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Research Article

DEVELOPMENT AND EVALUATION OF THEOPHYLLINE MICROBALLOONS DRUG DELIVERY SYSTEM

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ABSTRACT
The objective of the present investigation was to prepare theophylline microballoons loaded with sodium alginate, eudragit S 100 and sodium bi-carbonate as gas generating agent. The microballoons prepared by ionotropic gelation method were analysed for morphology, mean particle size, drug polymer interaction, entrapment efficiency and in-vitro drug release.
KEYWORDS: Microballoons; ionotropic gelation; Calcium alginate

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Many of the drug delivery systems, available in the market are oral drug delivery type systems. Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have a ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.[1]

Most of the floating systems are dominated by single unit formulations with main drawback of high variability in the GI transit time, due to its all or nothing emptying process.[2] The gastric emptying time has been reported to be from 2 to 6 hours in humans in the fed state. Drugs that are required to be formulated into gastroretentive dosage forms include : (a) acting locally and primarily absorbed in the stomach; (b) drugs that are poorly soluble at an alkaline pH; (c) those with narrow window of absorption; (d) drugs absorbed rapidly from GIT tract and (c) drugs that degrade in colon. Attempts to develop a single - dose therapy for the whole duration of treatment have focused attention on controlled or sustained release drug delivery system.[3]

Theophylline, a bronchodilator used in the treatment of asthma. The objective of the present investigation was to formulate microballoons of theophylline in order to achieve a prolonged retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability.

MATERIALS AND METHODS

Theophylline and eudragit S 100 were gift samples from Bakul aromatics pvt. Ltd. Mumbai and Evonik Degussa Pvt. Ltd. Mumbai respectively. Sodium alginate, sodium bi-carbonate were purchased from SD Fine Chem, Boisar, Maharashtra. All other chemicals used were of analytical grade.

PREPARATION OF MICROBALLOOONS

Sodium alginate was dissolved in distill water at a concentration of 2 % (w/v), the solution was stirred thoroughly after mixing drug and polymer. The calcium carbonate of different ratio (Caco3/sodium alginate = ¼, ½ and ¾ w/w)were added. The gelation medium was prepared by dissolving calcium chloride ($Cacl_2$) of concentration 2 % in 2 % glacial acetic acid. The homogenous sodium alginate solution was extruded using a 21 G syringe needle into the medium was about 10 cm. The microballoons formed were left in the solution with gentle stirring for 30 min at room temperature to be cured. After microballoons were collected, washed with distill water and dried overnight for 40º C.

CHARACTERIZATION OF THEOPHYLLINE MICROBALLOONS

Particle size analysis

The samples of prepared microballoons was randomly selected and their size was determined using an optical microscope (Olympia, India).

Fourier transform-infrared spectroscopic analysis

Drug polymer interactions were studied by FT-IR spectroscopy. IR spectrum of drug, physical mixture and drug loaded microballoons were recorded in the stretching frequency range 450-4500 cm^{-1} . The samples were prepared by KBr pellet technique.

Scanning electron microscopy(SEM)

The SEM analysis of the microballoons was carried out by using JEOL – 6360A analytical scanning electron microscope. The microballoons were viewed at an accelerating voltage of 5 KV.

Percentage yield

The prepared floating microballoons were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres.

$$\% \text{ yield} = \frac{\text{Actual weight of the product}}{\text{Total weight of excipient and drug}} \times 100$$

Drug loading and entrapment efficiency

To assess the entrapment efficiency, specific amount of crushed microballoons suspended in a 50 ml 0.1 N Hcl with agitating at room temp. for 24 hr. The solution was filtered through Whatman filter paper drug content was determined spectrophotometrically at the wavelength of 271 nm using 0.1N Hcl as blank.

It is calculated from formula:

$$\text{Encapsulation Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Percentage of floating behaviour

Microballoons (equivalent to 100 mg) were spread over the surface of a USP-XXIII paddle type apparatus filled with 900 ml .1 N Hcl. The medium was agitated with a paddle rotating at 50 rpm for 24 hrs. The floating and the settled portion of microballoon were recovered separately. The microballons were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microballoons that remained floating and the total mass of the microballoons.

$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating microballoons at time t}}{\text{Initial weight of microballoons}} \times 100$$

***In-vitro* drug release studies**

The in vitro dissolution studies were carried using USP-XXIII paddle type apparatus. Weighed amount of drug loaded microballoons (equivalent to 100 mg of drug) were introduced into 900 ml dissolution medium of pH 1.2 maintained at 37±0.5º at a rotation speed of 50 rpm samples were removed periodically for 24 hr. followed by the replacement of an equal volume of the test medium and analyzed at 271 nm to determine the concentration of drug present.

