Design and Evaluation of Ethyl Cellulose Sustained Release Matrix Tablets of Theophylline

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ABSTRACT: Ethyl cellulose matrix tablets were prepared for sustained delivery of theophylline, a bronchodilator. A wet granulation technique was employed to prepare matrix tablets by utilizing drug and different concentrations of polymer (10, 20, 30, 40 and 50% WIN) were included in the formulation containing 200 mg of theophylline. The prepared tablets were evaluated for various physicochemical parameters by official procedures. The *in vitro* release study of matrix tablets were carried out in phosphate buffers pH 1.2 and 6.8 for 12 hours. The prepared matrix tablets were showed 68.74%, 67.14%, 65.17%, 62.46%, and 57.24% release over a period of 12 hours. To investigate the drug release mechanism, the release data were fitted into exponential models such as Higuchi and Peppa's. Analysis of drug release rate drug from the matrix system indicated that the drug was released by anomalous diffusion obeying zero order kinetics.

KEY WORDS: Theophylline, Ethyl Cellulose, Matrix tablets, Higuchi and Peppa's model.

Introduction

Oral slow and sustained release drug delivery systems can release their drug content with a controlled manner, producing a desirable blood serum level, reducing drug toxicity and improving patient compliance by prolonging dosing intervals[1-4]. Matrix systems composed of polymers and other excipients as vehicles for drug delivery are extremely popular in controlling the release rate[5]. It is the system which prolongs and control release of drugs that is dissolved or dispersed[6]. Ethyl cellulose has been successfully used for many years to sustain the release rate of drugs[7]. Theophylline, and its derivatives have long been used for their bronchodilator properties in the management of asthma and chronic obstructive pulmonary disease (COPD)[8]. This drug has a great variability in clearance (elimination half life 3-4 hr, adults 6-12 hr) and also has a narrow therapeutic range (7.5-20 µg/ml). Once or twice daily administration of controlled release preparations in patients with COPD is recommended and improves patient compliance[9]. Hence, the objective of this work was to investigate the release of theophylline from tablets prepared with ethyl cellulose as matrix material.

Materials and Methods

Theophylline anhydrous was procured from Sigma, USA. Ethyl cellulose (20 cps) and lactose were purchased from S.D.Fine Chemicals, Mumbai. Magnesium stearate and talc were obtained from Loba chemie Pvt Ltd, Mumbai. All other ingredients used were of analytical grade.

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Preparation of SR Matrix Tablets

SR tablets of theophylline were prepared by using drug and different polymer concentration (10, 20, 30, 40 and 50%) by wet granulation technique as shown in Table 1. All the ingredients were passed through sieve no 100. Required quantities of drug, polymer and diluents were mixed thoroughly and sufficient quantity of granulating agent (isopropanol and water in the ratio of 3:1) was added to get dough mass. The mass was sieved through 22/40 mesh and dried at 50° for 2 hour. The dried granules retained on 40 mesh were mixed with 10% fines, 2% talc and 1% magnesium stearate. Tablets were compressed using 10 mm flat faced punches on a rotary tablet press (Remek, Ahmedabad) at an appropriate compression force with the hardness of all tablets maintained between 5-6 kg/cm^2.

Evaluation of granules

The angle of repose (è) was measured according to the fixed funnel and free standing cone method[10], which indicates the flowability of granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD=weight of the powder/volume of packing, TBD=weight of the powder/tapped volume of packing. Compressibility of the granules (CI) was calculated using the formula CI=TBD-LBD/TBD×100. The physical properties of granules were shown in Table. 2.

Physical characteristics of fabricated matrix Tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods[11] shown in Table 2.

Table 1. Composition of theophylline SR matrix tablets.

Ingredients	Formulation code				
	F1	F2	F3	F4	F5
Theophylline anhydrous	200	200	200	200	200
Ethyl Cellulose	50	100	150	200	250
Lactose	235	185	135	85	35
Talc	5	5	5	5	5
Magnesium stearate	10	10	10	10	10
Total weight	500 mg	500 mg	500 mg	500 mg	500 mg

Table 2. Evaluation data of granules and matrix tablets of theophylline.

