prepared by using solvent evaporation method. Combination of ploymers produces more appropriate formulation. As polymer is increased, the % release decreases. FTIR study shows no interaction between the drug and the polymers.So, it can be concluded that microballoons drug delivery system can be used as gastroretentive drug delivery system.

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