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Research Article

Formulation and Evaluation of Floating Microspheres of an Anti-Diabetic Agent

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Abstract

The controlled release drug delivery system possessing the ability of being retained in the stomach is called gastro retentive drug delivery system. They can help in optimizing the oral controlled delivery of drug having "absorption window" continually releasing the drug prior to absorption window for prolong period of time, thus ensuring optimal bioavailability. A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drug that are poorly soluble or unstable in intestinal fluids. Floating tablets and floating microspheres are common examples of floating system. Microsphere are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). 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 200 μm. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs.

Keywords: Microsphere; Metformin hydrochloride; Insulin; Drugs

Introduction

During the past four decades, the pharmaceutical industry has invested vast amounts of time and money in study of dosage forms. The aim of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration. Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the systemic delivery. All controlled release systems have limited applications if the systems cannot remain in the vicinity of the absorption site [1]. The controlled release drug delivery system possessing the ability of being retained in the stomach is called gastro retentive drug delivery system. They can help in optimizing the oral controlled delivery of drug having "absorption window" continually releasing the drug prior to absorption window for prolong period of time, thus ensuring optimal bioavailability. A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drug that are poorly soluble or unstable in intestinal fluids. Floating tablets and floating microspheres are common examples of floating system [2,3].

Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [4]. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improvesbioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [5].

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 200 μm. Microsphereare small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as micro particles. Microspheres can be manufactured from various natural and synthetic materials.

Metformin Hydrochloride is an oral biguanide anti-diabetic agent improving glucose tolerance in patients with Type 2 diabetes. It decreases hepatic glucose production thus decreasing intestinal absorption of glucose. It also works by improving insulin sensitivity by increasing peripheral glucose uptake and utilization.

Diabetes mellitus (DM), also known as simply diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Producing symptoms of frequent urination, increased thirst, and increased hunger. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes.

Experimental

Materials

Metformin hydrochloride was a gift from cadila, pharmaceuticals, Gujarat; ethyl cellulose was obtained from Ases chemical lab. cellulose acetate, HPMC, Hydrochloric acid, Acetone, Span 80, Petroleum ether and Calcium chloride from Loba chemie Pvt Ltd., Eudragit S100 Chemdyes corporation, liquid paraffin from Thermo fisher scientific India Pvt. Ltd. All chemicals and reagents used were of analytical grade [6-8].

Preparation of microspheres

- Microspheres were prepared by emulsion solvent evaporation technique.
- Polymers was dissolved in acetone; drug was dispersed and mixed thoroughly.
- This was then added slowly to 200 ml liquid paraffin.
- The mixture was stirred continuously at 700 rpm until the solvent evaporated completely.

- The formed microspheres were then filtered using whatmann filter paper, washed with petroleum ether, air dried and stored in desiccators over fused calcium chloride.

Characterization of microspheres

Particle size analysis: All the microspheres were evaluated with respect to their size using optical microspheres fitted with an ocular micrometer and a stage micrometer. The size more than 50 microspheres was measured randomly by optical microscope. The average particle size of microspheres was determined by the total size of the microspheres divided by the number of microspheres [9]. Least count of the ocular micrometer was calculated by the following formula:

$$Least\ count = \frac{No.\ of\ Division\ of\ Stage\ Micrometer}{No.\ of\ Division\ of\ Ocular\ Micrometer} \times 100$$

Scanning electron microscopy analysis: The shape and surface morphology of microsphere samples were observed under SEM microspheres were cluster on to double sided carbon dust which was placed on to sample carrier 9 aluminum stubs having double adhesive tape) in the shape of a cylinder with 5 mm of weight and 10 mm of diameter and were coated with AU- pd (Gold Platinum) mixture under vacuum 9100 m torr) with sputter coated to thickness of 50 nm. The samples were imaged using a 5-15 KV electron beam. The microsphotographs of suitable magnification were obtained for surface topography [10].

