

KINETIC STUDY OF THE IN VITRO RELEASE AND STABILITY OF THEOPHYLLINE FLOATING BEADS

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Received: 14 Oct 2012, Revised and Accepted: 16 Nov 2012

ABSTRACT

Theophylline floating beads have been investigated as a possible gastro-retentive dosage forms. Emulsion gelation method was used in the preparation of oil entrapped floating alginate beads. Drug content and floating properties of the prepared beads were determined. The data obtained from the *in vitro* release studies were fitted to different mathematical equations to describe the kinetic and the mechanism of the drug release from the prepared beads. The selected formulation was subjected to storage at 40 and 50°C / relative humidity of 75% for a period of three months. The dissolution profiles of both fresh and stored beads, for the selected formula, were compared on the basis of the similarity factor (f_2). Results revealed that theophylline alginate 1:1 ratio with oil concentration of 15% w/w showed optimum release (12 hrs) and floating time, more than 24 hrs, behavior. The kinetic models for the *in vitro* release data of the prepared formulations were in favor of Higuchi-diffusion and Korsmeyer Peppas models with non Fickian transport. It was proposed that, the prepared theophylline oil alginate beads delivered their active ingredient by coupled diffusion and erosion mechanisms. The stored beads showed good stability under the storage conditions for both temperatures relative to the fresh beads.

Keywords: Theophylline, Alginate, Floating bead, Kinetic models, Stability

INTRODUCTION

Floating drug delivery [1], mucoadhesion [2], and modified shape systems [3] are among the mechanisms available for controlling the gastric retention of solid dosage forms. Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and non-effervescent systems. Effervescent floating dosage forms are matrix types of systems prepared with the help of swellable polymers such as methylcellulose, chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms [4]. Roberto Ruiz-Caro et al reported the use of chitosan floating lyophilized formulations for gastric drug delivery of the antiviral acyclovir [5]. Bani-Jaber et al, evaluate the influence of Na-bicarbonate as an effervescent agent on the floating and sustained-release characteristics of tablets made of Eudragit E PO and/or Eudragit L-100- 55 as matrix formers [6]. Moreover, Das Saumya and Pattanayak Dharmajit prepared floating tablets of Glipizide employing Eudragit and two different grades of Hydroxy Propyl Methyl Cellulose polymers by effervescent technique in which sodium bicarbonate was incorporated as a gas-generating agent [7]. Non-effervescent floating dosage forms utilize a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form and the so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass [4].

Floating calcium alginate beads have been investigated as a possible gastro-retentive dosage form, and designed to enhance the bioavailability of certain drugs from oral preparations. These beads are prepared by dropping sodium alginate solution into a calcium chloride solution and the precipitated gel beads are then separated by filtration and freeze dried. Since, the density of the calcium alginate beads is less than that of gastrointestinal fluids; they therefore float [8]. These beads provide a sustained release formulation for 8-12 hours which was formulated hereafter utilizing oil entrapped alginate beads [9,10]

Theophylline is one of the xanthine drugs thought to be the most useful bronchodilators for moderate to severe reversible bronchospasm [11]. In addition, theophylline has been shown to have some anti-inflammatory activities, inhibiting the activity of CD4 lymphocytes *in vitro* and mediator release from mast cells. It can also inhibit bronchoconstriction produced by exercise and challenge testing. Despite the numerous attempts for new sustained release products of theophylline, an optimal therapeutic use continues to evolve [12].

The objective of the present study was to develop and evaluate theophylline gastro retentive drug delivery consisting of a drug-oil-alginate floating beads which used to control the release of the drug by the ionic gelation mechanism. Stability testing was investigated for the behavior of the prepared beads upon storage at variable temperatures.

MATERIALS AND METHODS

Materials

Theophylline Spectrum chemical Mfg. Corp., NJ, USA, Sodium alginate VWR Prolabo, UK, Calcium chloride Fluka Chemie, Buchs, Czech Republic, All other chemicals were of analytical grade.

Methods

Drug- Polymer Compatibility Studies

Infrared spectroscopy. Samples of approximately 2–3 mg of the pure drug, pure alginate and their physical mixture were mixed with KBr powder and compressed into transparent disc under pressure and then tested within the range of 4000–500 cm⁻¹ using FTIR spectrometer, Perkin Elmer Spectrum One, Model 16 PC, (Germany).

