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Release Kinetics of Theophylline Agar Microbeads.

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The major drawback of orally administered drugs like theophylline in the treatment of asthma is its short duration of action, which leads to repeated administration and patient non-compliance. To overcome these drawbacks an attempt has been made to develop a sustained release dosage form of theophylline embedded in agar microbeads with hydrocolloid. The agar microbeads with hydrocolloid (guar gum) were prepared by extrusion method and dispersed phase congealing technique. The microbeads were characterized by particle size determination and drug release studies. The mechanism of drug release and the effect of guar gum in controlling the theophylline release from prepared beads were also investigated. The results indicated that the surface adhering drug was found to release immediately and a constant release was obtained up to 5 h from all the batches. The results also indicated that the rate of release of drug from agar microbeads was found to decrease as the concentration of the added hydrocolloid was increased. The drug release was found to be by diffusion mechanism without any swelling of the agar microbeads. From the results, it was also observed that the added hydrocolloid (guar gum) improved the gel strength of agar and the release rate was controlled significantly.

Asthma is a reversible, obstructive airway disease characterized by bronchial hypersensitivity. The major drawbacks of the orally administered drugs like theophylline in treatment of asthma is it short duration of action which leads to repeated administration and increased cost of therapy. Various sustained release dosage forms have been developed by researchers by embedding the drug in agar and forming a gel[1-4]. Boriae[5] and Nakano[6,7] had investigated the release and bioavailability of sulphamethazole, theophylline and aminophylline embedded in agar microbeads. In this study an attempt has been made to develop a sustained release dosage form by formulating theophylline embedded agar microbeads with hydrocolloid. The microbeads with guar gum were prepared by extrusion method and spray congealing technique[8]. The prepared microbeads were characterized for particle size determination and *in vitro* drug release studies. The effect of concentration of the hydrophilic gum (guar gum) in controlling the release of theophylline from it agar microbeads was also investigated. The gel strength of agar was found to increase with the addition of hydrocolloid. An attempt was also made to understand the mechanism involved in the release kinetics of the agar microbeads with and without hydrocolloid.

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MATERIALS AND METHODS

Theophylline IP was obtained as a gift sample from Astra Drugs Ltd., Bangalore. Guar gum was of AR grade and purchased from Loba Chemie Pvt Ltd, Mumbai. Agar (bacteriological grade) was obtained from Himedia Ltd., Mumbai. All the other chemicals used in the present study were of AR grade.

Preparation of theophylline embedded agar microbeads:

Theophylline embedded agar microbeads were prepared by a two stage process involving extrusion and dispersed phase congealing technique. An 8.0% w/v solution of agar was prepared by using distilled water with vigorous

stirring to obtain a dispersion. This dispersion was heated to 90° with continuous stirring to form a clear solution. Guar gum in concentrations of 0.2%, 0.5%, 1.0%, 1.5%, 2.0%, and 3.0% of the weight of agar was added to agar dispersion with continuous stirring to get uniform distribution of the hydrocolloid in agar. Further, 5.0% w/v of drug (theophylline) was added to the dispersion with stirring to form a dispersion. This dispersion was extruded into a beaker containing 200 ml ethyl acetate maintained at 10°, using a syringe with stirring. After extrusion the beads were allowed to solidify for a period of 15 min. The solidified beads were filtered through Whatman No. 1 filter paper and were then dried at room temperature for 24 h. A batch of theophylline agar microbeads was also prepared without hydrocolloid.

Estimation of theophylline and particle size of microbeads:

Theophylline content in the microbeads was determined by spectrophotometric method as reported by Lalla[9]. Five portions each containing 200 mg were randomly picked from the prepared samples and placed in 100 ml of simulated gastric fluid (pH 1.1) and allowed to stand for a period of 24 h to determine the amount of theophylline. After 24 h the samples were filtered, suitably diluted and spectrophotometrically measured at 270 nm. The estimation was done in 5 replicates to determine the uniformity of drug distribution in microbeads. About 20 microbeads were randomly picked up thrice and their size was measured by using vernier caliper.

***In vitro* release of theophylline from prepared micro beads:**

In vitro release studies of the samples were carried out in 900 ml of both simulated gastric fluid (pH 1.1) and intestinal fluid (pH 7.5) using USP XXII apparatus at 70 rpm at a constant temperature of 37±0.5° for a period of 5 h. The maximum release rate that can be obtained from the microbeads in 5 h was determined in all the batches. A quantity of microbeads equivalent to 200 mg of theophylline were placed in the dissolution flask and release rate were determined. At periodic time intervals, 5 ml of sample was withdrawn, suitably diluted and absorbance was measured at 270 nm. Five milliliters of fresh dissolution medium was added each time to maintain sink condition.

RESULTS AND DISCUSSION

Theophylline embedded agar microbeads were prepared by extrusion method. Table 1 gives the drug content and uniformity data. The drug content was found to be uniform in the agar microbeads. This observation was well supported by low coefficient of variance obtained in the data.

