



BUOYANT SUSTAINED RELEASE TABLETS BASED ON POLYETHYLENE OXIDE

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ABSTRACT

The Purpose of the investigation highlights the formulation and optimization of floating tablets containing theophylline as a model drug. Formulations were optimized for type of filler and different concentration of polyethylene oxide. Sodium bicarbonate was used as a gas generating agent. A 3² randomized factorial design was employed in formulating gastric floating drug delivery system (GFDDS) with content of PEO (X₁) and ratio of starch 1500 to lactose as filler (X₂) were selected as independent variables. Study revealed that type of filler had significant effect on release of drug and floating property from different concentration of PEO. Lactose gave higher drug release with release mechanism towards zero order compared to starch 1500 which gave slow release with release mechanism towards diffusion based. Dissolution profiles were subjected to various kinetics drug release equations and found that drug release occurred in the direction of anomalous transport and diffusion mechanism with erosion. Optimized formulations were studied for effect of hardness on floating properties and dissolution medium on drug release. Hardness of tablet had major influence on floating lag time which might be due to decreased porosity. The predicted value agreed well with the experimental values, and the results demonstrate the feasibility of the model in the development GFDDS.

Keywords: Theophylline, factorial design, GFDDS, PEO, starch 1500 and lactose.

INTRODUCTION

Theophylline is a methyl xanthine derivative very effective in the chronic treatment of bronchial asthma and bronchospastic reactions. Its therapeutic concentration range is narrow (from 10 to 20 µg/ml) while toxicity usually appear at concentration above 20 µg/ml and the fluctuations of its serum concentrations can result in variability in clinical response.¹ In order to control these problem short biological half life of drug 8.7 hours favours development of sustained release formulation.^{2,3}

A traditional sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout GIT. About 40% of drug theophylline is bound to plasma proteins, primarily albumin.⁴

The Gastro retentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drug that have an absorption window in a particular region of gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability, reduces drug waste and improves solubility of drug that are less soluble in a high P^H environment.^{5,6}

The objective of this study was to develop an optimized GFDDS containing Theophylline as a model

drug. A peroral intragastric floating dosage form having a bulk density lower than that of gastric fluids and remaining buoyant on the stomach contents.⁷ several approaches are currently used to prolong gastric retention time. These include floating drug delivery system also known as hydrodynamically balanced system, swelling and expanding system, polymeric bioadhesive system, high density system and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. From the formulation and technology point of view, the floating drug delivery system is considerably easy and logical approach in development of gastro retentive drug delivery system.^{8,9}

Polyethylene Oxide (PEO) is among various hydrophilic polymers that, in presence of water, control the release of the active moiety either by swelling or swelling/erosion by forming a hydro gel. PEO has been proposed as alternative to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery system.¹⁰ Further it also has mucoadhesive properties which may assist in prolonging the gastric residence time.¹¹ The rate of drug release from hydrophilic matrix is dependent on various factors such as type of polymers, solubility of drug, polymer content, particle size of drug and polymer as well as types of filler used in the formulation.¹² The adjustment of polymer

concentration, viscosity grade and addition of different types and levels of excipients to the polymer matrix can modify the kinetics of drug release.¹³

MATERIALS AND METHODS

Theophylline was used as a model drug obtained as a gift sample from Micro Lab Ltd, Bangalore. Polyethylene oxide obtained from Ranbaxy Pvt. Ltd. Delhi. Starch 1500, Lactose, Sodium Bicarbonate and Microcrystalline cellulose were obtained as a gift sample from S.D. Fine chemicals Ltd, Bombay. Dicalcium phosphate and magnesium stearate were purchased from Loda chemie Ltd., Bombay. All other ingredients were of laboratory grade.

Full factorial design

Two factors were evaluated each at three levels and experimental trials were performed at all possible concentration. In the present investigation, content of PEO (X₁) and ratio of starch 1500 to lactose (X₂) were selected as independent variables. The diffusion exponent (n) and release rate constant (K), percentage drug release at 1 hour (Q₁), 4 hour (Q₄), 8 hour (Q₈) and 10 hour (Q₁₀) were selected as dependent variables. The experimental design with corresponding formulations are outlined in Table 1. Content of PEO was evaluated at 20%, 30% and 40% of total tablet weight while ratio of starch 1500 to Lactose was evaluated at 0:1, 0.5:0.5 and 1:0.