Differential scanning calorimetry. All the materials used in the infrared spectroscopic study were tested in this section. Around 4 mg of fresh samples were encapsulated into flat-bottom aluminum pans with crimped-on lids. The scanning was performed in a Shimadzu DSC TA-50 ESI DSC apparatus (Tokyo, Japan) at a speed of 10°C/min from 30–300°C in the presence of nitrogen at a flow rate of 30 mL/min.

Preparation and characterization of theophylline floating beads

Emulsion gelation method was used in the preparation of oil entrapped floating alginate beads (8; 13). Briefly, sodium Alginate was dissolved in water with stirring to give final concentration of

2%. Light paraffin oil (5-20% w/w) was added to the prepared polymer solution. Theophylline (200 mg) was then added. The mixture was homogenized for 15 minutes and was then extruded through 23G needle at a height of 20 cm in to 5% calcium chloride solution with gentle agitation at room temperature. The dropping rate was kept at 2ml/min. The formed beads were cured for 30 minutes, and were then separated by filtration. After washing the beads, they were dried in a tray dryer at temperature of 40 °C. The drug/polymer ratio was 1/1, 2/1 and 3/1 w/w.

The drug content in each formulation was determined by triturating known weight of the prepared beads in a glass mortar after which it was dissolved in 100 ml of 0.1N hydrochloric acid using water bath sonicator for 30 minutes. The resulting solution was filtered, diluted suitably and the absorbance of the resultant solution was measured using a UV/Visible spectrophotometer (PerkinElmer Lambda 25, Shelton, CT, USA) at 270.6 nm using 0.1 N hydrochloric acid as blank. The floating properties of the plain (no drug) and theophylline loaded beads were determined in which known weights of each formulation were placed in a 100 ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the beads to remain floated on the surface of medium was determined as the total floating time (TFT). The condition of the experiment was previously described by Rosa *et al* [14].

In vitro dissolution studies

United States Pharmacopeia (USP) Dissolution Testing Apparatus with paddle stirrer at 100 rpm was used to study the release rate of the prepared theophylline beads. The dissolution medium used was 900 mL of a 0.1 N HCl (pH = 1.2), and the temperature was kept at 37 °C. A quantity equivalent to 200 mg theophylline from each formulation was placed in the dissolution medium. Aliquots with replacements were withdrawn at a defined time intervals. The samples were filtered and diluted to a suitable concentration with 0.1N hydrochloric acid and the absorbance was measured spectrophotometrically at 270.6 nm. The percentage drug released was plotted against time to determine the release profile. Each sample was run in triplicate.

Kinetic study of the release data

The data obtained from the *in vitro* release studies were fitted to different mathematical equations to describe the kinetic and the mechanism of the drug release from the prepared beads. The kinetic models used were; zero order [15], Higuchi [16] and Korsmeyer-Peppas (17, 18) models. The goodness of fit was evaluated using the determination coefficient (R^2) values. Zero order release describes release that is independent on the concentration of the drug. Higuchi diffusion model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. Korsmeyer-Peppas model is used to analyze the release of

drugs from pharmaceutical polymeric dosage forms when the release mechanism is not well known or when more than one type of release phenomenon is involved. This model is useful for explaining the mechanism of drug release. The equations used for these kinetic models are listed below:

$$Q_t = k_0 t \text{ (zero order)..... Eq. 1}$$

$$Q_t = k_H t^{1/2} \text{ (Simplified Higuchi diffusion) Eq. 2}$$

$$M_t / M_\infty = Kt^n \text{ (Korsmeyer-Peppas equation) Eq.3}$$

Where Q_t is the amount of drug released at time (t), K_0 and K_H are the zero order release constant and Higuchi-diffusion rate constant, respectively, M_t/M_∞ corresponds to the fraction of drug released at time t , K is a constant comprising the structural and geometric characteristics of the microspheres, and n is the release exponent that depends on the release mechanism.

Stability studies

The selected formulation, F1, was subjected to storage at 40 and 50°C / relative humidity of 75% (maintained using a saturated solution of NaCl) for a period of three months [19]. At the end of the storage period, the formulation was tested for any change in the physical appearance, drug content, *in vitro* dissolution studies and floating behavior. The dissolution profiles of both fresh and stored beads were compared on the basis of the similarity factor (f_2) previously described by Moore and Flanner [20]. Each sample was run in triplicate.

