ORIGINAL ARTICLE

Formulation and Evaluation of Sodium Alginate Beads by Emulsion Gelation Method

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Abstract

Aim: The aim of the research work was formulation and evaluation of sodium alginate beads containing voglibose for the effective use in the treatment of hyperglycemia. **Materials and Methods:** The gel beads containing oil were prepared by gentle mixing or homogenizing oil and water phase, containing sodium alginate, which was then extruded into calcium chloride solution to produce gel beads. **Optimization:** The effects of types of oil, and its proportions, on the morphology and release characteristics were optimized. A variety of oils were used to study the effect on the sustaining property of the formed beads. **Results and Discussion:** The oil entrapped calcium alginate gel beads showed sustained release. Scanning electron photomicrographs demonstrated minute oil globules on the beads and also throughout the inner surface of the beads. The beads also showed floating behavior depending on the type of the oils used.

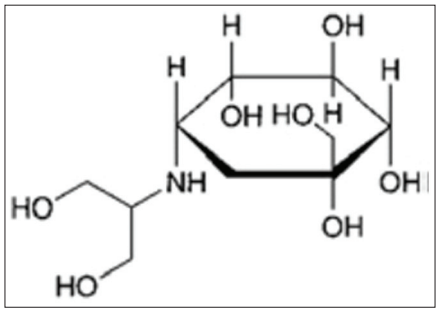
Key words: Voglibose, sodium alginate, sustained release gel beads, oil entrapment method, scanning electron microscopy, floating behavior

INTRODUCTION

The drug delivery systems that can precisely control the release rates or target drugs to specific body site have an enormous impact on the health-care system. The last two decades, in the pharmaceutical industry, have witnessed an avant-grade interaction among the field of polymer and material science, resulting in the development of novel drug delivery systems.[1]

The physicochemical characteristics of drugs vary considerably, so different microsphere formulations are often developed according to specific clinical needs.[2] Emulsion gelation methods are most commonly used to prepare microspheres.[3,4]

Diabetes mellitus (DM) is a chronic metabolic disorder affecting people worldwide, with significant morbidity and mortality caused by its micro- and macro-vascular complications, affecting various vital organs and structures in humans.[5] It has been estimated that by year 2030, the diabetic population will rapidly increase from 21.7 million to 79.4 million in India. However, prevalence is much more than this estimation, as many patients are asymptomatic and unaware about this and go undiagnosed. Voglibose belongs to class of competitive α-glucosidase inhibitors (α-GIs). It was discovered in Japan in 1981, after its isolation from validamyan on culture media-the producing organism being *Streptomyces hygroscopicus* var. limonons. However, it became commercially available treatment for DM in Japan from 1994.[6] Voglibose is an amine substituted cyclohexane polyol:[7]



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It is an antidiabetic drug used to treat noninsulin dependent DM-Type II diabetes, alone or in combination with other hypoglycemic agents. The drug reduces intestinal absorption of starch, dextrin and disaccharides by inhibiting the action of α-glucosidase in intestinal brush border. Inhibition of this enzyme halts the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects resulting in improvement of postprandial hyperglycemia and various disorders caused by hyperglycemia.[8] α-GIs do not stimulate insulin release, and therefore, do not result in hypoglycemia. The drug, a white crystalline powder, is used as monotherapy in elderly patients or in patients with predominantly postprandial hyperglycemia. It can be used in combination with other oral antidiabetic agents and/or insulin and should be administered at the start of the meal as it is poorly absorbed.[9]

