RESEARCH ARTICLE

Effect of hydrocolloid on the physicochemical properties of theophylline-loaded agar microspheres

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Theophylline-loaded agar microspheres were prepared and the effect of hydrocolloid on the physicochemical properties of the microspheres was investigated. Microspheres were prepared by the w/o emulsion solvent evaporation technique. Microspheres were spherical and free flowing, with particle size in the range of 105-123 µm. It was found that as the concentrations of the polymer and the hydrocolloid increased, the percentage yield, percentage encapsulation and percentage drug content also increased. An *in vitro* dissolution study was conducted according to the USP method (USP XXII) using apparatus I for 8 h. The dissolution profile of the developed formulation was compared with the marketed product (Theo SR). The similar results of prepared formulation (t_{50} = 211.78) and marketed product (t_{50} = 209.29) suggest sustained release of the drug.

Key words: *Agar microspheres, hydrocolloid, marketed formulation, theophylline*

INTRODUCTION

Anhydrous theophylline, a xanthine bronchodilator, is used in the treatment of both chronic and acute asthmatic attacks. Because of its small therapeutic range, within 5-20 µg/ml serum concentration, careful control of its release from dosage forms has to be ensured. Faulty formulation may results in dose dumping and hence could produce toxic effects.[1] The major drawback of orally administered theophylline is its short duration of action, requiring repeated administration, which leads to patient non-compliance. Thus, there was the need to develop a sustain release dosage form to reduce the frequency of administration and prolong the therapeutic effect of the drug.[2]

A number of methods and techniques have been implemented for manufacturing the oral extended-release dosage forms to deliver the drug at a controlled and pre-determined rate. Probably, the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix.[3]

Agar, in this regard, is one of the polymers that is prepared from various species of Gelidium and other red algae. It is an alternating copolymer of 3-linked ß-D galactopyranose and 4-linked 3-6 anhydro-a- L-galactopyranose. It has a molecular weight of 120,000. It is an unchanged polysaccharide having a low content of sulfate (<0.3% w/w) and carboxylate group. It is characterized by its gelling point (35-45°C for 1.5% gel). Agar is dissolved as a colloidal solution in water if heated to about 90°C and forms a solid gel on cooling below its gelling point. Agar gelation is thermoreversible, i.e. the gel remelts on heating to about 90°C.[4]

Gum Arabic or Acacia is a water-soluble natural polysaccharide obtained from the exudate of the acacia tree. This highly branched polysaccharide is a complex mixture of Ca, Mg and K salts of arabic acid that contains galactose, rhamnose, glucuronic acid, 4-O-methyl glucuronic acid and arabinose residues.[5] The molecular structure of gum Arabic mainly consists of three components, the major component being arabinogalactan (90%) having a low (0.5%) protein content, the second being arabinogalactan (<10%) with a high protein content (10%) and the third component consisting less than 1% includes glycoprotein having around 50% protein content.[6] It is extensively used as a food additive[7] and is reported to be fermented and metabolized in the caecum and the colon.[8,9]

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DOI: 10.4103/0973-8398.55051

Thus, the aim of the present work was to study the utility of agar as a polymeric material for the formulation and to study the effect of acacia, a viscosity imparting agent, on the physicochemical properties of microspheres.

MATERIALS AND METHODS

Theophylline: Sun Pharmaceuticals Ltd., Baroda, India.

Agar: Loba Chemie, Mumbai, India.

Acacia: Chiti Chem, Baroda, India.

Other chemicals are of AR grade.

Preparation of microspheres [Table 1]
The drug (50 mg) was dispersed in a solution of agar (4-8% w/v) and acacia (0.3-0.7% w/v) (disperse phase). The microspheres were formed by dropping the disperse phase through an 18-gauze syringe onto 150 ml of Dichloromethane (continuous phase) containing magnesium stearate and Span 80, with constant stirring on a magnetic stirrer. The formed microspheres were filtered, washed and air dried for 24 h at room temperature.

Characterization of the microspheres [Table 1]
Percentage yield =[(Weight of microspheres/weight of drug + polymer)] × 100.

Determination of drug content and encapsulation efficiency
About 200 mg of microspheres of each batch were triturated and samples of 50 mg of the triturate were weighed accurately. Each 50 mg sample was placed in a volumetric flask containing 25 ml phosphate-buffered saline (pH 7.4) and vortexed for 20 min. The content was shaken for 4 h at room temperature and The solution was then filtered through a 0.45 μm filter, diluted suitably and analyzed spectrophotometrically (Shimadzu Corp., UV-1201, Japan) at 270.0 nm to determine the amount of theophylline in each microsphere sample.

% EE = Weight of theophylline in microspheres × 100 − weight of theophylline added

% DC = Weight of drug encapsulated in microspheres × 100 − weight of microspheres

Average particle size
Particle size of 100 microspheres from each batch was measured for calculating the size distribution and the average particle size using the optical microscopic method.

In vitro drug release
Dissolution studies were conducted according to the USP method (USP XXII) using apparatus I. The USP basket system contains six baskets, rotated at 50 rpm. Each basket was filled with 900 ml phosphate-buffered saline, pH 7.4, maintained at 37 ± 1°C. After a pre-determined time interval, 5 ml of the sample was withdrawn. For each sampling, the volume was adjusted with 5 ml of fresh dissolution medium. This operation was continued for 8 h. The released drug was assayed using a UV spectrophotometer (Shimadzu, Japan) at λ max 270.0 nm. The drug concentration was calculated with the help of a straight-line equation obtained from the standard curve.