RESULTS AND DISCUSSION

Drug- Polymer Compatibility Studies

IR spectroscopy and DSC were used as tools to detect incompatibility between theophylline and sodium alginate. Figure [1] shows the IR spectra of the pure drug, pure sodium alginate and the combination formulation. A characteristic peaks due to the active functional groups for theophylline were observed at 1668, 1567 and 3121 cm^{-1} corresponding to the carbonyl group (stretching), vibration of the pyrimidine ring and asymmetric aliphatic CH_2 , respectively [21]. These peaks were also observed in the drug-polymer combination, which indicates that, no major interaction occurred between the functional groups of the studied drug and alginate upon mixing. The DSC results confirmed the FTIR finding. The DSC thermograms of the pure drug, sodium alginate and drug-polymer combination are illustrated in figure [2] in which the thermograph of theophylline alone showed a melting endothermic peak at a temperature around 274 °C, associated with the melting of the drug which complies with previous results of Fini *et al* [21]. The thermograph of the drug-polymer combination showed the same characteristic peak of the drug which confirmed that, mixing the drug with sodium alginate did not affect the drug stability.

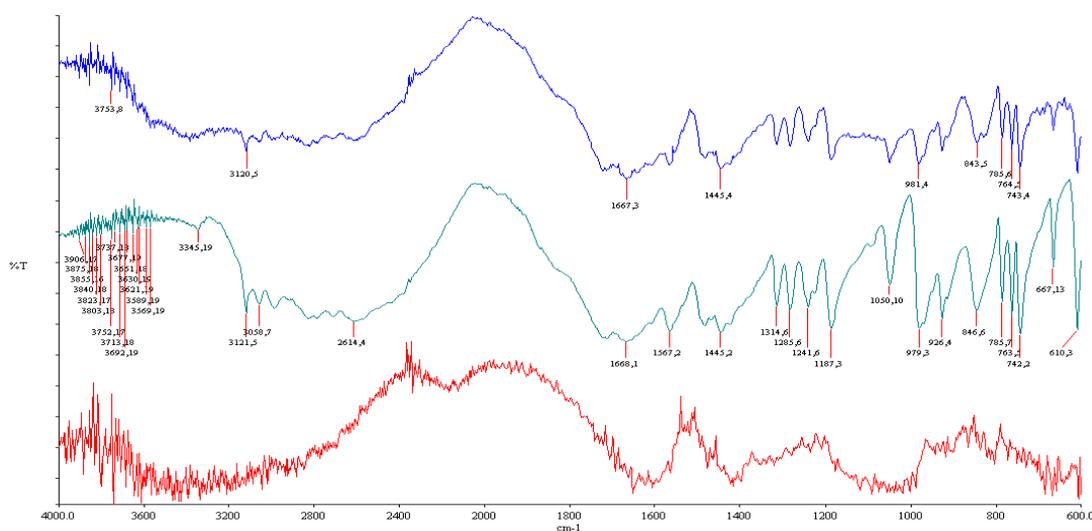


Fig. 1: FTIR spectrum of theophylline - sod. Alginate mixture, theophylline and sodium alginate

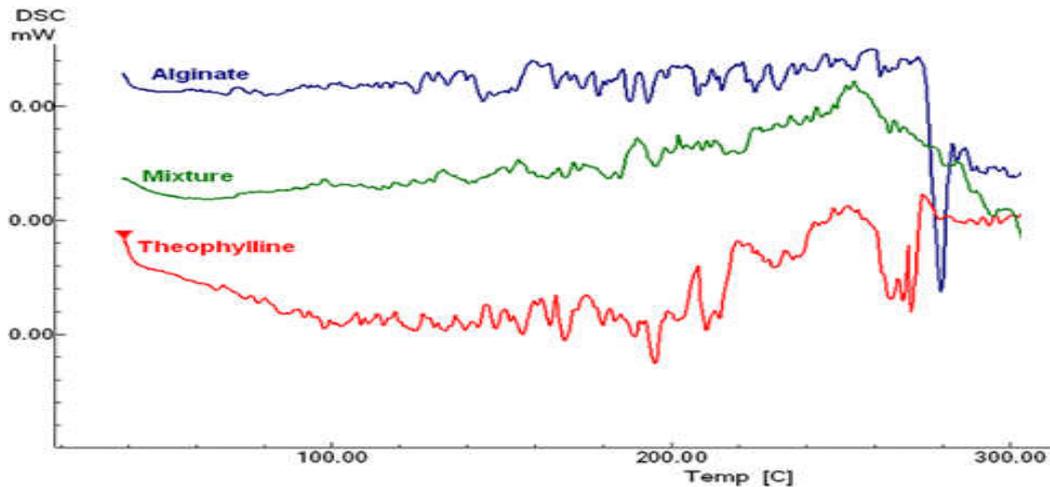


Fig. 2: DSC thermograms of pure theophylline (A), sodium alginate (B) and drug-polymer combination

