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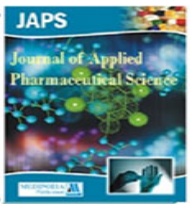

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Preparation and evaluation of calcium silicate based floating microspheres of amoxicillin

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ABSTRACT

The aim of the present study was to prepare and evaluate floating microspheres consisting of (i) calcium silicate (CS) as porous carrier; (ii) amoxicillin and (iii) hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) as polymers. The floating microspheres were evaluated for particle size, micromeritic properties, percent drug content, in *vitro* floating behavior, and *in vitro* drug release. The percentage yield of floating microspheres of formulations (AM1 to AM9) was found to be in the range of 78.21 ± 1.09 to 93.56 ± 2.79 %. Percentage drug content of formulations (AM1 to AM9) were found in the range of 79.89 ± 2.19 % to 87.74 ± 1.24 %. *In Vitro* Buoyancy percentage of the microspheres was found to be 98.75±3.62 At pH 1.2, drug release from floating microsphere containing amoxicillin formulation AM4 was found to be 98.87 ± 0.67 % at the end of 12 hr. While at pH 7.4, Formulation AM4 released 99.23 ± 0.94 % of drug at 12 hr respectively. The SEM photographs of formulation AM4 showed that the fabricated microspheres were spherical with a smooth surface and exhibited a range of sizes within each batch. The results suggested that Calcium Silicate is a useful carrier for the development of floating and sustained release preparations.

Key words: Floating microspheres, amoxicillin, Porous Calcium Silicate.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well accepted fact that it is difficult to predict the real *in vivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in gastrointestinal (GI) tract may be very short and highly variable in certain circumstances (Garg and Sharma, 2003). Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. Various attempts have been made to prolong the retention time of the dosage form in the stomach. One such method is the preparation of a device that remains buoyant in the stomach contents due to its lower density than that of the gastric fluids (Desai and Bolton, 1993). Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit forms has relative merits compared to a single unit preparation.

Indeed, the gastric emptying of a multiparticulate floating system would occur in consistent manner with small individual variations. On each subsequent gastric emptying, sink particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way. Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced (Iannuccelli *et al.*, 1998).

For the present investigation, In case of amoxicillin, Peak plasma amoxicillin concentration of about 5 µg/ml has been obtained 1 to 2 hrs after a dose of 250 mg with detectable presence for up to 8 hrs. The absorption of amoxicillin is not affected by the food. About 20% of the drug is bound to the plasma protein in the circulation and plasma half life of 1 to 1.56 hr has been reported

MATERIAL AND METHODS

Materials

Amoxicillin was received as a gift sample from Cadila Pharmaceutical Ltd., Ahmedabad. Sigma Aldrich Laborchemikalien GMBH Bombay India provided Porous calcium silicate (Florite® RE,FLR). Ethyl cellulose was procured from Himedia Laboratories Ltd., Mumbai, India. Hydroxypropyl methylcellulose was purchased from G.S. Chemical Testing Laboratories, New Delhi, India. Polyvinyl alcohol, hydrochloric acid and tween 80, Dichloromethane, ethanol All the other chemicals used were of analytical grade.

Preparation of Amox absorbed CS

CS (1.0 g) was dispersed in 10 ml ethanolic solution of amoxicillin to prepare a slurry. The slurry was ultrasonicated for 10 min in an ice bath at 40% voltage frequency using a probe sonicator (Soniweld, Imeco Ultrasonics, India) to entrap the drug solution and reducing agent inside the pores of porous carrier. The excess ethanolic solution was removed by filtration and then drying in vacuum, which resulted in amoxicillin absorbed CS powders.

Preparation of floating microspheres

Microspheres were prepared using a modified emulsion solvent diffusion technique (jain et al,2005) Briefly, the drug absorbed CS was added into the polymer solution of ethyle cellulose and HPMC in ethanol and dichloromethane (2:1) and sonicated using probe sonicator. The resulting suspension was poured into 200 ml aqueous solution of PVA (0.75% w/v) at 40 °C. The emulsion or suspension was stirred at 500 rpm for 3 h employing a propeller type agitator. The microspheres were separated by filtration, washed with water and dried at room temperature in a desiccator for 24 h.

Size and shape of microspheres

The size of microspheres was determined using microscope (Olympus NWF 10x, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) (Leo 430, Leo Electron Microscopy Ltd, Cambridge, England) was performed to characterize the surface of the formed microspheres. Microspheres were mounted directly onto sample stub and coated with gold film (~200 nm) under reduced pressure (0.133 Pa).

