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Formulation and Evaluation of Floating Microspheres of Boswellic acid

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Abstract: The present study involves prepration and evaluation of floating microspheres using boswellic (BA) as model drug for prolongation of the gastric retention time. BA is a lipophillic drug hence it is absorbed rapidly from the stomach and having the half life of 6 Hrs. So it is suitable candatate to formulate GRDDS.The microspheres were prepared by the solvant evaporation method using polymers hydroxypropylmethylcellulose (HPMC) in fixed ratio and Ethylcellulose in varrient ratios.The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. Drug polymer compatibility syudy was done by TLC and IR spectroscopy.The Percentage yield ,Particle size distribution, Buoyancy percentage, Entrapment Efficiency and *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. The prepared microspheres exhibited prolonged drug release (18h) and remained buoyant for > 12 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. *In vitro* studies demonstrated diffusion- controlled drug release from the microspheres.

Keywords: floating microspheres, Boswellic acid, Particle size distribution, Buoyancy percentage, Entrapment Efficiency, *in vitro* release.

INTRODUCTION

Floating systems first described by Davis (1986), are low-density systems that have sufficient buoyancy to float over the gastric content and remain in stomach for a prolonged period while the system floats over the gastric content, the drug is released slowly at the desired rate which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration[1, 2].

Gastro-retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs[3].

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix having a potential for controlled release of drug[4].

Floating microspheres; Despite tremendous advancement in drug delivery, oral route remains the perfect route for the administration of therapeutic agent, low cost of therapy and ease of administration leads to higher levels of patient compliance[1].Conventional oral dosage form such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuation in plasma drug levels.

Although a single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantages of all or nothing emptying process while the multiple unit particulate system pass through the GIT too avoid the vagaries of gastric emptying and thus release of drug is more uniformly[5,6].

HPMC is a hydrophilic polymer which is commonly used in the pharmaceutical applications, because of its safety, effectiveness, cost and availability. HPMC has been investigated for its number of applications including controlled release, dry coating, film coating, direct compression, flow property, and swelling etc. Ethyl cellulose, investigated as a hydrophobic sustained release carrier, which inhibit oxidation. At high-viscosity grades of ethylcellulose release of drug is a function of the microsphere wall thickness and surface area[7].

Boswellic Acid an anti-inflammatory drug used in treatment of arthritis. It is a lipophillic drug having a short half life of 6 hours. Boswellic acids are a series of pentacyclic triterpene molecules, Like many other terpenes, boswellic acids appear in the resin of the plant. It is estimated that they make up 30% of the resin of Boswellia serrata [8].Boswellic acids also exhibit anti-inflammatory behaviour by inhibiting leukotriene synthesis[9] .It inhibits, activity of the enzyme 5-lipoxygenase through a non-redox reaction [10].

MATERIAL AND METHOD

Materials

BA was obtained as a gift sample from Garlico Herbals, Daman (India).Hydroxy Propyl Methyl Cellulose (HPMC) and Chloroform were obtained from Hi Media Laboratories Pvt. Ltd.(India).Ethyl cellulose (EC) from LOBA CHEMIE Pvt. Ltd.(India) and Dichloromethane, Tween 80 were obtained from Merck Specialities Pvt. Ltd.(India). Ethyl Alcohol was from China Made (99%). All other chemicals/reagents used were of analytical grade.

Preparation of microspheres

Microspheres containing anti-inflammatory drug as a core material were prepared by Solvent Evaporation method. Drug (Boswellic acid), HPMC and EC were dissolved in a mixture of ethanol and dichloromethane (1:1) at room temperature (As in table I). This was poured into 250mL water containing 0.01% Tween-80 maintained at a temperature of 30–40 °C and subsequently stirred at 300rpm agitation speed for 45 minutes to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried in oven at 37°C.