Preparation and characterization of theophylline floating beads

Different formulations of Theophylline/ alginate were prepared using variable ratios of light paraffin oil (5-20%). At lower oil ratios (5-10%), the majority of the prepared beads were not able to float (results not shown). The emulsion property of the prepared beads was affected as the oil ratio increased [22]. In case of 20% oil ratio, oil began to leak and the prepared beads showed no significant difference in the release characteristics compared with the 15% oil ratio formulation. In addition, both oil ratios, 15% and 20%, showed floating time of more than 24 hrs. The results revealed that, the optimum floating behavior was achieved with 15% oil ratio.

The drug content of the selected formulations, F1, F2 and F3 formulae, is shown in Table [1]. The shape of the prepared floating theophylline beads varies from spherical to elongated or irregular shapes with changing sodium alginate concentration in the formulation (Figure 3). Spherical shape was obtained with plain beads formulation (no drug), 1:1 and 2:1 drug: alginate ratio. In case of 3:1 drug: alginate ratio the shape of floating beads was changed to irregular shape. This observation complies with the result obtained by Jaiswal et al., who showed that the spherical shape of the prepared beads is changed to disc like by the decrease in the

alginate ratio [9]. All the studied formulations (F1-F3) were shown to exhibit *in vitro* buoyancy and floatability of more than 24 hrs (table1). The presence of paraffin oil with lower specific gravity compared to simulate gastric fluids support this effect [13].

In vitro release studies

In vitro release studies performed in 0.1 N HCl revealed that higher concentration of oil slowed the release of the drug due to the formation of drug-oil dispersion system in the oil pockets of the beads (results not shown). The drug has to firstly diffuse from the oil pockets into the polymer matrix followed by transportation out of the polymeric matrix into the dissolution medium [23]. The optimum oil concentration was as 15% w/w.

It is evident that the release of theophylline from formulation F1-F3 containing 15% paraffin oil is retarded by decreasing drug: polymer ratio (figure 4). The amount released after 1hr (Q_{1hr}) and 8 hrs (Q_{8hr}) were significantly different at $p \leq 0.05$. This could be as a result of the higher alginate proportion. The increase in the amount of polymer leads to the formation of a thicker layer around the drug particles. Thus, the thicker polymer layers hold the drug effectively [9].