Determination of encapsulation efficiency: Drug entrapment efficiency of metformin hydrochloride microspheres was performed by accurately weighing 50 mg of microspheres and crushing them properly in a glass mortar and pestle. These weighed microspheres were suspended in 50 ml of hydrochloric acid buffer (pH 1.2) and it was kept aside for 24 hours. The, after suitable dilution, Metformin content in the filtrate was analyzed spectrophotometrically at 232 nm using U. V. spectrophotometer [11].

$$\%\ Encapsulation\ efficiency\ = \frac{Actual\ content}{Theoretical\ content} \times 100$$

***In vitro* floatability:** *In vitro* floatability studies on floating microspheres were carried out using USP apparatus II. To assess the floating properties, the microspheres were placed in 0.1 N hydrochloric acid containing 0.20% v/v Tween 80 surfactant to simulate gastric conditions [12]. The use of 0.02% v/v tween was to account for the wetting effect of the natural surface active agents such as phospholipids in the GIT. The buoyancy was calculated as:

$$\textbf{Buoyancy (\%)} = Q_r/(Q_r+Q_s) \times 100$$

***In vitro* drug release studies:** The drug release studies were carried out using six basket dissolution apparatus USP type II. The microspheres were placed in a non- reacting mesh that had a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres. The dissolution medium used was 900 ml of 0.1 N hydrochloric acid at 37°C. At specific time intervals, at hourly intervals up to 12 hrs. and then at 24 hrs, 5 ml aliquots were withdrawn and analyzed by UV spectrophotometer at 232 nm after suitable dilution. The withdrawn volume was replaced with an equal volume of fresh 0.1 N hydrochloric acid [13].

***In vivo* floating study:** These studies were conducted in dog at Government Veterinary Hospital, Udaipur. *In vivo* floating behavior was investigated by taking X-ray photographs of the floating microspheres loaded with barium sulphate in stomach. The floating microspheres were administered with 100 cm^3 of water after light meal [14].

Stability studies: Stability studies were carried out as per ICH guidelines. The floating microspheres were placed in a screw capped glass containers and stored at 25 ± 2°C (Room temperature), 2 to 8°C (Refrigeration temperature), 45°C for a period of 30 days (Tables 1-4 and Figure 1).

Results and Discussion

In vitro drug release

At the end of 12 hrs. the percentage cumulative release of Metformin Hydrochloride from Ethyl cellulose microspheres were found to be 72.48%, 83.51%, 79.85%for formulations A1, A2, A3 respectively. The percentage cumulative drug release from cellulose acetate microspheres were found to be 95.52%, 90.13%, 86.31% for formulations A4, A5, A6 respectively. The percentage cumulative drug release for Eudragit S100 and HPMC microspheres were found to be 85.29%, 80.0%, 76.05% for formulations A7, A8, A9 respectively [15]. It is observed that the percentage cumulative amount of drug release decreased as the concentration of polymer increase. The cumulative percentage drug release for Cellulose acetate microspheres was found to be maximum followed by Eudragit S100 and HPMC microspheres, followed by Ethyl cellulose microspheres (Figures 2-6 and Table 5) [16-18]. The rank order for cumulative percentage drug release was found as follows:

A4>A5>A6>A7>A8>A9>A1<A2>A3

A **B** **C**

Figure 1: (A) Ethyl cellulose microspheres, (B) Cellulose acetate microspheres, (C) Eudragit S100 and HPMC.

Stability study

From the stability studies of formulation A4 and A7. There was no significant change in drug loaded microspheres stored at 25 ± 2°C (Room temperature), 2 to 8°C (Refrigeration temperature), 45°C for a period of 30 days (Tables 6 and 7; Figures 7 and 8).