Preparation of Theophylline floating tablets

Theophylline (200mg) loaded floating tablets were prepared by direct compression using PEO, NaHCO₃ (15%) and filler by mixing in laboratory blender for 15 min. Amounts of various ingredients (mg) used in different formulation of gastro retentive tablets are presented in Table 1. The powder blend was then lubricated with magnesium stearate (1%) for additional 3 minutes and compressed on 16 station rotary tablet machine (cadmach, India). Compression force was adjusted to obtain tablets with hardness in range of 4-7kg/cm². All the preparations were stored in air tight container at room temperature for further studies.

Table 1: Formulation of theophylline floating tablet as per 3² factorial designs ^{14, 15.}

| FACTORIAL DESIGN 3 ² | 1:0 | 0.5:0.5 | 0:1 |
|---------------------------------|-----|---------|-----|
| p1 | F1 | F2 | F3 |
| p2 | F4 | F5 | F6 |
| p3 | F7 | F8 | F9 |

Polyethylene Oxide (PEO) concentration: p1-20%, p2-30%, p3-30%, Ratio of Starch 1500(PPS) to Lactose: 1:0, 0.5:0.5, 0:1, Each formulation contains: Theophylline - 200mg, Starch 1500 to Lactose - 15%, Sodium bicarbonate - 15%, Magnesium stearate - 1%, Microcrystalline Cellulose(MCC) - 4%, Di calcium phosphate Q.s.

In vitro buoyancy study

The In vitro buoyancy was characterized by floating lag time and total floating time. The test was performed using USP & XXIV type II paddle apparatus using 900ml of 0.1N HCl at paddle rotation of 100 rpm at 37 ±0.5°C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablets constantly float on dissolution medium were noted as floating lag time and total floating time respectively (n=3).¹⁶

Swelling study ¹⁷

Swelling of hydrophilic polymer such as PEO greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually also influence the release slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 8 hours. The percentage weight gain by the tablet was calculated by the formula.

$$\text{Swelling index (S.I)} = \{(W_t - W_0) / W_0\} \times 100$$

Where, S.I. = swelling index

W_t = Weight of tablet at time

W₀ = Weight of tablet before immersion.

In vitro drug release study

The in vitro drug release was performed using USP 24 Type II paddle apparatus using 900ml of 0.1N HCl at paddle rotation of 100 rpm at 37 ±0.5°C. The samples were withdrawn at predetermined time intervals for period of 10 hours and replaced with same volume of fresh medium. The samples were filtered through 0.45 µm membrane filter, suitably diluted and analysed at 271 nm using double beam UV/Vis spectrometer. The content of drug and cumulative percentage drug release was calculated using an equation obtained from standard curve. The times for 50% and 80% drug release were calculated based on korsmeyer and peppas model.¹⁸

kinetic modeling of drug release

The dissolution profile of all the batches was fitted to various models such as zero-order, first-order,¹⁹ Higuchi,²⁰ Hixcon-crowell²¹, Korsmeyer and peppas²²⁻²⁴ to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSION

Theophylline tablets provided good weight uniformity according to 5% of variation, referring to tablets with weight 800mg. All the formulations were within USP limits for friability (greater than 1% weight loss), hardness, and diameter as shown in Table.2

Table 2: It shows tablets data from physicochemical analysis and drug content. Relative standard deviations (%) are in parenthesis.

| Batch Code | Evaluation Parameters | | | | Drug Content (% w/w) |
|------------|--------------------------------|--------------------------------|----------------|--|-----------------------|
| | Average weight of tablets (mg) | Hardness (Kg/cm ²) | Friability (%) | | |
| F1 | 800±1.52 | 6.5 | 0.532 | | 103.44 |
| F2 | 800±1.80 | 5.5 | 0.658 | | 99.07 |
| F3 | 800±1.63 | 4.5 | 0.758 | | 101.01 |
| F4 | 800±1.23 | 7.0 | 0.498 | | 93.38 |
| F5 | 800±1.05 | 6.5 | 0.456 | | 97.60 |
| F6 | 800±1.65 | 6.2 | 0.689 | | 96.78 |
| F7 | 800±1.40 | 7.5 | 0.374 | | 98.65 |
| F8 | 800±1.80 | 6.5 | 0.412 | | 95.01 |
| F9 | 800±1.24 | 6.2 | 0.553 | | 94.74 |