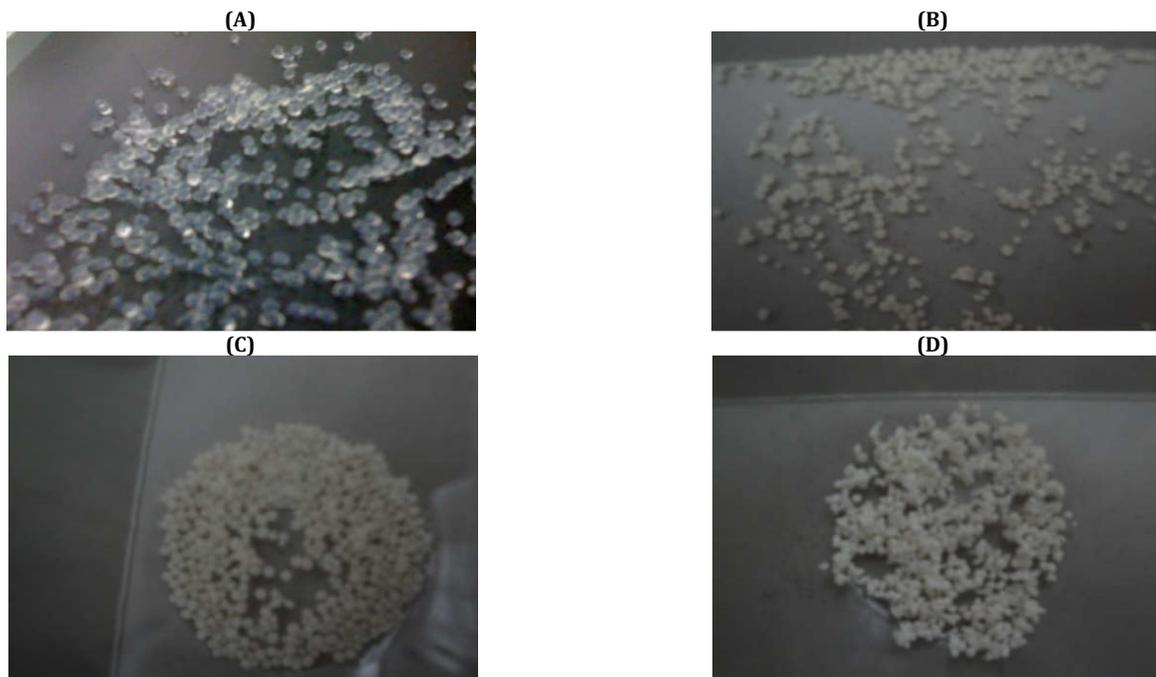
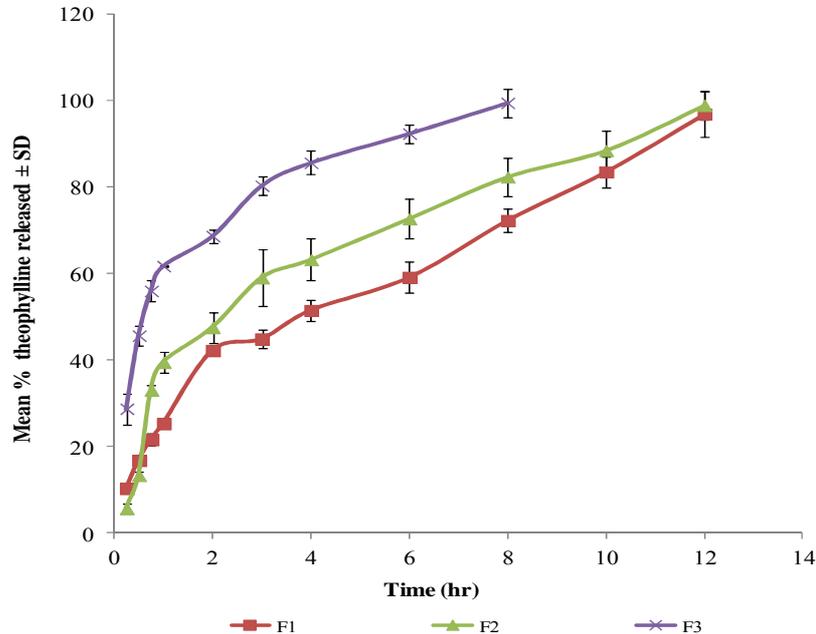


Fig. 3: Photoimages of plain floating beads (A), and medicated 1:1 (B), 2:1 (C), 3:1 (D) after drying.

Table 1: Theophylline floating beads composition, buoyancy, and drug content of the obtained beads

Criterion	F1	F2	F3
Drug to polymer ratio	1:1	1:2	1:3
Oil ratio (%)	15	15	15
Buoyancy (hr)	> 24	> 24	> 24
Drug Content (%)	60	78.5	75
Time for total amount released (hrs)	12	12	8

Fig. 4: Release profile of theophylline from different oil-alginate beads. Data presented as mean% dissolved \pm SD, n=3.

Kinetic study of the *in vitro* release data

To investigate the kinetics and mechanism of drug release, the release data were fitted to zero, Higuchi and Korsmeyer-Peppas models. The 'n' value that can be obtained from the slope of a plot of $\log M_t/M_\infty$ versus \log time (Korsmeyer-peppas model) is indicative of drug release mechanism. If n is 0.45 or less, the release mechanism follows Fickian diffusion, higher values (0.45 < n < 0.89) for mass transfer follow a non-Fickian model (anomalous transport), where release is controlled by a combination of diffusion and polymer relaxation. When n reaches a value of 0.89 or above, the mechanism of drug release is regarded as case-II transport or super case-II transport which means the drug release rate does not change over time and involves polymer

relaxation and chain disentanglement [24, 25]. It is worthy note that for determination of the exponent n, only the first 60% of drug release data should be used [17].

The kinetic analysis of the *in vitro* release data of theophylline from the prepared oil alginate beads microcapsules are presented in Table [2]. According to the determination coefficients (R^2), the *in vitro* release data were in favor of Higuchi-diffusion kinetics (F2) and Korsmeyer Peppas model (F1 and F3). The values of n were >0.45 and <0.89 indicating non Fickian (anomalous) transport for all the investigated formulations. Thus, it was proposed that these formulations delivered their active ingredient by coupled diffusion and erosion.