EVALUATION OF FLOATING MICEOSPHERS OF BOSWELLIC ACID:

Percent yield of microspheres: The prepared microspheres are collected and weighed. The measured weight was divided by the total amount of excipient and the amount of drug[11].

$$\text{Yield\%} = \frac{\text{Actual weight of product}}{\text{Total weight of excipient \& drug.}} \times 100$$

Particle size distribution of microsphere: The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. It is carried out by using a compound microscope at 10 axis lower and 6axis upper lances. Dried microspheres were first re-dispersed in distilled water and placed in a glass slide and the number of division of calibrated eye piece was counted by a micrometer using a stage micrometer. The average size of 100 particles was determined by the given equation[12].

$$\text{Mean particle size} = \frac{\text{Total sum of particle size}}{\text{Total number of particles}}$$

Buoyancy percentage: microspheres will be spread over a surface of a USP XXIV dissolution apparatus type II filled with 900ml 0.1 mol/lit HCl containing 0.02% tween 80.The medium is to be agitated with a paddle rotating at 100 rpm for 12 hrs.The floating and the settled portion of microsphere will be recovered separately. The microsphere will be dried and weigh buoyancy percentage will be calculated as the ratio of the mass of the microspheres that remain floating and the total mass of the microsphere[12].

$$\text{Buoyancy\%} = \frac{W_f}{(W_f + W_s)} \times 100$$

{Wf =weight of floating microspheres}
{Ws =weight of settled microspheres}

Table-I: Batch specifications of the prepared microspheres.

Batch. No.	Polymer ratio (HPMC:EC)	Drug (Boswellic acid)	Temperature °C	Solvent ratio(1:1) ethanol/DCM
A1(1:1)	250mg:250mg	100mg	30-40	5ml:5ml
A2(1:2)	167mg:333mg	100mg	30-40	5ml:5ml
A3(1:3)	125mg:375mg	100mg	30-40	5ml:5ml
A4(1:4)	100mg:400mg	100mg	30-40	5ml:5ml
A5(1:5)	83mg:417mg	100mg	30-40	5ml:5ml
A6(1:6)	72mg:428mg	100mg	30-40	5ml:5ml

Incorporation Efficiency: To determine Incorporation efficiency, 100 mg microspheres were taken and dissolved in 100 ml of ethyl alcohol and kept for 24 hrs. Then it was filtered and filtrate was assayed by UV spectrophotometer after diluting its one ml with 10 ml of ethyl alcohol. The drug content is analyzed spectrophotometrically at 239.2nm[13].

$$IE = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Drug polymer interaction studies: Two methods were employed for studying drug
polymer interaction-

- IR spectroscopy.
- TLC of drug and formulation.

IR Spectroscopy: There is always a possibility of drug polymer interaction in any formulation due to their intimate contact. The technique employed in the present study for this purpose is IR spectroscopy.IR spectroscopy is one of the most powerful analytical techniques, which offers the possibility of chemical identification. The IR spectra of Boswellic acid and formulation A2 were obtained by KBr pellet method employing Shimadzu 24505 IR series[12].

TLC of Drug and Formulation: TLC of drug (pure) and of formulation was prepared by
using solvent system Ethyl alcohol: Dichloromethane: chloroform 5: 5 : 0.5 respectively. A pure sample was dissolved in ethanol. Similarly, microspheres were separately dissolved in ethanol. These solution were spotted in a pre coated thin layer chromatography (TLC) plate and marked. Then the plate was placed in closed vessel containing solvent system. The developed TLC plate were observed under UV chamber at 365nm and the Rf value were measured using following equation.

Microscopy:

- **Optical microscopy:** optical microscopy was carried out for confirmation of the shape of micro sphere.
- **Scan electron microscopy:** SEM was performed to characterize the surface formed. Surface and shape characteristics of microspheres were evaluated by means of scanning electron microscopy. The scanning electron microscopy samples will be prepared by lightly sprinkling the microsphere powder on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of ~300 Å using a sputter coater[12].

In Vitro Release: A USP basket apparatus was used to study in vitro drug release from microsphere. In the study, drug release was studied using a modified USP XXIV dissolution apparatus type I at 100 rpm in distilled water & 0.1 mol/lit HCl (pH 1-2) as dissolution fluid (900 ml) maintained at 37 ±0.5 □C withdraw sample (10ml) will be analyzed by spectrophotometrically. The volume was rebalanced with the same amount of fresh dissolution fluid to maintain sink condition[14].

RESULT AND DISCUSSION

Floating microspheres were prepared by the solvent evaporation method using HPMC and EC (Table I). Without changing any formulation variability, only as the concentration of the ethyl cellulose gradually increases in the formulations, percent yield of the formulations also increase.The percent yield was obtained in between 62% (Batch A1) to 76.833% (Batch A6) for all formulation batches. The percent yield is greatly affected by the solvents and their ratios. The optical microscopic and SEM photographs (In Fig. 3 and 4) showed that the fabricated microspheres were spherical smooth surface with a internal hollow cavity and exhibited a range of sizes within each batch. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range52.349% (Batch A1) to 79.781% (Batch A6), (Table II).

