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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 73.7 % obtained yield, 65.932 % drug content and 75.169 % buoyancy. Microballoons prepared were spherical in size with smooth surfaces concluding it to be optimized formulations.

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[1]. 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 [2].

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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 [3]. 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 [4].

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 [5].

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 [6].

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 [7]. Both natural and synthetic polymers have been used to prepare floating microspheres [8].

The current study includes preparation and evaluation of microballoons using emulsion solvent evaporation method. The current study includes Telmisartan which is 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 [9].

MATERIALS AND METHODS

Materials

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

Preparation of microballoons of Telmisartan

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 min. 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 h. After 3 h, add 10 ml n-hexane to the solution. The prepared microballoons were washed, filtered, collected and dried[7] (Table 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.

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

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[10]:

$$\% \text{ yield} = \frac{\text{weight of dried microballoons}}{\text{total polymer weight+weight of drug taken}} \times 100$$

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 [11].

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 [12]:

$$\% \text{ buoyancy} = \frac{\text{weight of floating microballoons}}{\text{weight of floating + weight of settled microballoons}} \times 100$$

Drug Content

Microballoons equivalent to 50 mg drug were crushed in glass mortar. Volume was then make up to 100ml with the solution of 0.1 N HCl. Solution was then filtered and absorbance was noted at 295 nm[13].

In Vitro diffusion studies

50 mg of microballoons was filled in hard gelatin (No. 0). The study was carried out at a temperature of 37 ±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 hour interval and analyzed 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[14,15,16].

RESULTS AND DISCUSSION

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 [17]. n- Hexane is added as a hardening agent for the quick precipitation of polymer leaving a porous surface.

Drug polymer 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 (Figures not shown). There was no interaction seen between the drug and the polymers.

Particle size

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), 1(b). At higher concentration, the viscosity of medium also increases, hence, greater particle size are obtained. Smaller microballoons were prepared at lower polymer concentration alone and incombination. Span 80 was found to produce stable emulsion when oil is used as the dispersion medium[18].

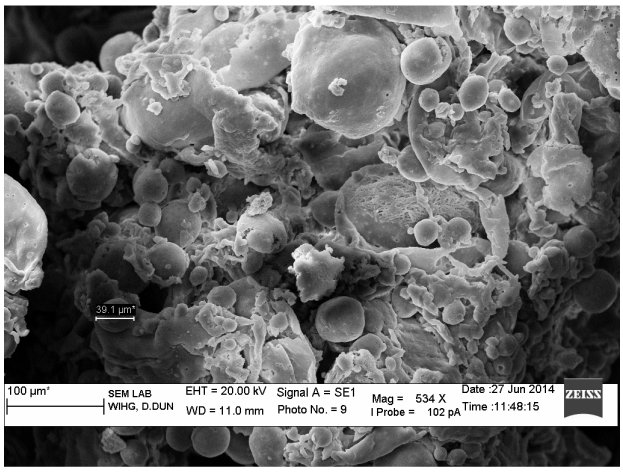

Figure 1(a): SEM image of formulation F4

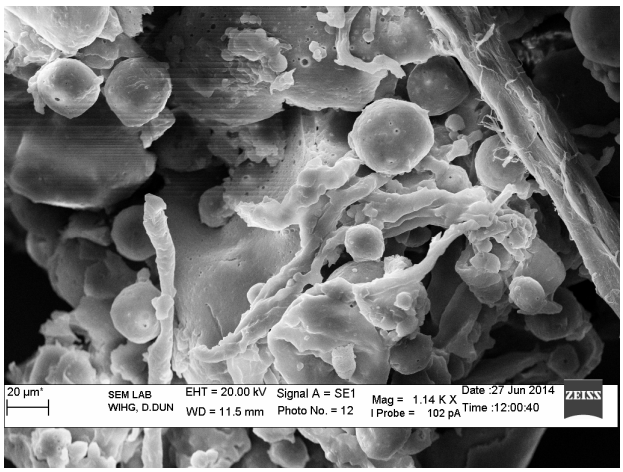

Figure 1(b): SEM image of formulation F5

Buoyancy studies

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 2 as shown below.

Table 2: Results of Various evaluation parameters

Sl. No	Formulation	Percentage yield	% Drug release	% Buoyancy	Drug content
1	F1	56.6	79.330	67.943	48.632
2	F2	64.9	70.620	72.222	59.917
3	F3	68.6	62.201	73.384	62.072
4	F4	73.7	78.362	75.169	65.932
5	F5	70	73.959	65.551	64.874
6	F6	71.5	60.024	70.437	62.711
7	F7	68.8	74.879	60.140	59.962
8	F8	63.4	71.927	57.142	56.783