In this investigation, a formulation of voglibose, capable of providing detectable blood levels over 10 h was formulated using expandable, gelling, swell able hydrocolloid polymer along with various oils. The polymer used was sodium alginate, which is an inexpensive, nontoxic product extracted from kelp of brown algae. Alginic acid, also called algin or alginate, is an anionic polysaccharide distributed widely in the cell walls of brown algae, which on binding with water forms a viscous gum. It is capable of absorbing 200-300 times of water. Alginates refined from different species of brown seaweed have variations in their chemical structure, resulting in different physical properties. Some may yield an alginate that gives a strong gel, some a weaker gel; some may readily give a cream/white alginate, while some with difficulty and is best used for applications where color does not matter. Sodium alginate has been used as thickening and gelling agent and because it reduces interfacial tension between an oil and water phase and it is used for preparation of emulsion. Alginate is a linear copolymer composed of two monomeric units, D-mannuronic acid and L-guluronic acid. These monomers occur in the alginate molecule as regions made up exclusively of one unit or the other, referred to as M-blocks or G-blocks, or as regions in which the monomers forms an alternating sequence. The calcium reactivity of alginates is a consequence of the particular molecular geometries of each of these regions.[10] Sodium alginate is capable of forming rigid gels by the action of calcium ion or multivalent cations. It is relatively easy to describe alginates in terms of M and G units but the detailed molecular compositions of alginates in terms of block lengths and block distributions are quite difficult to determine.[11]

The oil entrapped calcium pectinate beads have been used in various ways for sustained release of drugs or for the targeting drugs to colon.[12] Theophylline tablets composed of mineral oil entrapped agar for the controlled release have been reported.[13] While sodium alginate emulsion beads used for extended release formulations have not been tested. The effects of factor like type of oil, proportion of oil on the prepared beads have been investigated in this study.

MATERIALS AND METHODS

Sodium alginate was obtained from Central Drug House, New Delhi, and voglibose was gifted by Morepen Laboratories Limited, Baddi (H.P.). Castor oil, liquid paraffin, almond oil and vegetable oil were of standard pharmaceutical grade and all other chemicals used were of analytical grade.

Preparation of gel beads

The oil entrapped calcium alginate beads were prepared by emulsion gelation method. The polymer was dissolved in water with stirring at 100 rpm. Selected oils (2.5 ml) were added to polymer solution. The drug 50 mg was added to it. The homogenized or nonhomogenized mixture was extruded into 5% calcium chloride solution with gentle agitation 37°C ± 0.5°C at room temperature. The formed beads were allowed to stand for 5 min in the solution, decanted, filtered, and finally dried overnight at room temperature [Table 1].

Size distribution and size analysis

Gel beads were separated into different size fractions by sieving for 10 min using a mechanical shaker containing standard sieves as per Indian Pharmacopoeia specifications. The particle size distribution was determined and means particle size of gel beads was calculated by the formula [Figure 1].

Study of morphology of gel beads

The mean diameter of 50 dried beads and morphological examination of dried beads were performed using optical microscopy.

Scanning electron microscopy (SEM)

The samples for the SEM analysis were prepared by sprinkling the gel beads on one side of the double adhesive

Table 1: Drug-alginate gel beads formulation constituents

Voglibose oil entrapped alginate beads				
Code	**Drug**	**Polymer**	**Oil (2.5 ml)**	**D:P**
VO1	+	+	-	1:2
VO2	+	+	Castor oil	1:2
VO3	+	+	Liquid paraffin	1:2
VO4	+	+	Almond oil	1:2
VO5	+	+	Soya bean oil	1:2

D: P: Drug polymer ratio, (+): Present, (-): Absent

stub. The stub was then coated with fine gold dust. The gel beads were then observed with the SEM (JEOL Model JSM - 6390 LV) at 15 kv [Figure 2].

Measurement of buoyancy property

For the evaluation of floating property, approximately 100 beads were counted and pasted on one side of the glass slide secured to the United States Pharmacopoeia disintegration apparatus. The apparatus was run for 5 h, and at predetermined time interval (30 min), the slide was taken out and the number of beads still adhering to the slide was counted [Table 2].

In vitro release studies

Preparation of standard plot in methanol

Voglibose (10 mg) was dissolved in 100 ml of methanol. It was then suitably diluted for graded solutions in range of 0-90 µg/ml. the absorbance was read using an ultraviolet (UV) spectrophotometer at 282 nm-λ max [Table 3 and Figure 3].