In the present study considering its widespread applicability and excellent gelling activity in sustained release formulation Na₂CO₃ generates CO₂ gas in the presence hydrochloric acid present in dissolution medium. The gas generated is trapped and protected within the gel, thus decreasing the density of the tablet. As the density of the tablet falls below (density of water) the tablet becomes buoyant.

All the tablet of factorial design batches showed good invitro buoyancy, having the lag point between 4 and 5 minutes and remaining buoyant for 12 hours. Thus formulation F7 was selected for further studies as an optimized formulation because it gave best results in terms of the required floating behavior (lag time 4

minutes and duration 12 hours) and drug release was in accordance with the USP specification.

Cellulose polymers showed to be efficient to control the theophylline release from the tablets. As polymer percentages increased in tablet formulations, the amount of drug delivered decreased in dissolution test. The effect of fillers on drug release was observed in formulations using 20%, 30% & 40% and PEO with different ratio of starch 1500 to Lactose. Higher quantities of drug dissolved were obtained from formulations containing more amount of lactose as fillers. Release profile of theophylline from 3² factorial designs are shown in fig.1

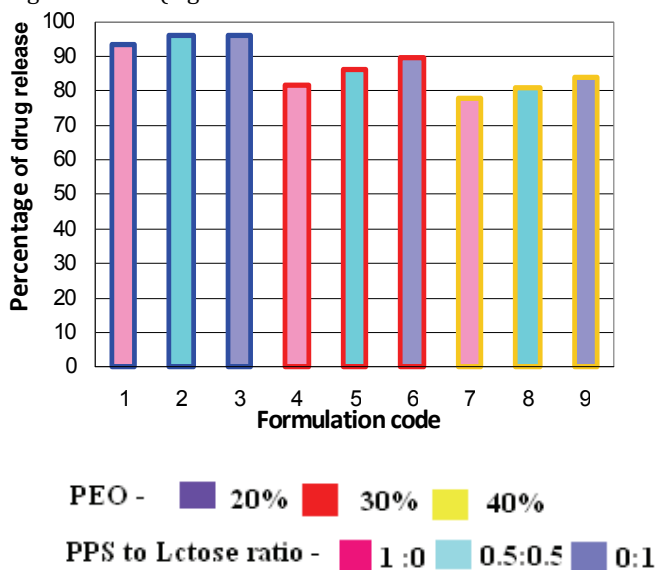


Fig. 2: Percentage drug release for Theophylline floating tablet on F1-F9 formulations.

In the present study, the higher swelling index was found for tablets of F7 containing 40% polyethylene oxide and starch 1500 to lactose ratio (1:0). Thus, the concentration of polymer and ratio of starch to lactose had major influence on swelling process, matrix

integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and concentration of starch ratio as shown in Figure 2.a, b, c