Kinetics of drug release mechanism

In order to understand the mechanism and kinetics of drug release, the release data of the *in- vitro* dissolution study was analyzed with various kinetic equations like zero order , first order, Higuchi and peppas equation. Coefficient of correlation (r) values calculated for the linear curves obtained by regression analysis of the plots.

RESULT

Particle size analysis

Average particle size of microballoons was in the range of 916±0.06 to 1.16±0.08 µm. The mean size of microballoons depend on the gas forming agent. The size of the microballoons increased prominently over the control of the gas forming agent.

FTIR interpretation of drug, polymer and microballoons

A characteristic IR spectra of Theophylline showed at 3347 cm^{-1} for N-H,3060 cm^{-1} for C-H str, 1666 cm^{-1} for C-O str, 1241 cm^{-1} for C-N str, 847 cm^{-1} for C-N-H, 786 cm^{-1} for C-H bend, 743 cm^{-1} for C-C=O, 668 cm^{-1} for N-C=O, 610 cm^{-1} for N-C=C.

All these prominent peaks of drug is observed in formulation F 5. Thus, indicating the compatibility of drug with polymers and excipient used. Here, the FT-IR Spectrum of theophylline and "F 5" are matching with each other. So there is no interaction take place in optimized formulation.

Scanning electron microscopy (SEM):

Morphology of microballoons was examined by scanning electron microscopy. The view of the microballoons showed a hollow spherical structure with discrete shape and porous nature. It shows the pore formation on the surface due to gas forming agent. Out ward dents observed in formulation indicate collapse of the walls of the microballoons during the drying process.

Percentage yield

The average percentage yield was found in the range of 67.64 % to 82.05 %. It is observed that increasing the gas forming agent in formulation significantly produced high degree of porosity which results in the diffusion of the material during and after gelation.

Drug loading and entrapment efficiency

Drug loading was in the range of 20% to 29%. Drug loading was fond to be low, due to hydrophilic nature of the drug. It is observed that drug loading was decreased with increase in the concentration of gas forming agent. Entrapment efficiency was in the range of 67.6±0.21 to 82±0.11. The use of acetic acid in solvent system improved the encapsulation efficiency.

Floating ability of microballoons

Floating ability of microballoons is directly depend on the gas forming agent. It was found to be in the range of 94.77±1.1 to 98.97±2.1 of formulation F 1 to F 6.

***In-vitro* drug release studies**

The in vitro release of theophylline from the different formulations was examined. F 1 to F 6 were in the range of 84.315 to 93.078. Among all formulations F 5 was found to be the best formulation as it release theophylline 93.078 % in a sustained manner with constant fashion over extended period of time (for 24 hr).

Kinetics of drug release

To ascertain the drug release mechanism, the in-vitro data were subjected to Higuchi diffusion. The 'r' values of Higuchi diffusion was in the range of 0.9273 to 0.9780 of all formulation F 1 to F 6. It suggests that the Higuchi diffusion plots of all the formulations were fairly linear because 'r' values near about 1 in all the cases. So it confirms the drug release by Higuchi diffusion mechanism.

The release mechanisms of theophylline microballoons also evaluated on the basis of Peppas model. The n value of all formulations F 1 to F 6 are in the range of 0.9445 to 0.9868 which is in the range of $0.5 < n > 1.0$, which indicate that tne mechanism of release of theophylline microballoons are anomalous (non-Fickian) transport.

CONCLUSION

In this study, theophylline microballoons were successfully designed and prepared by ionotropic gelation method for use in floating drug delivery system. Concentration of gas generating agent influenced drug loading, entrapment efficiency, particle size, shape, buoyancy and drug release profile of microballoons. The FTIR study did not reveal that any significant drug interactions. Hence, the microballoons of theophylline prepared with formulation variables such as polymer, gas generating agent and calcium chloride may provide a convenient dosage form for achieving better floatation and drug release.

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Table 1: Composition of Theophylline microballoons formulation

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Theophylline (gm)	0.5	0.5	0.5	0.5	0.5	0.5
Sodium alginate (gm)	2	2	2	2	2	2
Eudragit L 100 (gm)	0.4	0.4	0.4	-	-	-
Eudragit S 100 (gm)	-	-	-	0.4	0.4	0.4
Sodium bi-carbonate (gm)	0.5	1	1.5	0.5	1	1.5