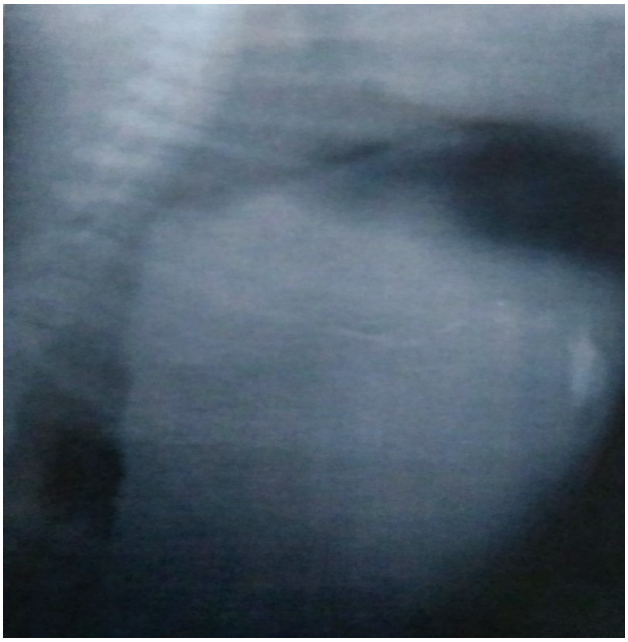

Figure 2: X-ray photograph of dog stomach showing floating behavior of cellulose acetate floating microspheres.

Figure 3: Zero order plots of formulation A1 to A9.

Figure 4: First order kinetics plots of formulation A1 to 9.

Figure 5: Higuchi plots of formulation A1 to A9.

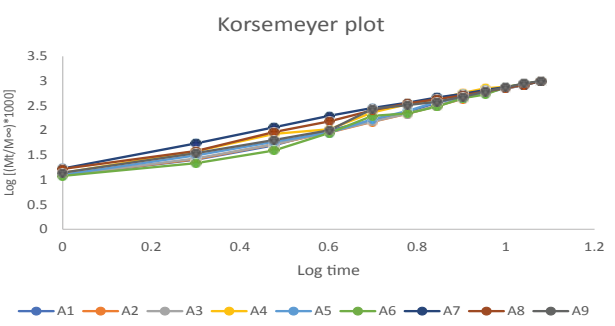

Figure 6: Korsemeyer plots of formulation A1 to A9.

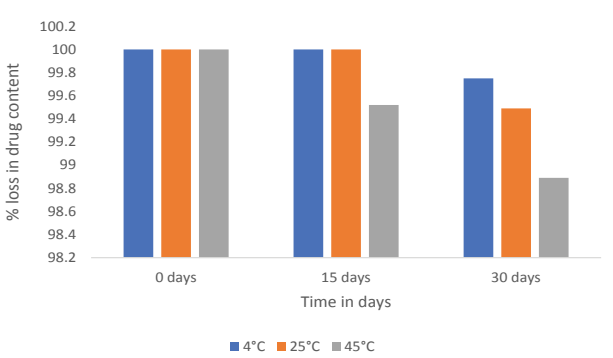

Figure 7: Stability studies of formulation A4.

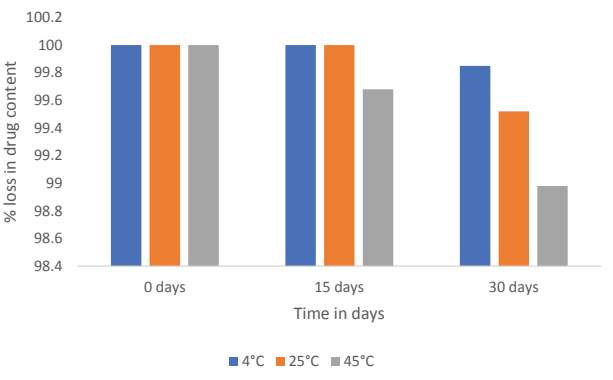

Figure 8: Stability studies of formulation A7.

S. No.	Formulation code	Polymer	Drug: polymer con.
1	A-1	Ethyl cellulose	1:1
2	A-2	Ethyl cellulose	1:2
3	A-3	Ethyl cellulose	1:3
4	A-4	Cellulose acetate	1:1
5	A-5	Cellulose acetate	1:2
6	A-6	Cellulose acetate	1:3
7	A-7	Eudragit+HPMC	1:1
8	A-8	Eudragit+HPMC	1:2
9	A-9	Eudragit+HPMC	1:3

Table 1: Formulation table for floating microspheres of Metformin HCl.