A random sample of 20 microbeads was taken and their sizes were determined by using a Vernier caliper in triplicate. The bead size was found to be in the range of 1.75 to 2.55 mm in diameter with a coefficient of variance value of 0.096. The shape of the agar microbeads was found to be perfectly spherical in nature. The surface of the microbead was found to be smooth and almost of monosize.

TABLE 1: DRUG CONTENT UNIFORMITY DATA

Replicates	Concentrations of Guar gum					
	0.2%	0.5%	1.0%	1.5%	2.0%	3.0%
1	61.11	61.02	61.00	60.35	60.30	58.40
2	60.83	60.99	60.31	57.00	59.39	56.75
3	59.41	59.02	58.24	57.43	56.53	54.37
4	59.77	58.15	59.44	57.85	57.81	55.65
5	60.35	59.35	57.78	59.65	56.95	54.80
Mean	60.294	59.706	59.354	58.456	58.312	55.994
S.D	0.6344	1.1308	1.2123	1.3078	1.5265	1.4520
C.V.	1.0522	1.8939	2.0424	2.2373	2.6177	2.5931

Drug content uniformity of agar microbeads with guar gum. Each value represents mean±SD of value of n=3 observations. C.V. stands for Coefficient of Variance.

Theophylline release from the agar microbeads was studied in both 900 ml of simulated gastric fluid (pH 1.1) and simulated intestinal fluid (pH 7.5) for 5 h in USP XXII dissolution rate test apparatus at a temperature 37±0.5°. Figs.1 and 2 show the *in vitro* release profiles of agar microbeads with hydrocolloid in simulated gastric and intestinal fluid respectively. First order rate constants were also calculated from the release data of microbeads to study the effect of concentration of guar gum in controlling the drug release from agar micro beads. From the release profiles it was observed that the drug present at the surface was found to be released immediately and constant release of 40 % was achieved during 5 h of the release study in simulated gastric and intestinal fluid respectively. It was also found that the release was found to be uniform and constant during the study period. From these findings it can be suggested that the gel strength of the agar would have played a significant role in controlling the release rate of theophylline.

It was also observed that the release of drug from the prepared batches was found to decrease as the concentration of the added hydrocolloid was increased. The possible mechanism suggested for such type of release behavior is that the added hydrocolloid would have increased the gel strength of the agar in agar microbeads and thereby further decreasing the release rate from the microbeads. From the *in vitro* release data it was observed that the rate of drug release from the microbeads could be controlled by increasing the concentration of the added hydrocolloid (guar gum).

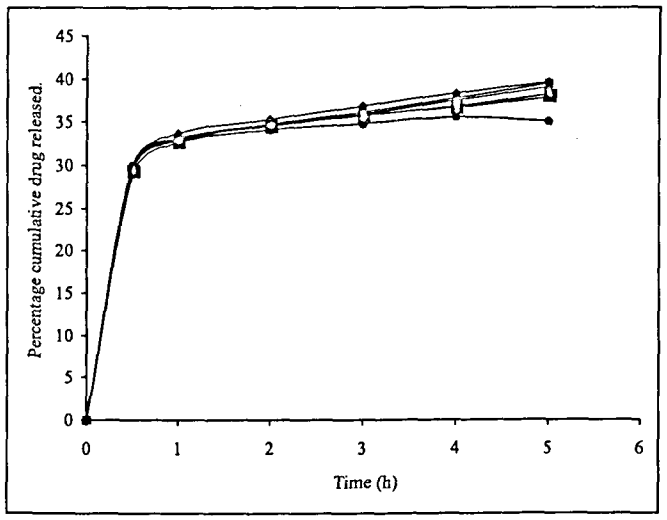

Fig. 1: Release profiles of Theophylline agar microbeads.

Release of theophylline from agar microbeads loaded with guar gum 0.2% (♦), 0.5% (¤), 1.0% (▲), 1.5% (+), 2.0% (○) and 3.0% (●) in simulated gastric fluid (pH 1.1).

The release data and rate constants obtained were subjected to analysis of variance test and 'F' values were calculated. From the 'F' values obtained it was observed that the added hydrocolloid had a significant effect in controlling the release of drug from its microbeads. Higuchi plots

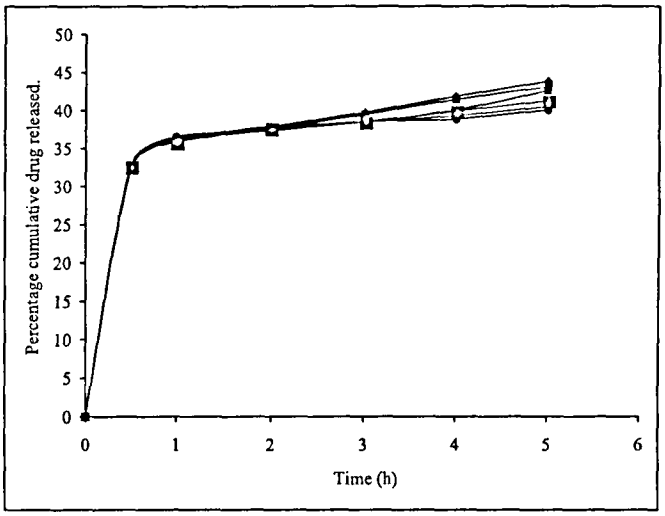

Fig. 2: Release profiles of Theophylline agar microbeads.