In vitro release of microspheres

The *in vitro* release studies were carried out at 37°C ± 0.5°C and at 100 rpm by buffer change method using 0.1 N HCl (1 h), 4 pH (1 h), 6 pH (3 h), 6.8 pH (3 h), and 7.4 pH (2 h) phosphate buffers (200 ml) in sink conditions using a diffusion cell. Accurately weighed samples of gel beads were added to the donor cell. At pre-set time intervals; 5 ml of aliquots are withdrawn and replaced by an equal volume of fresh dissolution medium. The aliquots were analyzed UV spectrophotometrically at 282 nm-λ max after proper dilution.

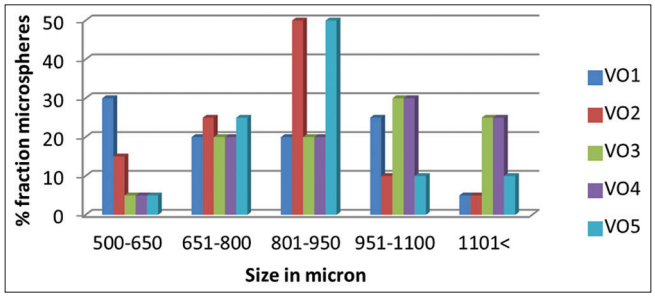

Figure 1: Particle size distribution of drug-alginate gel beads

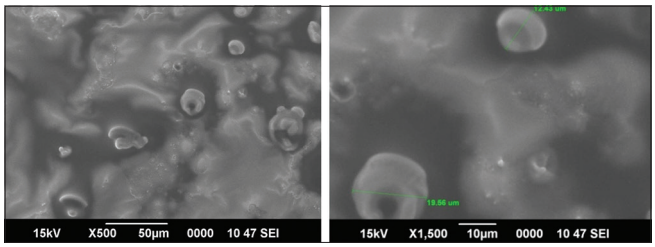

Figure 2: Alginate gel bead showing drug particle on the surface (1), alginate beads showing presence of oil filled pores on the surface of gel beads (2)

Stability studies of voglibose formulations

Stability testing is an integral part of the formulation development. It generates information about shelf life of drug substances and their produced formulations and recommends appropriate guidelines for storage [Figure 4].

Morphological characteristics and release profile

Microspheres were stable during the entire period of study of 3-month. Alginate containing microspheres showed change in color at high temperatures. Significant changes in morphology and the release behaviors were seen with oil entrapped formulations. At accelerated stability conditions, the oil phase started to come out from the formulations leaving the surface hydrophobic. This effect was prominent with castor oil, liquid paraffin, and soybean oil. Almond oil microspheres were comparatively stable. This loss of oil increased with rise in temperature and produced rancid odor. Floating characteristic decreased with increase in oil loss from the formulations.

RESULTS AND DISCUSSION

The formation of gel beads of calcium alginate using various oils is a simple and rapid process. The incorporation of oil into the drug-alginate solution was done with and without