RESULTS AND DISCUSSION

The microspheres obtained were quite spherical in shape and free flowing, with particle sizes ranging between 105 and 123 μm [Figure 1]. As the concentrations of the polymer and the hydrocolloid were increased, the percentage yield, percentage encapsulation and percentage DC were found to be increased. This was due to the fact that a higher polymer concentration affords a higher viscosity of the dispersed phase and an earlier recovery. Similarly, higher viscosity effectively slows down the drug dissipation into the continuous phase and results in better drug encapsulation, which increased the loading efficiency. When the hydrocolloid level is increased in the polymeric beads, the elevated hydrocolloid level formed a thicker gel in contact with the dissolution fluid with reduced porosity and higher tortuosity. Increased gel thickness also increased the path-length of diffusion of drug from polymeric beads, which virtually elevated the time required for dissolution of the drug from the

Table 1: Physicochemical properties of various formulations of microspheres

Batch no.	Agar (% w/v)	Acacia (% w/v)	% yield (mean ± SD)	% EE (mean ± SD)	% DC (mean ± SD)	APS (μm) ± SD	t_{50} min
A1	4	0.3	41.31 ± 0.76	21.54 ± 1.18	5.57 ± 0.20	105.17 ± 4.24	175.36
A2	4	0.4	41.99 ± 1.53	21.63 ± 1.56	5.59 ± 0.20	107.74 ± 3.03	179.86
A3	4	0.5	43.83 ± 1.20	23.10 ± 0.21	5.61 ± 0.20	115.37 ± 8.96	192.24
A4	4	0.6	47.47 ± 1.19	25.37 ± 1.59	5.64 ± 0.21	118.89 ± 15.8	211.78
A5	4	0.7	48.24 ± 0.73	26.29 ± 1.37	5.65 ± 0.21	119.32 ± 2.42	201.83
A6	8	0.3	74.07 ± 0.57	76.39 ± 1.31	5.92 ± 0.06	106.03 ± 2.55	185.32
A7	8	0.4	74.25 ± 0.49	78.17 ± 0.05	6.01 ± 0.06	108.86 ± 14.5	184.97
A8	8	0.5	74.77 ± 0.57	79.73 ± 0.83	6.07 ± 0.10	123.60 ± 2.79	139.71
A9	8	0.6	75.23 ± 0.57	81.70 ± 2.54	6.17 ± 0.20	117.86 ± 10.3	139.18
A11	8	0.7	74.15 ± 0.32	84.27 ± 3.71	6.35 ± 0.39	112.27 ± 2.13	170.71

Note: EE = Encapsulation efficiency; DC = Drug content; APS = Average particle size

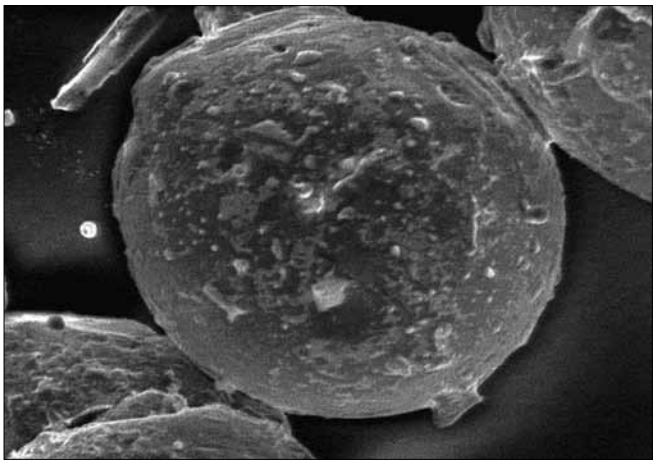

Figure 1: Photomicrograph

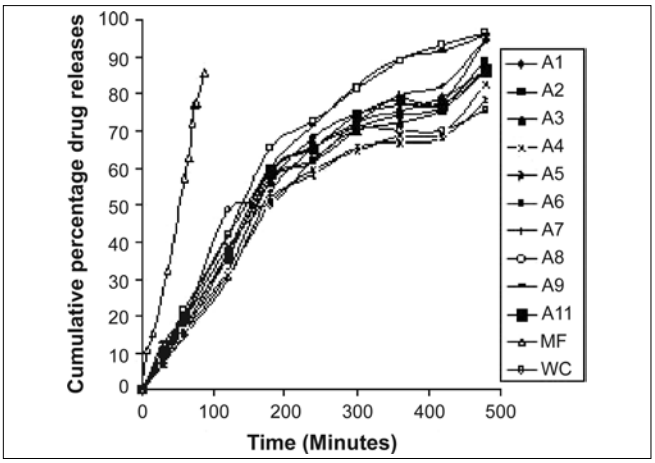

Figure 2: Cumulative percentage drug releases (MF, marketed formulation; WC, without hydrocolloid)

dosage form. This factor can be attributed to the reduction of the release rate with increment of the hydrocolloid level in agar beads. Here again, a good linearity was found, indicating that the drug molecules were homogeneously dispersed in the beads [Figure 2]. The marketed product (Theo SR) was subjected to dissolution and studied similar to the conditions followed for the developed formulation. Comparison of drug release profiles are represented in Figure 2. The results showed a similar t_{50} of the prepared formulation ($t_{50} = 211.78$) and the marketed product ($t_{50} = 209.29$), suggesting sustained release of the drug.

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Source of Support: Nil, **Conflict of Interest:** None declared.