AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Development and Evaluation of Novel Floating Osmotic Capsule for Zero Order Delivery of *Andrographis Paniculata* Extract

Suresh D Sanja[*1], Kilambi Pundarikakshudu[2], Moinuddin M Soniwala[1]
1. Department of Pharmacy, B K Modi Govt Pharmacy College, Rajkot
2. Deparment of Pharmacy, L J Institute of Pharmacy, Ahmedabad

ABSTRACT

Andrographis paniculata (Kalmegh, family: Acanthaceae) is used extensively in the Indian traditional system of medicine as a hepato-protective and hepato-stimulative agent. Osmotic drug delivery systems are the best amongst promising strategy based reliable drug delivery systems employed for controlled drug delivery. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. Different quantities of cetosteryl alcohol ranging from 50 mg to 200 mg have been checked for floating lag.

Keywords: GRDDS, floating osmotic capsule, *Andrographis paniculata,* hepatoprotective

*Corresponding Author Email: sureshsanja@gmail.com
Received 13 October 2014, Accepted 17 October 2014

Please cite this article in press as: Sanja SD *et al.*, Development and Evaluation of Novel Floating Osmotic Capsule for Zero Order Delivery of *Andrographis Paniculata* Extract. American Journal of PharmTech Research 2014.

INTRODUCTION

Andrographis paniculata (Kalmegh, family: Acanthaceae) is used extensively in the Indian traditional system of medicine as a hepato-protective and hepato-stimulative agent. The aqueous extract of the leaves of this plant has traditionally been used for treatment of various liver disorders and jaundice. Basically, the taste of Andrographis is very bitter. This bitterness is related to its various pharmacological properties such as antibiotic, antiviral, antimicrobial, anti-inflammatory, antivenom, Immunostimmulatory, anticancer, anti-HIV, anti-allergic, and hypoglycemic activity. These properties are due to the presence of distinct lactones and flavones. Osmotic drug delivery systems are the best amongst promising strategy based reliable drug delivery systems employed for controlled drug delivery. There are numerous drug delivery systems and devices designed for osmotic drug delivery in the past two three decades, over numerous patented osmotic pumps have been reviewed. The elementary osmotic pump (EOP) was first introduced in the 1970s.[1] They are comparatively simple to manufacture and are able to release drug at an approximate zero-order rate. However, the limitation of this type of EOP is that it is only suitable for the delivery of water soluble drugs. The design performance characteristics of osmotic systems result in better clinical performance including constant drug plasma concentrations, not affected by food, and, better *in vitro in vivo*. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small.[2] These delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of the drug, the residual system is emptied from the stomach. These results in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. [3] The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder). These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation.[4, 5] On the other hand multiple-unit

floating systems may be an attractive alternative since they have been shown to reduce the inter and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating systems like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery systems.[6, 7]

MATERIALS AND METHOD

Andrographis paniculata was purchased from Sanjivani Aushadhalay, Bhavnagar, Gujarat. Ceto-stearyl alcohol, sodium chloride, lactose, mannitol, formaldehyde were purchased from S D fine chemicals, Mumbai. Transparent hard gelatin capsule shells were received as a gift sample from capsugel India ltd.

Extraction method of ethanolic extract of *Andrographis paniculata*

The aerial part of *Andrographis paniculata* were shade dried followed by drying in hot air oven at 50^{O}C for 30 min, then it was powdered in a mechanical grinder. The dried powders were then used for extraction with suitable solvents. The coarse dried powder of the aerial part (1000 g) was subjected to extraction with 2 lit of 50 % w/v ethanol for 48 h. The ethanol extract was collected, filtered and concentrated in vacuum under reduced pressure and dried in desiccators. This procedure was repeated another two times with 1.5 and l lit of 50 % v/v ethanol respectively. The yield was about 12.11 % (w/w). [8]

Pre-formulation study

Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre-formulation studies is to develop a portfolio of information about the drug substance, so that this information is useful to develop formulation. Pre-formulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Pre-formulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. [9, 10]

Organoleptic Characteristics

The color, odour, and taste of the andrographolide extract were characterized and recorded using

descriptive terminology

Bulk Density

An accurately weighed quantity of powder extract, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula[1].