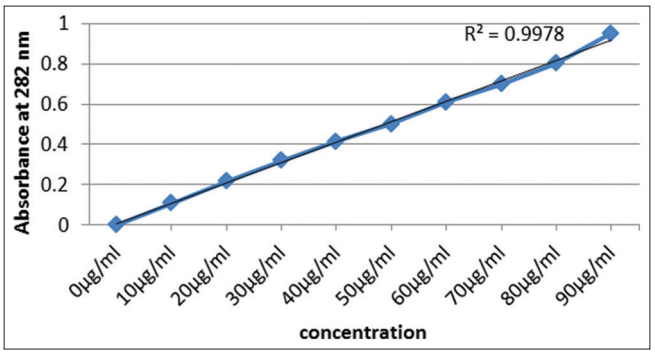

Figure 3: Calibration curve of voglibose in methanol

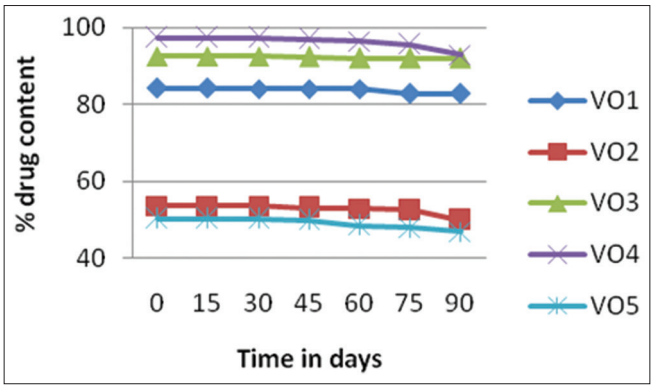

Figure 4: Effect of storage on drug content of at 45°C temperature

Table 2: Physiochemical properties of the voglibose oil entrapped gel beads (*n*=3) for all results

Oil entrapment microspheres of voglibose					
Code	**% entrapment±SD**	**Angle of repose (degree)±SD**	**Tapped density**	**% swelling index±SD**	**Buoyancy property (%)±SD**
VO1	86.6±0.07	21.50±1.9	0.324±0.008	18.2	56.1±0.5
VO2	79.8±0.15	21.68±1.7	0.359±0.007	20.1	54.0±0.2
VO3	89.5±0.07	21.18±1.6	0.343±0.010	22.4	75.6±1.2
VO4	74.7±0.07	22.47±1.5	0.348±0.009	17.3	78.3±1.5
VO5	93.0±0.11	21.51±1.9	0.352±0.006	15.6	80.1±1.8

SD: Standard deviation

homogenization. Without homogenization, oil started separating out and resulted in uneven sized beads, while increasing the homogenization time, resulted in smaller but uniform beads. The proportion of drug and polymer was kept constant for all formulation while type of oil utilized was altered.

The beads prepared using liquid paraffin, castor oil and soybean oil were off white in color, owing to original color of oil phase while those prepared using almond oil were white in color [Table 4].

The mean diameter of conventional calcium alginate beads was in the range of 780-900 µm [Figure 1] while the oil entrapped formulations ranged from 840 µ to 1.1 mm. The results showed that the amount of oil affected the morphology of beads, i.e., an increase in concentration of oil increased the size and sphericity of the beads, due to their density and volatility. The greater the density of the oil used, the larger was the size and better the sphericity. Beads prepared using oils with less density had increased volatility and on drying resulted in uneven beads formation. There was decrease in the original size because volatile component evaporated quickly.

Increased size of the beads, it showed emulsifying property of the alginate. The homogenization process resulted in fine dispersion of oil and water phase. When this emulsion was extruded in calcium chloride solution, the gel was formed by the action of calcium on negatively charged groups of alginate. The prepared beads were analyzed by optical microscopy and SEM for their surface morphology and size analysis. Sponges like internal structure were seen with a few crystals of drug on the surface. Oil filled pores were visible on the surface with size ranging from 0.5 to 49 µm [Figure 2]. The uneven size of the pores could be due to the coalescence of the oil droplets during the gelling process. The release profile indicates that the sustaining action was more pronounced with almond oil followed by liquid paraffin >castor oil > soybean oil alginate beads. As compared to conventional (no oil) beads, the release of the drug was sustained for more than 8 h in simulated gastric juice (without pepsin).