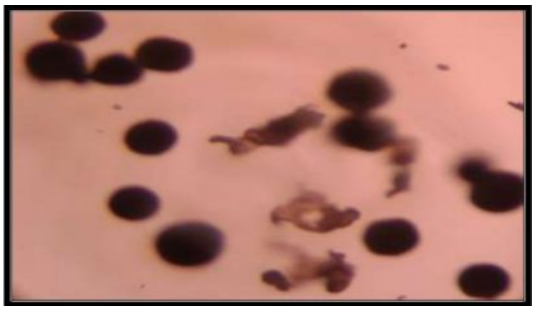

Fig.-1: Optical microscope picture before drying.

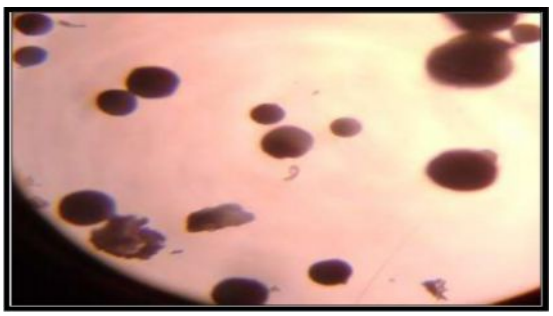

Fig.-2: Optical microscope picture after drying.

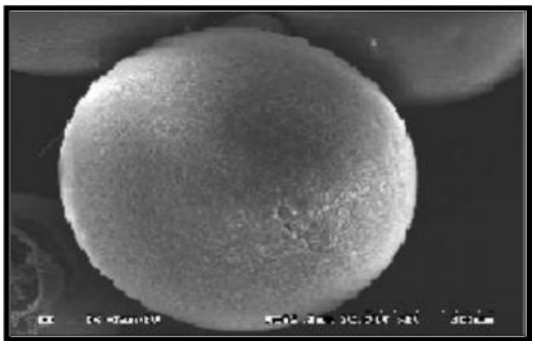

Fig.-3: SEM photograph of the microsphere.

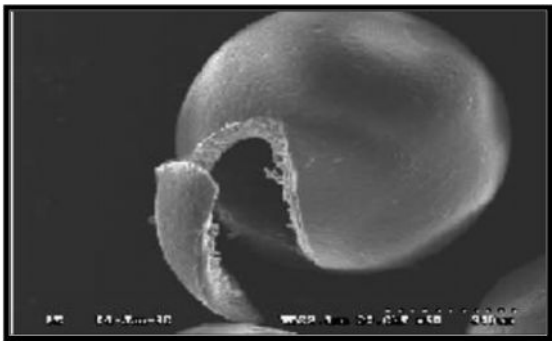

Fig.-4: SEM photograph of the microsphere showing its hollow cavity.

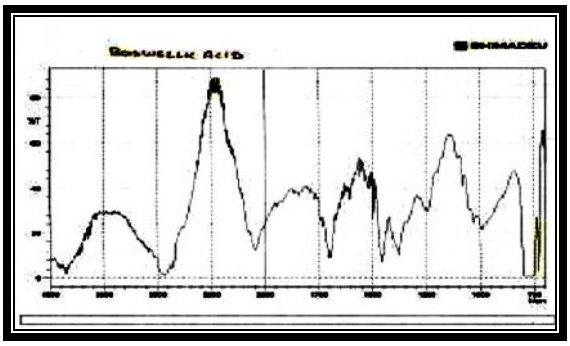

Fig.-5: IR spectra of dug Boswellic acid

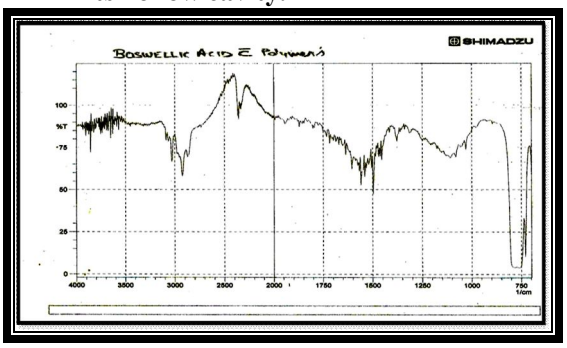

Figure-6: IR spectra of polymers with drug.

Fig-7: TLC of formulation and pure drug.

Table-II: Various formulation parameters for microspheres.