Bulk density = Weight of powder / Bulk volume

Tapped Density

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula [1].

Tapped density = Weight of powder / Tapped volume

Angle of repose

Angle of repose was determined by measuring the height, radius of the heap of the powder blend. A cut system funnel was fixed to a stand and bottom of the funnel was fixed at a height of 2 cm from the plane. Powder blend was placed in funnel and allowed to flow freely and measured the height and radius of the heap.

$$\mathbf{Tan}\ \theta = \mathbf{h}/r$$

Where, h = height of heap r = radius of heap

Preparation method for a novel Floating-osmotic capsule

The preparation method for a novel floating-osmotic capsule involves four major steps.

Preparation of cross linked hard capsule shells

Capsule shells of 00 (capacity 0.735 ml) size were kept in the desiccator containing formaldehyde by opening cap for a period of 24 h for the cross linking. After a day the shells were taken out and were kept for the air drying for the period of 24 h at room temperature in well ventilated area.

Filling of waxy material into body of capsule

Take 1 gm of cetostearyl alcohol in a porcelain dish and put it for melting in porcelain dish maintained at 40^{o}C in water bath. With the help of syringe 0.15 ml wax was filled in each of the capsule bodies. Cool it properly for rigidization. Now inject 10 % gelatin solution as a thin layer over it and cool it properly for rigidization. Now again put it for cross linking for 1 day in

desiccator with formaldehyde and after 2 days it was air dried for a period of 24 h at room temperature in well-ventilated area.

Filling of *Andrographis paniculata* extract and osmogent

The extract and osmogent were precisely weighed as per the formula, passed through sieve 40 and mixed homogeneously. This mixture was filled in the capsule body with the help of spatula. The final quantity which is 500 mg was maintained using mannitol as diluent in each formulation.

Preparation of extract releasing orifice in the capsule shell

Orifice was prepared with the help of standard 24'gauze (outer diameter 0.5652 ± 0.0064 mm) in the cap.

Sealing of the filled capsules

After filling lock the body part with cap and seal it with 10 % gelatine solution to ensure elementary osmotic delivery. 2 % w/v solution of ethyl cellulose in acetone was used to protect the pore during storage. Crosslinking with formaldehyde was carried out in a desiccator for a period of 1, 2 and 3 days. Different amount of cetostearyl alcohol was utilized ranging from 50 to 200 mg to check effect on buoyancy. To check the effect of osmogent, sodium chloride and lactose were used. The extract was taken in the quantity of 200 mg with quantity of NaCl was 100 (P1), 150 (P2), 200 (P3) and 250 (P4) mg while two batches with 250 (P5) and 300 (P6) mg lactose were prepared ;in all the batches mannitol was taken as diluents to make up the quantity up to 500 mg. In the case of ratio of osmogent was taken 50:50 (P7) and 25:75(P8) (sodium chloride to lactose, 250mg) and its effect on release was checked (Table 1).

Table 1: Composition of batches for selection of osmogent selection

Ingredients(mg)	P1	P2	P3	P4	P5	P6	P7	P8
Extract	200	200	200	200	200	200	200	200
NaCl	100	150	200	250	-	-	125	62.5
Lactose	-	-	-	-	250	300	125	187.5
Mannitol	200	150	100	50	50	-	50	50

*22'gauze was used to form pore in cap while 150mg cetostearyl alcohol as floating agent (All ingredients are in mg)

Evaluation of the Floating-osmotic capsules

***In-vitro* buoyancy studies**

The prepared capsules were placed in 900 ml 0.1N HCl. The time required to float was considered as floating lag time while the time period for which it remains buoyant was taken as the floating time. [11, 12]

***In-vitro* release studies**

It was carried as described by Dalavi et al (2009) and Deshpande et al. (1997) using USP dissolution apparatus (Type II). 0.1N HCl (900ml) was taken as dissolution medium; at 100 rpm and 37 ± 0.5^{o} C. Aliquots of 5ml was withdrawn at predetermined times, filtered through 0.22 µ Whatman filter paper and absorption of the filtered liquid was taken at 270 nm. [13, 14]

RESULTS AND DISCUSSION

Pre-formulation study

Pre-formulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Organoleptic properties of the extract

Results of organoleptic properties were shown in Table 2.