Table 3: Voglibose pure drug absorbance in UV

S. No	Concentration (µg/ml)	Absorbance at 282 nm
1	0	0
2	10	0.110
3	20	0.217
4	30	0.319
5	40	0.415
6	50	0.501
7	60	0.609
8	70	0.699
9	80	0.802
10	90	0.950

UV: Ultraviolet

Table 4: Physical properties of the drug-alginate gel beads (D:P:1:2)

Oil entrapped gel beads of voglibose			
Code	**% yield**	**Shape**	**Color**
VO1	72.0	spherical	Off white
VO2	94.6	spherical	Off white
VO3	66.6	spherical	Off white
VO4	80.0	spherical	White
VO5	86.6	spherical	Off white

D:P: Drug polymer ratio

An additional property of buoyancy was observed for the oil-entrapped beads, which was due to incorporation of oil having density less than water. The lower the density of the oil, the lesser was the amount of the oil required to give it a buoyant nature.[14]

Formulation of an extended release dosage form, for this water-soluble drug voglibose by this method is a better option. The pores of the beads containing oil limited the release of drug. This could be attributed to an additional diffusion layer for the release of the drug. The SEM shows the presence of oil droplets throughout the alginate matrix. The initial burst effect seen was due to some amount of the drug, which might have been dragged to the surface during

the processing. When calcium ions are added to a sodium alginate solution, alignment of the G-blocks occurs; and the calcium ions are bound between the two chains such as eggs in an egg box. Thus, the calcium reactivity of algins is the result of calcium-induced dimeric association of the G-block regions. Depending on the amount of calcium present in the system, these interchain associations can be either temporary or permanent. With low levels of calcium, temporary associations are obtained, giving rise to highly viscous, thixotropic solutions. At higher calcium levels, precipitation or gelation occurs from permanent associations of the chains.[15]

When a drug is incorporated in a hydrophilic matrix, it swells upon ingestion and forms a gel layer on the surface. This gel layer fills the interstices. Dissolution rate of soluble drugs is controlled by both diffusion through the gel layer and by matrix erosion as seen from the release kinetics values [Table 5 and Figure 5].

The data shows that the release mechanism is chiefly by zero order kinetics. The release of cationic drugs is more retarded than anionic drugs, which could be due to the electrostatic interaction between the negative charge of the ionized carboxyl group in alginate chain and positive charge of the cationic drug.[14,16] Voglibose is a cationic drug, thus its release could be retarded by an interaction with alginate. By using alginate and employing oil entrapment technique, the absorption of even a water soluble drug can be retarded in the stomach.

Table 5: Release properties of the voglibose oil entrapment microspheres

Type of oil	Z.O	F.O	Higuchi	Korsm Peppas	Hixon Crowell
	R^2				
Without oil	0.943	0.956	0.937	0.780	0.963
Castor oil	0.984	0.993	0.981	0.737	0.992
Liquid paraffin	0.954	0.936	0.959	0.807	0.952
Almond oil	0.943	0.937	0.947	0.706	0.958
Soyabean oil	0.985	0.968	0.982	0.754	0.976

Z.O: Zero order, F.O: First order

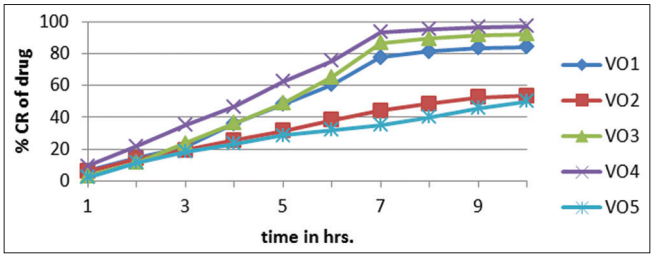

Figure 5: *In vitro* cumulative percent release of voglibose gel beads

CONCLUSION

A new sustained release system of oil entrapped calcium alginate beads were formulated by an emulsion gelation method. Its morphological and release characteristics were studied. The beads were easy to prepare and the mean diameter of beads increased with increase in the amount of the oil phase. The pore size of oil-entrapped beads was affected by the concentration of the oil. The beads showed excellent sustaining properties as compared to the conventional beads. Thus, oil entrapment technique appears to be a useful tool for the development of multi-particulate system even for a water-soluble drug.

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