Formulation code	Loose bulk density (LBD) (g/ml)	Tapped bulk density (TBD) (g/ml)	Compressibility Index (%)	Drug content (%)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)
F1	0.461±0.04	0.526±0.03	12.36±0.05	99.8±0.4	0.20	5.5±0.9	3.59±0.41
F2	0.473±0.05	0.535±0.04	11.59±0.04	99.5±0.9	0.23	5.3±1.1	3.65±0.47
F3	0.479±0.04	0.547±0.02	12.43±0.03	99.7±0.6	0.25	5.4±0.8	3.62±0.43
F4	0.510±0.02	0.574±0.04	11.15±0.06	101.2±0.5	0.22	5.5±0.7	3.61±0.42
F5	0.520±0.05	0.580±0.05	10.34±0.03	99.8±0.5	0.20	5.6±0.8	3.68±0.40

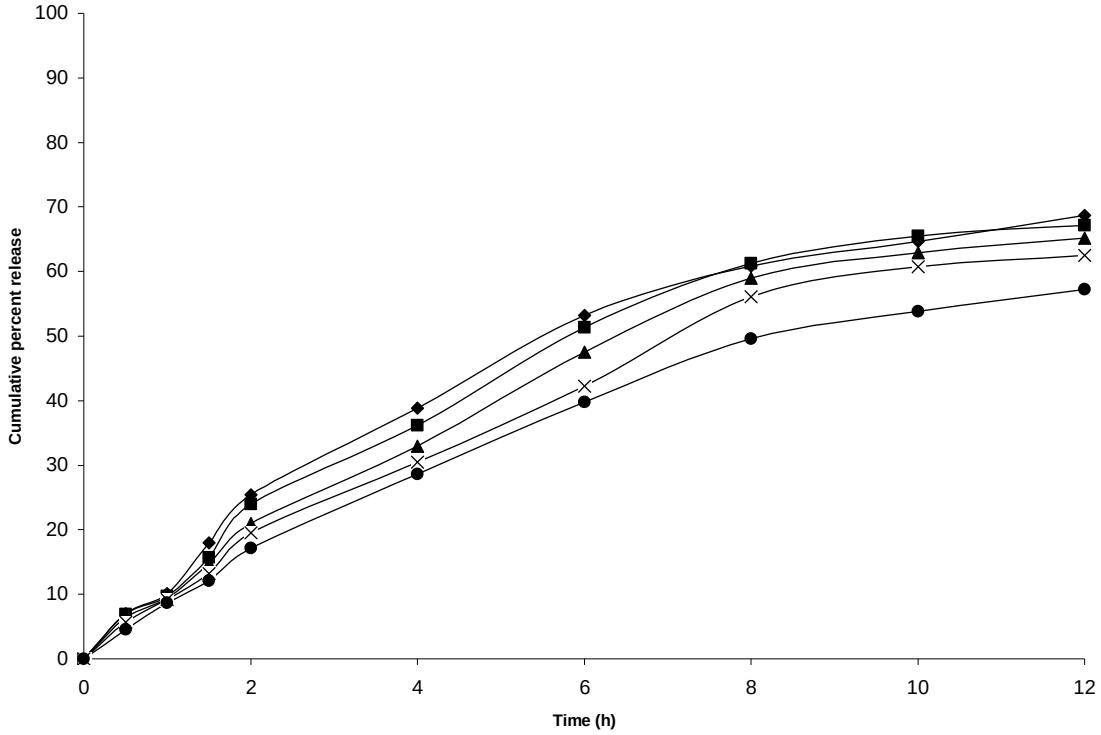

Fig 1. Cumulative percentage of release of theophylline from the matrix tablets F1(♦), F2(■), F3(▲), F4(×) and F5(●). Samples were withdrawn at different time intervals and theophylline was estimated by UV spectrophotometer.