Flow properties

The flow properties of microspheres were characterized in terms of angle of repose, carr index and hausner ratio (Sinha *et al.*, 2005). For determination of angle of repose (θ), the microspheres were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The microspheres were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the height of the pile / radius of its base gave the angle of repose. Microspheres were poured gently through a glass funnel into a graduated cylinder cut exactly to 10ml mark. Excess microspheres were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and carr index (IC) were calculated according to the two equations given below:

$$HR = \rho t / \rho b$$

$$IC = (\rho t\% \ \rho b)/\rho t$$

In vitro buoyancy

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 mL of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres (Srivastava *et al.*, 2005). Development and evaluation of floating microspheres of amoxicillin.

Incorporation efficiency (IE)

To determine incorporation efficiency floating microspheres were dissolved in a minimal amount of dichloromethane and the drug was extracted into a suitable aqueous media (0.1 N hydrochloric acid) by evaporating dichloromethane. The solution was filtered through 0.45 m membrane, diluted suitably and analyzed for drug content spectrophotometrically at 277 nm using 0.1 N hydrochloric acid as blank.

In vitro drug release studies

The drug release was studied using a USP 24 dissolution apparatus type I (Veego Scientific, Mumbai) at 100 rpm in 0.1N hydrochloric acid as dissolution medium (900 mL) maintained at 37±1°C. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1 N hydrochloric acid. Absorbance of these solutions was measured at 277 nm using a SYSTRONICS 2202 UV/visible spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

The floating microspheres were prepared by emulsion solvent diffusion technique reported in the literature. A solution or

Table 1 Formulation chart floating microspheres of amoxicillin

Formulation Code	Amount of Drug (mg)	Total Amount of Polymer (mg)	Amount of Ethyl Cellulose (mg)		Amount of HPMC (mg)		Amount of calcium silicate (gm)	Amount of Ethanol/ DCM 2:1 (ml)	Amount of PVA (ml)
			%	mg	%	mg			
AM1	500	500	100	500	0	0	2.5	30	200
AM2	500	1000	100	1000	0	0	2.5	30	200
AM3	500	1500	100	1500	0	0	2.5	30	200
AM4	500	500	66.66	333.3	33.33	166.6	2.5	30	200
AM5	500	1000	66.66	666.6	33.33	333.3	2.5	30	200
AM6	500	1500	66.66	999.9	33.33	499.9	2.5	30	200
AM7	500	500	50	250	50	250	2.5	30	200
AM8	500	1000	50	500	50	500	2.5	30	200
AM9	500	1500	50	750	50	750	2.5	30	200

suspension of polymer (HPMC and EC) and amoxicillin absorbed porous calcium silicate (CS) in ethanol and dichloromethane was poured into an agitated aqueous solution of polyvinyl alcohol (PVA). The subsequent evaporation of the entrapped dichloromethane led to the formation of internal cavities within the micro particles. The incorporation of drug absorbed CS into the formulation might have produced porous structure within the microspheres.

The flow properties of microspheres were characterized in terms of angle of repose, bulk density, tapped density and carr index. All formulation showed excellent flowability as expressed in term of angle of repose (< 40^0). Angle of repose of the developed formulations AM1 to AM9 varied from 18.52 ± 0.73 % to 24.44 ± 0.35 %. Formulation AM2 (ethyl cellulose) has angle of repose (19.65 ± 0.44 %). Carr's Index of formulations AM1 to AM9 varied from 16.2 ± 2.94 % to 25.23 ± 7.88 %. The formulation AM4 shows lowest value of Carr's index (16.2 ± 2.94 %). Angle of repose and carr index were determined to predict flow ability. Therefore all prepared floating microspheres showed better floability.

The percentage yield of floating microspheres of formulations (AM1 to AM9) was found to be in the range of 78.21 ± 1.09 to 93.56 ± 2.79 %. The percentage yield of microspheres prepared with ethyl cellulose formulation AM1 was found to be 93.56 ± 2.79 %. Percentage drug content of formulations (AM1 to AM9) were found in the range of 79.89 ± 2.19 % to 87.74 ± 1.24 %. As the concentration of total amount of polymer was increased, drug entrapment efficiency (drug content) was also increased. Formulation AM3 showed good % yield (87.74 ± 1.24 %). The high entrapment efficiency of amoxicillin may attributed to their poor aqueous solubility . The size of microspheres formed may be a function of many factors such as stirring speed, viscosity of the dispersed phase and dispersion medium, temperature, conc. of polymer, amount and size of porous carrier. Particle size was found to be increasing with the increasing ethyl cellulose concentration Particle sizes of products were found to be between 88.13-108.17 µm. *In Vitro* Buoyancy percentage of the microspheres amoxicillin was in the range of 88.36 ± 4.85 to 98.75 ± 3.62 % at the end of 12 h above 88 %). The nature of the polymer influenced the floating behavior of the microspheres. Good *in vitro* floating behavior was observed for all the microsphere formulation. This may be attributed to the low density CS within the system.