Release of Theophylline from agar microbeads loaded with guar gum 0.2% (♦), 0.5% (¤), 1.0% (▲), 1.5% (+), 2.0% (○) and 3.0% (●) in simulated intestinal fluid (pH 7.5).

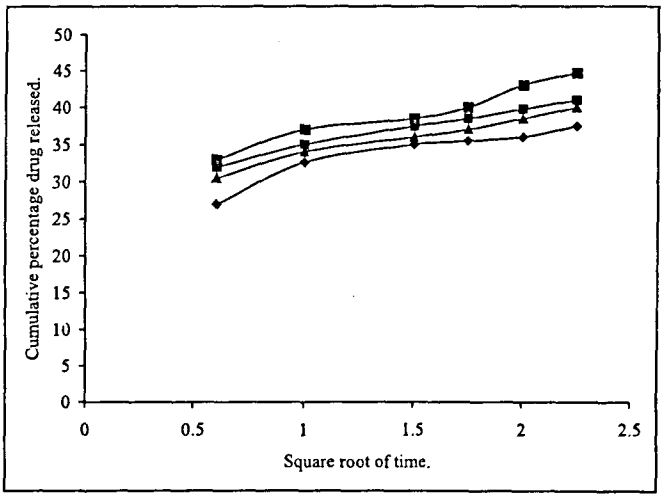

Fig. 3: Higuchi plots of agar microbeads with 3% guar gum.

Cumulative percentage drug released Vs square root of time plots of Theophylline agar microbeads, with 3% guar gum in simulated gastric fluid (♦), simulated intestinal fluid (¤), Agar alone in simulated gastric fluid (▲) and Agar alone in simulated intestinal fluid (+).

TABLE 2: KINETICS DATA OF AGAR MICROBEADS

Concentration In % w/w of agar	Graphical values for Release kinetics			Percentage of surface drug	Regression Coefficient 'r'
	Intercept	Slope	K/hr		
0.2	1.841	-0.0129	0.0298	30.65	-0.9609
0.5	1.845	-0.0130	0.0299	30.01	-0.9753
1	1.843	-0.0122	0.0281	30.33	-0.9659
1.5	1.842	-0.0110	0.0255	30.49	-0.9500
2	1.839	-0.0100	0.0231	30.97	-0.9583
3	1.842	-0.0080	0.0184	30.49	-0.8614

Kinetics data of agar microbeads with guar gum in simulated gastric fluid. (pH 1.1).

TABLE 3: KINETIC DATA OF AGAR MICROBEADS

Concentration In % w/w of agar	Graphical values for Release kinetics			Percentage of surface drug	Regression Coefficient 'r'
	Intercept	Slope	K/hr		
0.2	1.827	-0.0161	0.0372	32.85	-0.9800
0.5	1.828	-0.0153	0.0352	32.70	-0.9812
1	1.827	-0.0136	0.0313	32.85	-0.9704
1.5	1.824	-0.0116	0.0268	33.31	-0.9635
2	1.821	-0.0098	0.0227	33.77	-0.9399
3	1.819	-0.0091	0.0210	34.08	-0.8907

Kinetics data of agar microbeads with guar gum in simulated intestinal fluid (pH 7.5).

were plotted for microbeads with 3 % guar gum to study the mechanism of drug release. The data perfectly obeyed Higuchi's equation and it was observed from the plot (Fig .3) that there was an upward trend of release was achieved between 0.5-1 h and after 1 h, a perfect linearity was evident up to a period of 5 h. These observations from the plots clearly indicates that the bead geometry of the preparations with guar gum had not changed during the period of dissolution where as slight swelling of beads, leading to change in geometry of the microbeads was observed in preparations without guar gum. This is supported by the evidence obtained from the plots, which shows a slight deviation in the graph plotted for agar microbeads without guar gum. From all these observations, it can be said that the mechanism of drug release from the prepared microbeads with guar gum was mainly due to diffusion without any swelling of the microbeads. The mechanism suggested for this type of drug release was that the added guar gum would have increased the gel strength of agar and would have assisted in maintaining the integrity of the beads during the dissolution period.

Table 2 and 3 gives the kinetic data for agar microbeads calculated from their release data. The data was found to be perfectly linear with a slope value of less than 0.5 and it clearly supports the mechanism of drug release by diffusion without any initial swelling from agar microbeads. The results were well supported by the mechanisms suggested by Bamba[10] in his work. The results indicated that the release of drug from the prepared microbeads perfectly obeyed first order kinetics and clearly supports that the release of drug from microbeads after reaching the constant state is linear. The kinetic data results also supports that there was a progressive decrease in the rate of release of drug from the microbeads, as the concentration of added hydrocolloid was increased from 0.2% to 0.3%. Thus the results support that guar gum had reduced the release of drug from agar microbeads significantly.

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