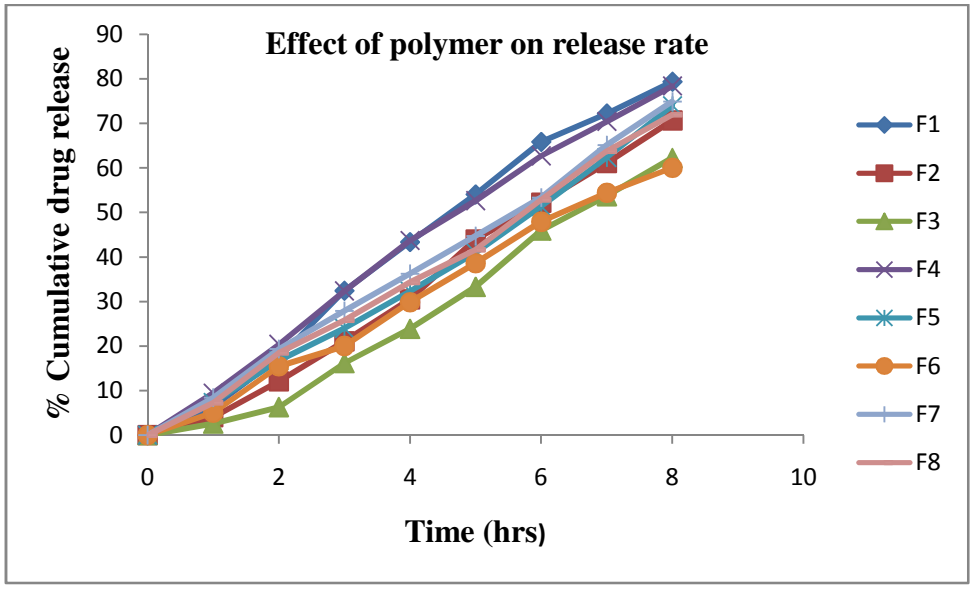

Figure 2: *In-vitro* drug release profile of Telmisartanmicroballoons using various polymer concentrations

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).

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 [19]. 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.

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 polymers 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. The optimized formulation was F4 with optimum results.

REFERENCES

[1] Joshi VK, Jaimini M. Microballoons for drug delivery: A review. Asian Journal of Pharmaceutical Research and Development 2013; 1 (1):07 –17.

[2] Arora S, Ali J, AhujaA, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review. AAPS Pharm Sci Tech2005; 6 (3): E372-E90.

[3] VinodKR, Sri AP, David B, Anbazhagan S, Santhosh V, Sandhya S.Fabrication and Optimization of Oral Sustained Release Floating Lansoprazole Microspheres. International Journal of Pharmaceutical Sciences 2010; 2 (2): 60-64.

[4] Bhardwaj P, Chaurasia H, Chaurasia D, Prajapati SK, Singh S. Formulation and In-Vitro Evaluation of Floating Microballoons of Indomethacin. Acta Poloniae Pharmaceutica -Drug Research 2010; 67 (3): 291-98.

[5] Yadav A, Jain DK. *In-vitro* Characterization of gastroretentive microballoons prepared by the emulsion solvent diffusion method. Journal of Advanced Pharmaceutical Technology & Research 2010; 1 (1): 56-67.

[6] Kemala T, Budianto E, Soegiyono B. Preparation and characterization of microspheres based on blend of poly(lactic acid) and poly(e-caprolactone) with poly(vinyl alcohol) as emulsifier. Arabian Journal of Chemistry 2012; 5: 103–08.

[7] Mitra J,Davoud H, Farhad K, Badir DL, Sara A. Preparation and Determination of Drug-Polymer Interaction and *In-vitro* Release of Mefenamic Acid Microspheres Made of Cellulose Acetate Phthalate and/or Ethyl cellulose Polymers. Iranian Journal of Pharmaceutical Research 2011; 10 (3): 457-67.

[8] Sharma AK, Keservani RK, Dadarwal SC, Choudhary YL, Ramteke S. Formulation and in vitro characterization of cefpodoxime proxetil gastroretentive microballoons. DARU 2011; 19(1): 33-40.

[9] Bansode SD, Kasture VS, Pawar SS, Kasture SB. Formulation and evaluation of Telmisartan microspheres by emulsion solvent evaporation technique. Journal of Applied Pharmaceutical Science2012; 2 (10): 113-16.

[10] Jagtap YM, Bhujbal RK, Ranade AN, Ranpise NS. Effect of Various Polymers Concentrations on Physicochemical Properties of Floating Microspheres. Indian Journal of Pharmaceutical Sciences 2012; 74(6):512-20.

[11] Raut NS, Somvanshi S, Jumde AB, Khandelwal HM, Umekar MJ, Kotagale NK. Ethyl cellulose and hydroxypropyl methyl cellulose buoyant microspheres of metoprolol succinate: Influence of pH modifiers. International Journal of Pharmaceutical Investigation 2013; 3 (3): 163-70.

[12] Jain SK, Agarwal GP, Jain NK. Evaluation of Porous Carrier-based Floating Orlistat Microspheres for Gastric Delivery. AAPS PharmSciTech 2006; 7 (4):E1-E8.

[13] Patel A, Ray A, Thakur RS. In vitro evaluation and optimization of controlled release floating drug delivery system of Metformin hydrochloride. DARU 2006; 2: 57–64.

[14] Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63: 235–59.

[15] Dinarvand R, Mirfattahi S, Atyabi F. Preparation characterization and *in vitro* drug release of isosorbide dinitrate microballoons. J Microencapsul 2002; 19:73–81.

[16] Abrol S, Trehan A, Katare OP. Formulation, characterization, and *in vitro* evaluation of silymarin-loaded lipid microballoons. Drug Deliv2004;11:185–91.

[17] Pachuau L, Mazumder B. A study on the effects of different surfactants on Ethylcellulose microspheres. International Journal of PharmTech Research 2009; 1(4): 966-71.

[18] Phutane P, Shidhaye S, Lotlikar V, Ghule A, Sutar S, Kadam V. *In vitro* Evaluation of Novel Sustained Release Microspheres of Glipizide Prepared by the Emulsion Solvent Diffusion-Evaporation Method. J Young Pharm 2010; 2(1): 35–41.

[19] Jelvehgari M, Nokhodchi A, Rezapour M, Valizadeh H. Effect of Formulation and Processing Variables on the Characteristics of Tolmetin Microspheres Prepared by Double Emulsion Solvent Diffusion Method. Indian J Pharm Sci 2010; 72(1): 72–78.