Table 2: Organoleptic properties of andrographolide extract

Properties	Result
Description	Amorphous powder
Taste	Intensely bitter
Color	Light brown
Odor	Slightly characteristic

Powder extracts blend properties

The angle of repose of all the powder extract fell within the range of 24.97 ± 0.18 to 29.09 ± 0.14 i.e. powders were of good flow properties. The bulk density and tapped density of powder blend (1:1: extract: osmogent [50:50 and 25:75]) was found to be between 0.536 ± 0.03 to 0.760 ± 0.05 g/cm^3 and 0.675 ± 0.06 to 0.953 ± 0.05 g/cm^3 respectively (Table 3). This indicated good packing capacity of powder extract blend. Figure 1 shows the variables which might affect the release of extract from the floating osmotic capsule. It was very crucial stuff to fetch the most important variable in order to optimize the extract release from the osmotic capsule.

Table 3: Powder blend properties of APE and excipients

Parameters	APE	Lactose	Mannitol	NaCl
Bulk density	0.536 ± 0.03	0.73 ± 0.03	0.760 ± 0.05	0.848 ± 0.03
Tapped density	0.675 ± 0.06	0.922 ± 0.05	0.953 ± 0.05	0.907 ± 0.25
Angle of Repose*	30.97 ± 0.18	29.09 ± 0.14	22.32 ± 1.3	31.32 ± 0.6
Particle Size(µm)	180-550	65- 175	90-190	200-350

** The values represent mean ± S.D; n=3*

Degree of cross-linking

Cross linking of the capsules was carried out for one, two and three days and their solubilities were checked in 0.1 N HCl for 24 h. After the completion of cross-linking they were first air dried for 24 h in a well ventilated room. Few samples were selected and were exposed to in 0.1 N HCl for 24 h and 6.8 buffer for 8 h. All the cross-linked capsules ranging from one day to three days remained insoluble in the dissolution medium.

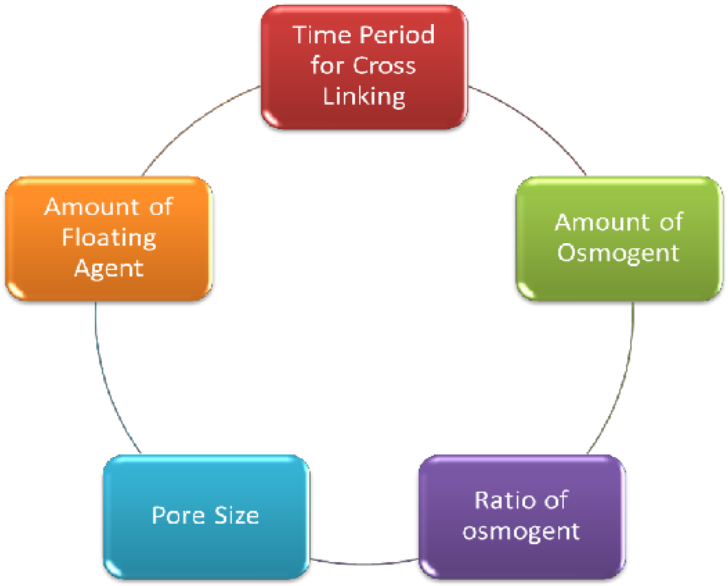

Figure 1: Formulation variables affecting drug release from floating osmotic capsule

Amount of Floating agent

Different quantities of cetosteryl alcohol ranging from 50 mg to 200 mg have been checked for floating lag. After filling of measured quantity of wax in the body and proper drying the capsules were filled with 500 mg of mannitol. In case of 50 mg and 100 mg cetostearyl alcohol first capsule sinks then after 5 min it floats again then it sinks while no lag was found in higher amount. Hence it was decided to go for 150 mg cetostearyl alcohol with no lag time and to decrease the number of formulation variables.