Batch No.	% Yield	Particle size Distribution	%Buoyancy	% Incorporation Efficiency	% Drug release
A1	62 %	11.16±0.02µm	52.349 %	58.462±2.2776 %	91.02±2.84 %
A2	63.5 %	12.36±0.04µm.	59.375 %	65.385±1.9357 %	84.28±1.89 %
A3	65.5 %	13.44±0.04µm.	64.024 %	68.462±0.6574 %	76.73±3.07 %
A4	69.167 %	14.84±0.02µm.	70.833 %	70.769±0.9759 %	69.55±1.22 %
A5	72.333 %	19.43± 0.05µm	75.439 %	73.846±3.8460 %	59.79±1.65 %
A6	76.833 %	21.48± 0.03µm	79.781 %	76.923±1.5385 %	47.52±2.79 %

Microspheres were prepared using a gradually increasing EC concentration in combination with a fixed concentration of HPMC to assess the effect of polymer concentration on the size of microspheres. The mean particle size of the microspheres significantly increased with increasing ethyl cellulose concentration and was in the range 11.16 ± 0.02 µm (Batch A1) to 21.48 ± 0.03µm. (Batch A6), (Table II). The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities[15]. This results in the formation of larger particles.The percentage entrapment of Boswellic acid formulation was found to be good at all loadings, it was found to be 58.462±2.2776 % (Batch A1) to 76.923±1.5385 % (Batch A6). Incorporation efficiency was increased with, increasing polymer concentration. The high entrapment efficiency of Boswellic acid in microspheres may be attributed to its poor aqueous solubility. The extent of loading influenced the particle size distribution of microspheres. When the loading was high, the proportion of larger particles formed was also high. With more than 75% drug entrapment, the particles were in the size range of 21.48 ± 0.03µm,

which is suitable for oral administration.

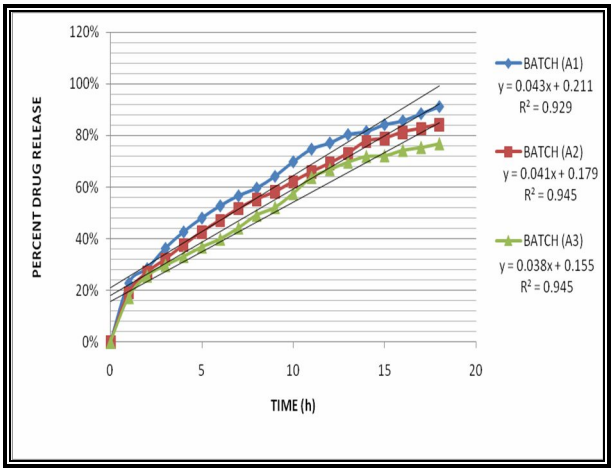

Fig-8: Cumulative percent drug release of formulation A1, A2 and A3.

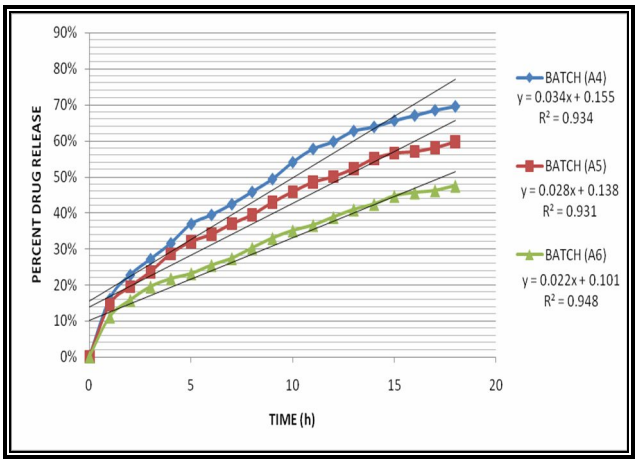

Fig-9: Cumulative percent drug release of formulation A4, A5 and A6.

In vitro BA release studies were performed in 0.1 mol L–1 HCl for 18 h. The cumulative release of BA significantly decreased with increasing ethyl cellulose concentration (In Fig.8 and 9). The increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

The data obtained for *in vitro* release were fitted into equations for the zero-order and Higuchi release models. The interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release[16].

CONCLUSIONS

In vitro data obtained for floating microspheres of Boswellic acid showed excellent buoyancy , good Entrapment Efficiency and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, Boswellic acid is most suitable drug candidate for arthritis, pain and inflammatory conditions so, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to the disease which shows circadian variation.

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