Table 2 Micromeritic properties of floating microspheres of amoxicillin

Formulation Code	Angle of repose (º)	Bulk density (gm/ cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)
AM1	20.18± 0.37	0.5428±0.01	0.6485± 0.03	16.78±1.91
AM2	19.65 ± 0.44	0.5294±0.01	0.6435± 0.02	17.72±0.47
AM3	22.2± 0.33	0.5531±0.02	0.6593± 0.01	19.09±3.75
AM4	18.52± 0.73	0.4762±0.01	0.6156± 0.03	16.2±2.94
AM5	21.41± 0.51	0.4589±0.03	0.6279± 0.01	23.83±6.21
AM6	24.14± 0.23	0.4678±0.03	0.6630± 0.02	25.23±7.88
AM7	20.53 ± 0.96	0.5676±0.02	0.6876± 0.03	17.3±5.03
AM8	19.47± 0.33	0.5643±0.01	0.6743± 0.01	18.26±3.98
AM9	24.44± 0.35	0.5541±0.02	0.7106± 0.01	22.02±2.80

*Average of 3 determination ± standard deviation.

Table 3 Physicochemical properties of floating microspheres of amoxicillin.

Batch	Percentage Yield* ± S.D.	Percentage Drug Entrapment Efficiency* ± S.D.	Percentage Buoyancy* ± S.D.	Particle size (µm)
AM1	93.56±2.79	80.28±1.65	96.21±3.92	103.90
AM2	86.14±1.43	84.17±1.63	97.90±3.79	104.12
AM3	79.37±1.69	87.74±1.24	98.75±3.62	108.17
AM4	92.11±1.27	81.49±2.12	94.21±2.53	88.13
AM5	85.49±2.12	82.09±1.92	96.95±3.47	95.36
AM6	80.19±1.37	85.61±2.21	97.56±3.86	98.65
AM7	91.71±1.23	79.89±2.19	91.12±2.87	88.87
AM8	83.94±2.35	81.97±2.41	95.26±2.37	93.15
AM9	78.21±1.09	83.65±2.35	97.05±3.29	102.95

*Average of 3 readings

CONCLUSION

Floating microspheres of amoxicillin was prepared by emulsion solvent evaporation method. Calcium silicate has been used as carrier. On the basis of results obtained in these investigations, the following conclusions may be drawn:

- It is possible to prepare an intragastric floating and sustained release preparation using calcium silicate (FLR) as the floating carrier by covering the pores of the FLR particles with adsorbed drug by a polymer solution containing both of HPMC and EC in suitable proportions.

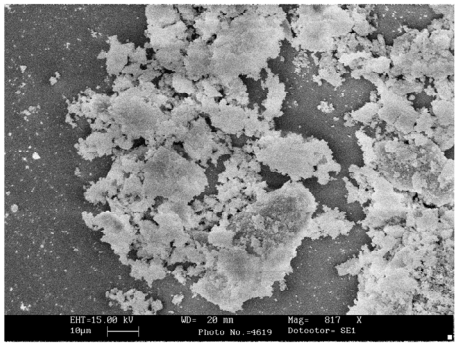

Fig. 1 SEM View of porous Calcium Silicate Particles (FLR).

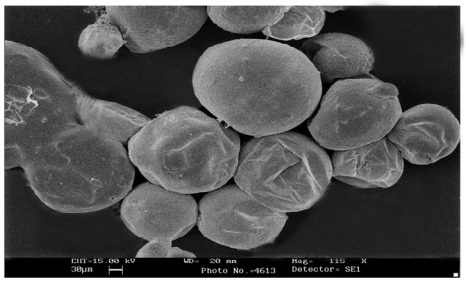

Fig. 2 SEM View of Calcium Silicate based floating microspheres of amoxicilline.

- FLR based floating drug delivery system provides the possibility of enhancing the bioavailability and control the release of amoxicillin exhibiting absorption window by prolonging the gastric emptying time of the dosage form, ensuring availability of drug at the absorption site for the desired period of time.
- As the FLR microsphere with adsorbed drug and polymer coating showed a good floability and drug release, it has a great potential for its use powder form encapsulation.