Table 2: Micromeritic properties of Theophylline microballoons

Formulation Code	Mean Particle Size (µm)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausners Ratio	Carr's Index	Angle of Repose
F 1	0.921±0.03	0.801±0.02	0.867±0.02	1.17±0.03	14.78±2.1	19.35±2.41
F 2	0.944±0.16	0.804±0.01	0.871±0.01	1.19±0.09	16.14±1.4	20.38±1.84
F 3	0.916±0.06	0.815±0.02	0.881±0.02	1.14±0.05	15.77±1.1	18.28±2.3
F 4	1.06±0.07	0.799±0.02	0.848±0.01	1.17±0.02	16.45±1.9	16.96±1.47
F 5	1.16±0.08	0.784±0.03	0.851±0.02	1.16±0.05	14.24±1.7	15.1.2±1.55
F 6	0.977±0.10	0.802±0.01	0.874±0.03	1.13±0.09	13.33±1.6	17.44±1.86

Table 3 : Percentage yield, % Drug loading, Entrament efficiency and Percent buoyancy of Theophylline microballoons

Formulation Code	Percentage Yield	% Drug Loading	Entrapment Efficiency	Percent Buoyancy
F 1	67.64±1.5	20.05±1.1	67.6±0.21	94.77±1.1
F 2	72.82±1.0	22.25±1.7	72.8±0.57	97.98±1.7
F 3	76.36±1.4	28.47±0.8	76.2±0.91	98.47±0.8
F 4	73.52±0.47	21.46±1.4	73.4±0.28	95.47±1.4
F 5	82.05±1.7	24.55±1.8	82±0.11	98.78±1.8
F 6	79.09±2.0	29.33±2.1	79±0.33	98.97±2.1