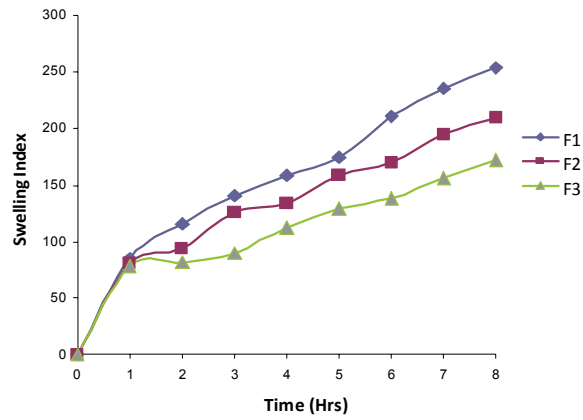


Fig. 2a: Swelling index of Theophylline floating tablet Formulations F1,F2 &F3

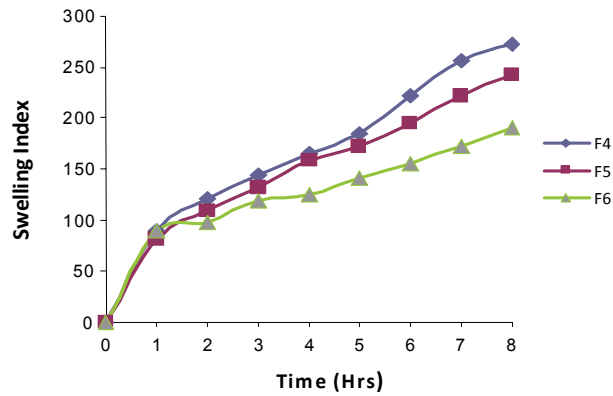


Fig. 2b: Swelling index of Theophylline floating tablet Formulations F4, F5 & F6.

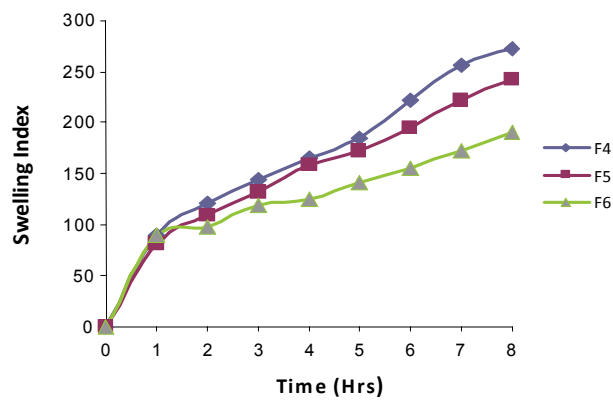


Fig. 2c: Swelling index of Theophylline floating tablet Formulations F7, F8 & F9.

It was found that drug release rate decreased as the concentration of polyethylene oxide (PEO) increased.

It was also concluded that the drug release rate was decreased as the starch 1500 (PPS) to lactose ratio

increased. As the lactose ratio increased then, the rate of drug release increased. The results of dissolution data from dissolution profile fitted to various drug release kinetic equations of zero order, first order, Higuchi, Hixon-crowell and korsmeyer-peppas having r , n and k . ' r ' is value of correlation coefficient, k is a release rate constant and n is the diffusional release exponent that could be used to characterize the different release mechanism as $n=0.5$ (Fikian diffusion), $0.5 < n < 1$ (anomalous transport), $n=1$ (case II transport i.e. Zero order release) and $n > 1$ (super case II transport) . The Higuchi model and peppas model found to be best fitted for all formulations F1-F9.

The Higuchi model and peppas model found to be best fitted in all formulations F1-F9. And higher correlation co-efficient value followed by first order kinetic drug release equation and the value of n was found to range from 0.510 2to 0.5923 which increases as the concentration of polymer increases, showing that the release mechanism shifted in the direction of anomalous transport and diffusion mechanism with erosion.

The result of invitro dissolution studies of formulation F1-F9 showed that tablet hardness had no (or little) effect on the release profile but was found to be determining factor with regards to buoyancy of the tablets.

A difference in tablet hardness resulted in differences in density and porosity, which are supposed to result in different release pattern of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet and formation of the gel barrier. Thus, tablets with low hardness and less floating lag time showed faster drug release compared with those having higher hardness as shown in Table 2.

CONCLUSION

This study discusses the preparation of gastro retentive tablets of theophylline. The effervescent-based floating drug delivery was a promising approach to achieve invitro buoyancy. The addition of gel forming polymer PEO and gas generating agent NaHCO_3 was essential to achieve invitro buoyancy. The results indicated that different concentration of PEO may play a dominant role in controlling drug release due to faster and stronger formation of gel layer which may nullify the influence of other variables.

In conclusion, PEO levels may be responsible for critical performance of hydrophilic matrixes as compared to ratio of starch 1500 to lactose, where

higher concentration of starch 1500 had certain degree of contribution to the kinetics of drug release.

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