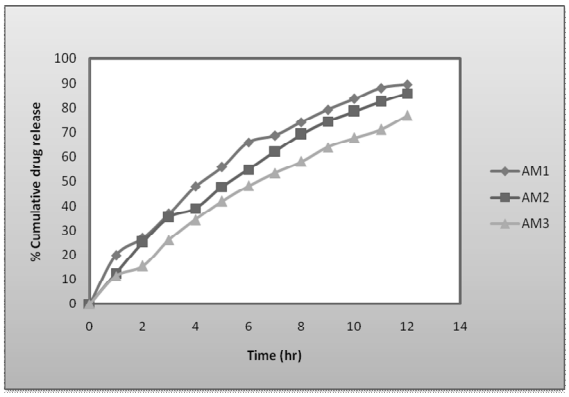

Fig 1: *In-vitro* drug release profile of amoxicillin from floating microspheres formulations AM1 to AM3 (pH 1.2)

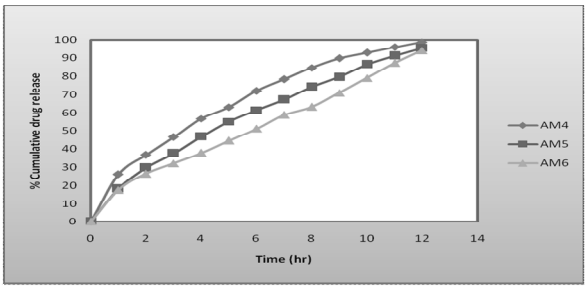

Fig 2: *In-vitro* drug release profile of amoxicillin from floating microspheres formulations AM4 to AM6 (pH 1.2)

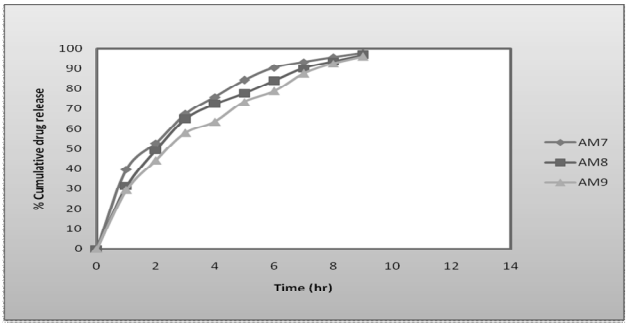

Fig 3: *In-vitro* drug release profile of amoxicillin from floating microspheres formulations AM7 to AM9 (pH 1.2)

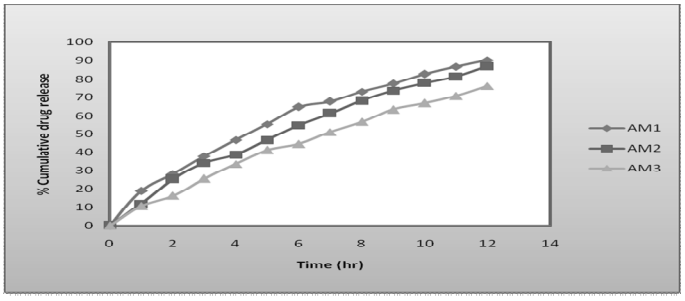

Fig 4: *In-vitro* drug release profile of amoxicillin from floating microspheres formulations AM1 to AM3 (pH 7.4)

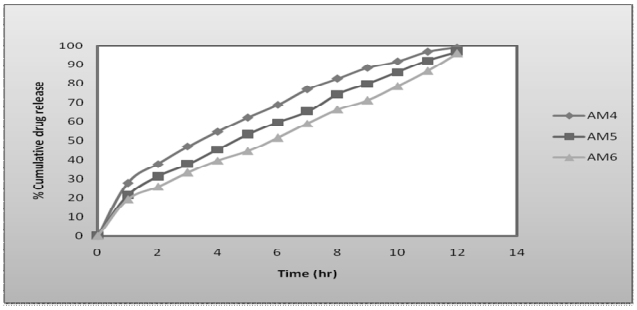

Fig 5: *In-vitro* drug release profile of amoxicillin from floating microspheres formulations AM4 to AM6 (pH 7.4)

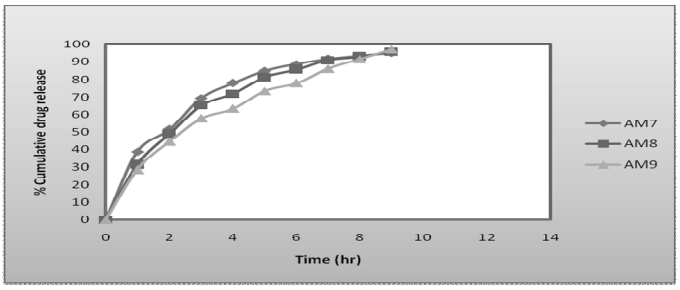

Fig 6 % *In-vitro* drug release profile of amoxicillin from floating microspheres formulations AM7 to AM9 (pH 7.4)

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