Code	Mean particle size (µm)
A1	293.50 ± 0.707
A2	302.85 ± 0.636
A3	309.63 ± 0.042
A4	344.70 ± 3.818
A5	360.75 ± 5.303
A6	382.50 ± 5.091
A7	252.45 ± 0.636
A8	253.80 ± 1.273
A9	279.00 ± 1.273

Table 2: Particle size determination.

Formulation	Theoretical loading (%)	Practical loading (%)	Encapsulation efficiency (%)
A1	50%	38.2%	76.4%
A2	33.3%	27.52%	82.6%
A3	25%	19.92%	79.6%
A4	50%	38.6%	77.4%
A5	33.3%	28.2%	84.6%
A6	25%	20.4%	81.6%
A7	50%	37.72%	75.4%
A8	33.3%	28.02%	84.2%
A9	25%	20.6%	82.4%

Table 3: Percentage encapsulation efficiency.

Formulation	% Buoyancy		
	4 Hrs.	8 Hrs.	12 Hrs.
A1	75.7 ± 0.424	59.4 ± 1.909	49.4 ± 1.909
A2	77.1 ± 1.202	56.1 ± 0.354	46.4 ± 1.697
A3	74.2 ± 0.283	58.8 ± 2.263	47.0 ± 1.344
A4	82.4 ± 0.566	76.5 ± 2.121	62.6 ± 0.849
A5	84.6 ± 0.283	78.2 ± 3.111	63.9 ± 1.273
A6	86.4 ± 0.566	78.5 ± 2.121	64.5 ± 2.121
A7	81.4 ± 0.849	78.9 ± 1.202	60.5 ± 0.636
A8	80.8 ± 0.566	75.4 ± 1.697	62.0 ± 1.414
A9	79.4 ± 0.849	74.8 ± 2.192	66.9 ± 0.141

Table 4: *In vitro* floatability.

Time (h)	Cumulative% drug release								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
1	1.088	1.042	1.027	1.32	1.14	1.04	1.442	1.344	1.064
2	2.27	2.194	2.168	3.62	2.82	1.88	4.678	3.11	2.642
3	4.434	4.374	4.182	8.13	5.32	3.39	9.884	7.526	4.868
4	8.922	7.576	7.444	10.12	8.14	7.74	16.913	12.35	7.692
5	14.164	12.498	12.124	22.13	15.16	17.05	24.342	20.666	20.76
6	21.062	18.242	17.528	32.49	22.36	19.13	31.113	28.314	24.802
7	32.192	26.252	25.372	41.23	30.44	26.23	39.741	34.756	29.072
8	43.656	36.354	35.318	55.03	41.12	38.96	47.013	41.31	36.496
9	57.578	52.138	46.462	68.49	52.14	46.31	56.341	49.846	46.502

10	63.142	59.184	57.624	73.31	65.2	65.49	64.648	58.312	56.77
11	72.488	69.244	67.123	80.08	78.58	75.92	71.991	67.974	67.796
12	88.45	83.51	79.85	95.52	90.13	86.31	85.292	80.76	76.058

Table 5: *In vitro* drug release study.

Time (Days)	% Drug Content		
	4°C	25°C	45°C
0	100	100	100
15	100	100	99.52
30	99.75	99.49	98.89

Table 6: Stability studies of selected formulation A4.

Time (Days)	% Drug Content		
	4°C	25°C	45°C
0	100	100	100
15	100	100	99.68
30	99.85	99.52	98.98

Table 7: Stability studies of selected formulation A7.

Conclusion

The incorporation of the highly water soluble antidiabetic drug metformin hydrochloride was done using ethylcellulose, cellulose acetate, Eudragit S100 and HPMC as the polymer. The formulations exhibited sufficient floating properties and it was seen that with the increase in concentration of polymer decreased the particle size and cumulative% drug release. Percentage drug release study was affected by the polymer concentration.

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