Table 2: Kinetic analysis and release data of theophylline from the prepared oil-alginate beads

Formulation	Determination coefficient (R^2)			n	Release mechanism	Q_{1hr}^*	Q_{8hr}^*
	Zero	Higuchi	Korsmeyer-Peppas				
F1	0.9462	0.9869	0.9904	0.553	Non-Fickian diffusion	25.30 \pm 0.31	72.25 \pm 2.78
F2	0.9137	0.9606	0.9276	0.879	Non-Fickian diffusion	39.50 \pm 2.47	82.31 \pm 4.30
F3	0.9748	0.9921	0.9927	0.561	Non-Fickian diffusion	61.73 \pm 0.11	99.46 \pm 3.32

* Q_{1hr} (amount released after 1 hr), Q_{8hr} (amount released after 8 hrs)

* Data presented as mean \pm SD (n=3)

Stability studies

The floating theophylline-oil-alginate beads formulation F1 was selected for stability studies based on their buoyancy and *in vitro* release data. The stability study was performed at 40°C and 50°C for 3 months. The relative humidity was kept constant at 75% R.H. The stored beads did not show any changes in their appearance or buoyancy behavior throughout the storage period. The drug content

remained within the acceptable limits with no significant change at $p \leq 0.05$.

The mean release data of fresh and stored beads were analyzed using the model independent mathematical approach of Moore and Flanner [20]. The similarity factor; f_2 , was calculated for comparison of dissolution profile before and after stability studies and found to be 77.04 and 66.08 after storage at 40°C and 50°C; respectively.

These values indicate good similarity between the dissolution profiles of fresh and stored beads at both temperatures (difference of less than 10%). The good similarity of the dissolution profiles is

clearly demonstrated in figure [5]. Thus, it is concluded that the selected formulation showed good stability under these storage conditions for at least 3 months.

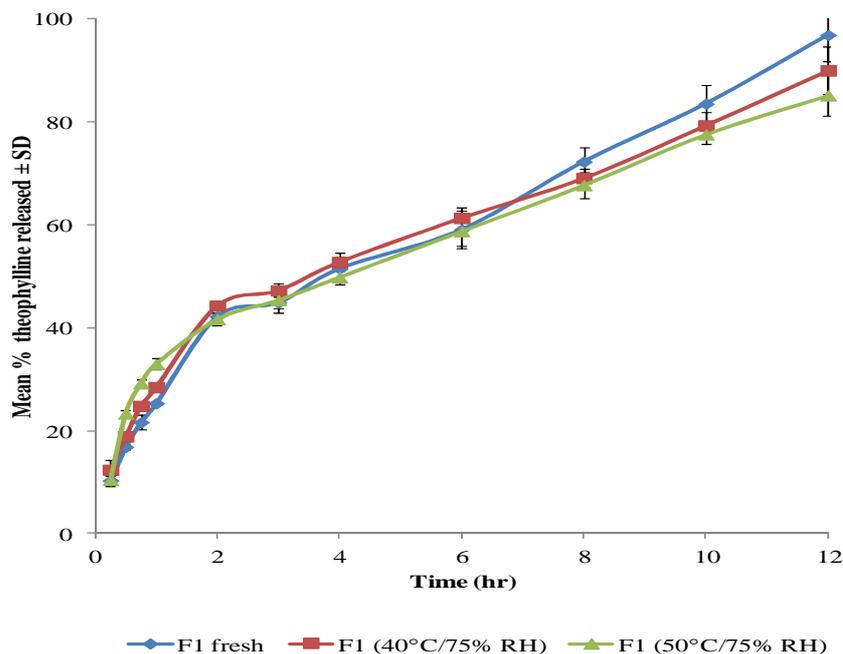


Fig. 5: Release profile of theophylline from fresh F1 formulation (F1 fresh), after 90 days storage period of relative humidity of 75% for F1 formulation at 40 °C (F1 °C/75%) and 50 °C (F1 °C/75%). Data presented as mean% dissolved \pm SD, n=3.

CONCLUSION

In conclusion, floating beads prepared by emulsion gelation method containing 15% oil remain buoyant for more than 24 hours and were successfully able to sustain the release of Theophylline for about 12 hours. The prepared beads delivered their active ingredient by coupled diffusion and erosion mechanisms. The floating beads of the selected formulae showed good stability for three months with respect to the release profile.

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