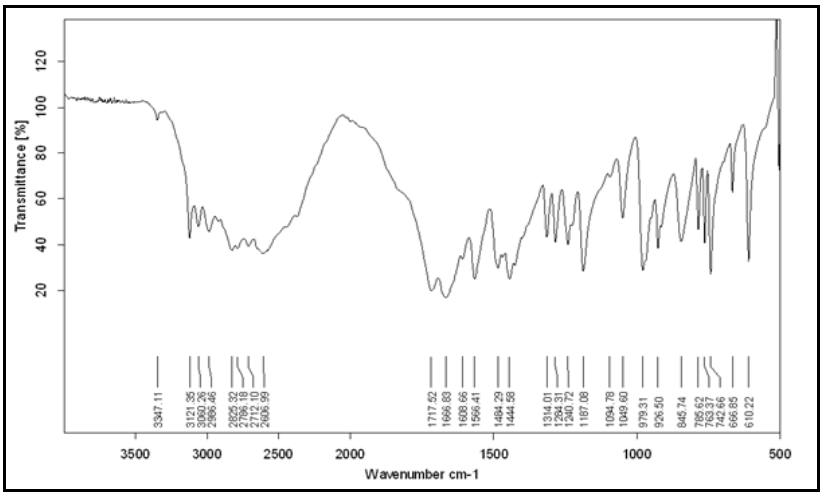


Figure 1: I.R. Spectrum of Theophylline

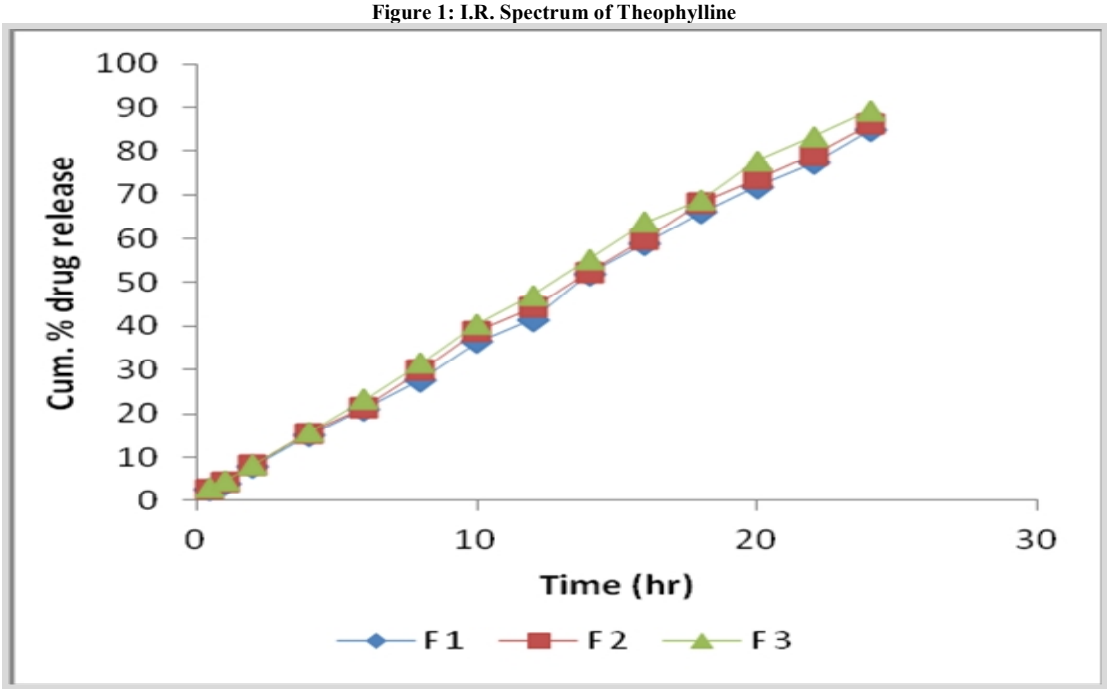


Figure 2: In-vitro release data of formulation F 1 to F 3

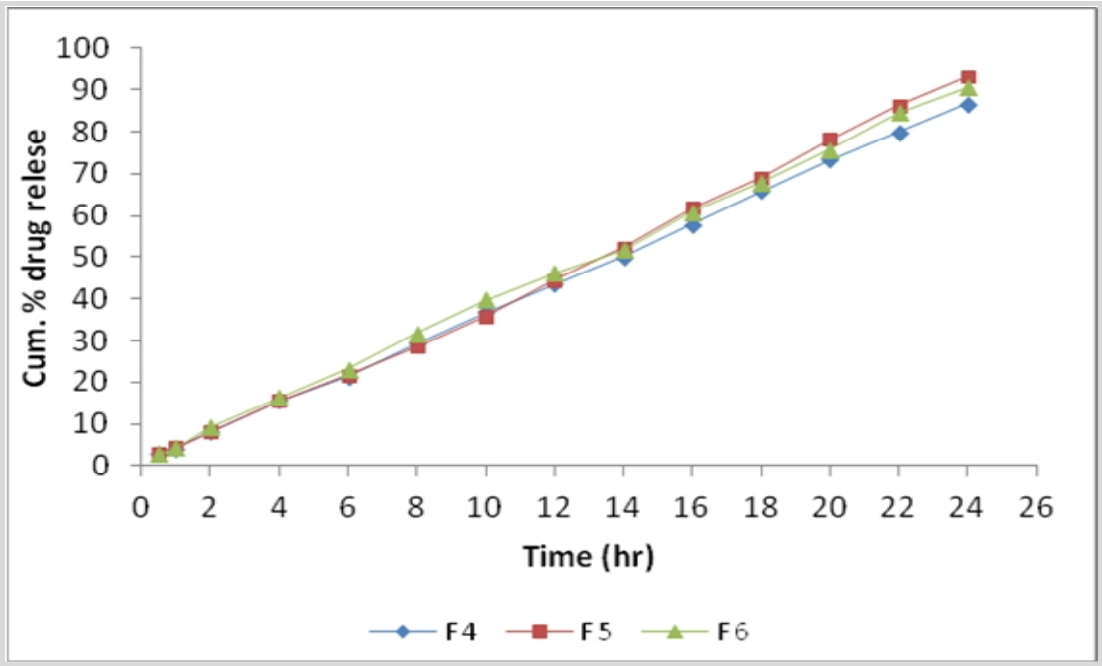


Figure No 3: In-vitro release data of formulation F 4 to F6

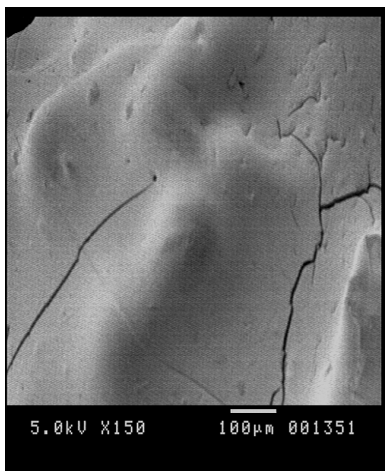
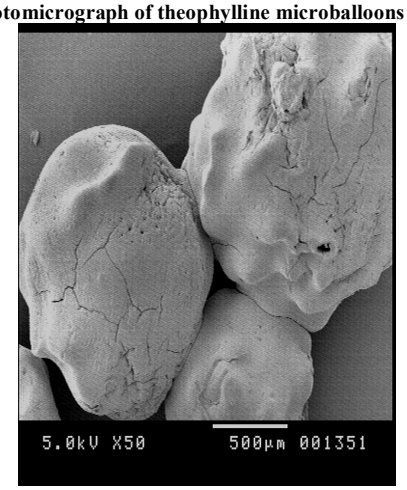


Figure 4 SEM photomicrograph of theophylline microballoons of formulation F 5



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