Amount of Osmogent

As sodium chloride is a common salt with higher osmotic pressure, it was selected as osmogent. Sodium chloride in quantity ranging from 100 mg to 250 mg was checked. As observed from Figure 2, at 12 h the extract release was found to be 92 % in P1 which was 84 % in P2. With 150 mg (P3) and 100 (P4) mg NaCl the extract release was 75 and 68 % respectively. Another osmogent checked was lactose with 300 (P5) and 400 (P6) mg of lactose monohydrate and the release was 63 and 75 % at 10 h (Figure 3). The extract release was lower but with good linearity. It is clearly seen from the graph that as the quantity of sodium chloride increased the release also increased. It was observed that due to incomplete release sodium chloride and lactose could

not be selected as osmogent. Hence various ratios of sodium chloride to lactose (50:50 and 25:75) were taken and its effect was found to be significant on extract release. As observed from Figure 4, batch P8 containing sodium chloride to lactose in ratio of 25:75 gave complete extract release within 12 hours.

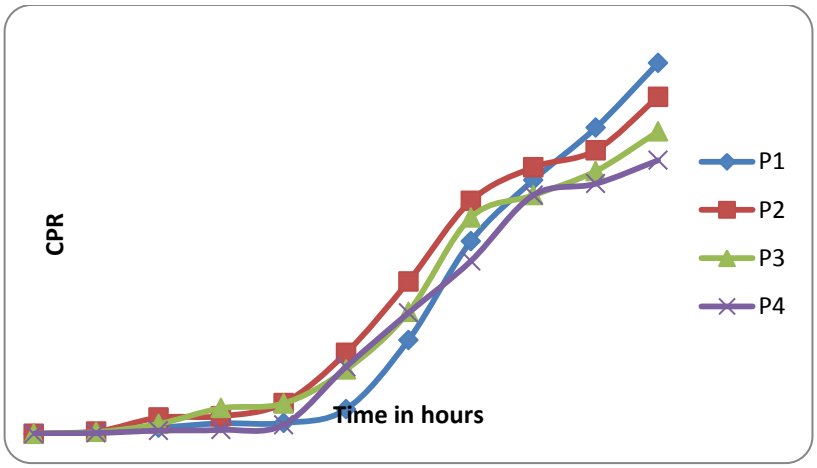

Figure 2: Release profile of andrographis extract with sodium chloride as osmogent