Estimation of drug content in matrix Tablets

Ten tablets from each formulation were powdered. To 500 mg of the powder, 100 ml of 0.1 N hydrochloric acid was added and digested for 15 min at 60º C and filtered. The filtrate was then suitably diluted with 0.1 N hydrochloric acid and analyzed against a blank by spectrophotmetrically at 275.5 nm using a Schimadzu double beam spectrophotometer[12].

In vitro release studies

In vitro drug release studies were carried out using tablet dissolution test apparatus USP XXIII. The dissolution medium consisted of 0.1 N hydrochloric acid (pH 1.2) for first 2 hours and phosphate buffer (pH 6.8) for subsequent 10 hours. An amount of 900 ml of the dissolution fluids were used at 37±1° C with a stirring speed of 70± 2 rpm. Aliquots of 5 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution media maintained at the same temperature was replaced. The samples were analyzed by measuring the absorbance at 275.5 nm by UV spectrophotometer.

Data Treatment

Experimental results were fitted according to the following exponential equation[13].

$$M_t/M_8 = Kt^n$$

where, M_t/M_8 is the fractional solvent absorbed or drug released at time 't'; 'k' denotes a constant incorporating properties of the macromolecular polymeric system and 'n' is a kinetic constant which depends on and used to characterize the transport mechanism. For example, n=0.45 for case I or Fickian diffusion, when n=1, which is characterized by a square root of time dependence in both the amount diffused and the penetrating diffusion from portion n=0.89 for case II transport, which is completely governed by the rate of polymer relaxation, exhibits a linear time dependence in both the amount diffused and the penetrating swelling portion, n=0.45<n<0.89 for anomalous behavior or non-fickian transport, which exhibits whenever the rates of fickian and polymer relaxation are comparable.

Results and Discussion

The present investigation was undertaken to design, formulate and evaluate theophylline matrix tablets for sustained release dosage form. IR studies indicated good compatibility between drug, polymer and excipients. The granules of different formulation were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index. The granules indicated good flowability with the angle of repose values ranging from 25 to 27° according to fixed funnel method. The results of loose bulk density, tapped bulk density and compressibility index are shown in Table 2. The result of compressibility index was between 10.34±0.05 to 12.43±0.03, which is below 15%, indicating good to excellent flow properties. All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range (Table 3). The weight variation test indicates that all the tablets were uniform with low standard deviation values. The thickness and diameter values ranged from 3.59±0.041 to 3.68± 0.047 and 10.72±0.05 to 10.97±0.07 mm respectively. The hardness of all the tablets were between 5.3±1.1 and 5.6±0.8 kg/cm^2. The loss in total weight in friability test was in the range of 0.20 to 0.25%. The percentage drug content for different tablets formulations were varied from 99.5% to 101.2% indicating the uniformity in drug content as shown in Table 2. The matrix tablets containing 10% ethyl cellulose released 68.74% of drug at the end of 12th hour study, whereas drug release from tablets containing 20%, 30%, 40% and 50% of ethyl cellulose were 67.14%, 65.17%, 62.46% and 57.24 respectively, at the end of 12th hour. An inverse relationship was observed between concentration of polymer and release rate of theophylline from the matrix tablets. Upon model fitting analysis of matrix tablets, Peppa's model with 'n' values 0.8253 to 0.8860 and the correlation coefficient 'r' were found to be in the range of 0.9701 to 0.9746. This indicates that the release of theophylline from matrix tablet follow zero order kinetics with anomalous diffusion (Table 3).

Table 3. In vitro release kinetics of theophylline SR Matrix tablets

Formulation code	Higuchi	Peppa's	
	r	n	r
F1	0.9889	0.8253	0.9701
F2	0.9866	0.8468	0.9774
F3	0.9864	0.8572	0.9821
F4	0.9855	0.8703	0.9810
F5	0.9879	0.8860	0.9746

Conclusion

Formulation and evaluation of SR matrix tablets containing theophylline was found to be potential, cost effective and satisfactory *in vitro* release studies. In turn, it may enable to release the drug in a sustained manner for prolonged time and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance.

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