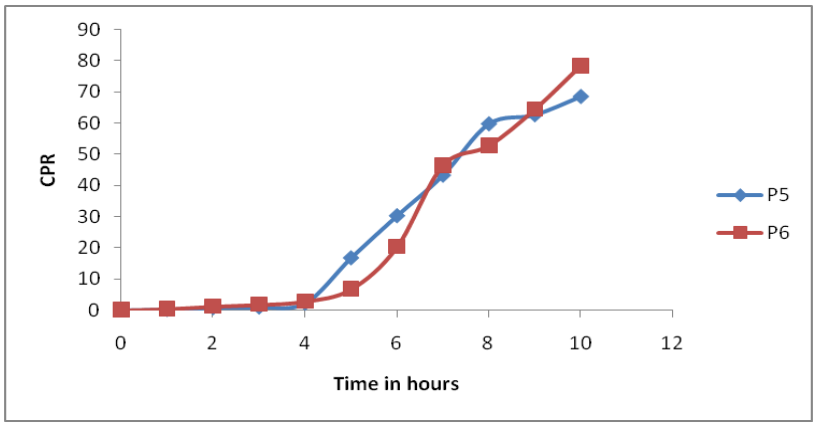

Figure 3: Release profile of andrographis extract with lactose as osmogent

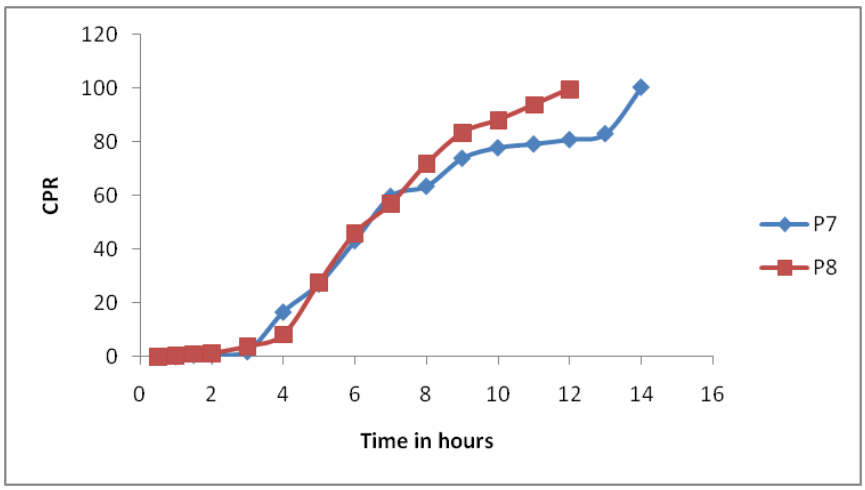

Figure 4: Release profile of andrographis extract with lactose/NaCl mixture as osmogent

CONCLUSION

The present work was aimed at formulating a novel osmotic capsule for *Andrographis paniculata* extract (APE) to maintain the constant extract level in the blood, avoid dose dumping and improve the therapeutic efficacy in liver disorders. It also encompasses the concept of floating providing prolonged gastric residence. The osmotic capsule will be retained in the stomach; extract will continuously release at the site of absorption thereby improving the therapeutic efficacy of the treatment.

REFERENCES

1. Theeuwes F., et al. U.S.Patent 4455143 (1984).
2. Singh BN, Kim KH. floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel 2000;63: 235-59.
3. Streubel A, Siepmann J, Bodmeier R.. Multiple unit Gastro retentive drug delivery: a new preparation method for low density microparticles. J Microencapsul 2003;20: 329-347.
4. Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195: 125-135.
5. Sungthongjeen S, Paeratakul O, Limmatvapirat S, Puttipupathachorn S. Preparation and in-vitro evaluation of multiple-unit floating drug delivery system based on gas formation technique. Int J Pharm. 2006; 324: 136-143.
6. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci 2003;18: 37-45.
7. Yeole PG, Khan S, Patel VF. Floating Drug Delivery System: Need and Development. Ind. J Pharm Sci 2005;67: 265-272.
8. Mishra U, Mishra A, Kumari R, Murthy P , Naik B Antibacterial activity of ethanol extract of *Andrographis paniculata*. Indian J Pharm Sci 2009; 71:436-438.
9. Wells J. Pharmaceutical Preformulation. Pharmaceutics: The Science of Dosage Form Design. ME Aulton. Eds, 3rd, Edinburgh London: Melbourne and New York 1998:235,248.
10. Indian Pharmacopoeia. Stability Testing Guidelines, Stability testing of a new drug product and new drug substance, Vol. 2, Controlled of Publication, Delhi, 1996: 625.
11. Sharma MC, Sharma S, Kohli DV, Chaturvedi S.C. Formulation In-Vitro Evaluation, study of effect of Hardness on Buoyancy the time of Gastro retentive Flim and Floating Tablet J. Optoelectronic and Biomedical Materials. 2009; 1: 353-358.

12. Mehta K, Patel NK, Ganatra MH, Patel TD, Patel NJ. Formulation and optimization process of gastroretentive Floating Tablets of ondasetron HCL. JPRHC, 2007; 2(3): 253-257.
13. Dalavi V. Gastro retentive drug delivery system of an antiretroviral agent. AAPS Pharm Sci. Tech 2009; 1: 1678-1684.
14. Deshpande AA, Shah NH, Christoper TR, Malik W. Development of Novel Controlled Release System for Gastric Retention. Pharm. Res 1997; 14: 815- 819.
15. Richard TG, Levitto W, Barry W, Dresher PA. (2004) Triggered response compositions. US patent 2004/0018952 A1. Jan 29, 2004.