Research Article**Formulation development and evaluation of sustained release matrix tablets of Theophylline and Etophylline and study of polymers effect on dissolution rate****Mohammad Azaz Khan*, Senthil Selvi, P. Perumal***Department of Pharmaceutics, J.K.K. Natarajah College of Pharmacy, Komarapalayam – 638183 Tamil Nadu, India*

Received: 6 August 2018

Revised: 25 September 2018

Accepted: 27 September 2018

Abstract

Objective: The present investigation an effort has been made to increase therapeutic efficacy, reduce frequency of administration and improve patient fulfilment, by developing SR matrix tablets of Theophylline and Etophylline by using wet granulation technique incorporating different polymers combinations and fillers. **Materials and methods:** SR tablets of various combinations were prepared by using hydrophilic polymer: HPMC, sodium alginate and starch as fillers. The drug excipient mixtures were subjected to preformulation studies. The formulated tablets (F1-F10) were evaluated for different physicochemical properties and comply with the official standards. FTIR studies shown there was no interaction between drug and polymers. The optimized formulations (F3) were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Assay of the drug and formulation was carried out by using RP-HPLC method. **Results:** The in vitro release studies exhibits the release up to 82%, over a prolonged period of time which confirms the extended release profile of formulation (F3) after 6 hrs as compared to marketed formulation thus, drug in combination with HPMC were found to be effective in retarding the release of drugs. **Conclusion:** The SR matrix tablets of theophylline and etophylline shown better bioavailability, efficacy and potency compared with official standards.

Keywords: Theophylline, Etophylline, wet granulation technique, HPMC K100m, RP-HPLC, preformulation studies

Introduction

The oral route of administration is deliberate as the most widely accepted route because of its feasibility of self administration, solidity and easy manufacturing (Sastry et al., 2000; Seager, 1998). Though, it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route. Continuation of drug delivery systems in the stomach prolongs overall GIT time recuperating oral bioavailability of the drugs that are having site specific absorption from the stomach or upper part of the small intestine. Consequently different approaches have been proposed to hold the dosage form in the stomach including swelling, bio adhesive systems, and expanding systems and delayed gastric emptying devices to achieve gastric dwelling time for sustained drug release (Gambhire et al., 2007). The objective of any drug delivery

system is to provide a therapeutic amount of drug to the proper site in the body to attain rapidly and then continue the desired drug concentration (Gordon et al., 1990). This conscious control of drug release is achieved in sustained release dosage form as it prolongs the therapeutic effect by constantly releasing medication over an extended time after administration of a single dose (Vayas and Khar, 2002). The most employed method to adapt the sustained drug release is to include it in a matrix system. Matrix tablet is one of the most appropriate approaches for the preparation of the sustained release dosage forms. In real practice direct compression of drug, retardant material and additives is done to form a tablet in which drug particles are ingrained in the matrix core of the retardant. Dry or wet granulation technique may also be employed for the preparation of this type of tablets. Among the diverse approaches to prolong the drug action, formulation of matrix tablet has gained enormous popularity now days because it has the advantage of simple processing and a low cost of fabrication (Reddy et al., 2003). The loading dose is most suitable to include in a separate layer or in a coating applied to the tablet. An equation was developed by Higuchi (Higuchi, 1961; Higuchi, 1963) to

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DOI: <https://doi.org/10.31024/ajpp.2019.5.1.15>

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explain the drug release from the matrix base, which was later on extrapolated to the diffusion of solid drug dispersed in homogenous polymer matrices. Sustained release matrix tablet can be prepared in two ways, one is direct compression of the powder blend containing the drug, polymer and other additives and another one involves granulation prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients. Theophylline is a methylxanthine derivative and it is very efficient in the chronic treatment of bronchial asthma and bronchospastic reaction. The drug is well absorbed from GIT with 90-100% bioavailability. Its therapeutic concentration range is narrow from 10 to 20 µg/ml while toxicity usually appears at concentration above 20 µg/ml (Ojoe et al., 2007). Since theophylline having narrow therapeutic index and short half life (8 hrs in adults). Because of the relatively short plasma half life of theophylline. It can be used as a controlled release product so as to protect asthma patients from frequent attacks and to prevent from toxic side effects (Nandi, 1997). Etophylline or hydroxyl ethyl theophylline is a bronchodilator and is normally applied in combination with theophylline. The pharmacological actions of the etophylline are generally considered to be similar to those of theophylline (Tanaka et al., 2005). Unlike other xanthine derivatives, etophylline does not convert into theophylline in the body. Etophylline is mainly excreted unchanged by the kidneys and only a small fraction of it is metabolized by hydroxylation (Chauhan et al., 1986). This offers a wide therapeutic window and combination of etophylline and theophylline exhibits less frequent adverse side effects than an equivalent dose of theophylline alone. This study is an attempt to formulate theophylline and etophylline as sustained release matrix tablet for extending its release rate for prolong period of time thus increasing the bioavailability.

Materials and methods

Materials

Etophylline and theophylline were received as a gift sample from Arbro Pharmaceuticals Ltd, New Delhi (India). Acetonitrile, methanol and ortho-phosphoric acid were of HPLC grade supplied by Merck Ltd., India. Ammonium thiocyanate, ammonium di-hydrogen phosphate, cobalt (II) chloride, sodium hydroxide were purchased from S.D. Fine Chem. Ltd. Mumbai. Hydroxy propyl methyl cellulose, colloidal silicon dioxide, magnesium stearate were purchased from Himedia Chem Lab, Mumbai. Magnesium stearate and sodium alginate, starch was purchased from Loba chemicals Pvt. Ltd. Mumbai. Deriphyllin Retard 300 (German Remedies' Pvt. Ltd.) tablet was purchased from local market. All other ingredients used were of analytical grade. Triple distilled water was generated in house.

Drug excipient compatibility studies

Drug and excipient were analyzed by IR spectral studies by KBr pellet technique using Jasco FTIR-410. In this method, the drug and KBr were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FTIR spectra were recorded using KBr pellet method in the region of 400-4000 cm⁻¹. Spectra were recorded for pure drug, pure excipients and drug with excipients.

Particle size (Sieving methods)

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drug but also, in some instances, on their biopharmaceutical behaviour. Size also plays a role in the homogeneity of the final tablet size can also be a factor in stability. Many pharmaceutical powders, though, range in size from 1 to 120 µm. This test was performed with the help of sieves of different size. They were fitted in the platform of sieve shaker in such a way that the coarse sieve was placed on top corresponding to the finer sieves. Placed 10 gm of the etophylline & theophylline on the top and runned the machine to separate out the powder and after some time off the machine and took the weight of the powder remain on the sieve(s). Finally, calculated the % of powder retained on each sieve by the following equation:

$$\% \text{ powder retained} = \frac{\text{amount of powder retained}}{10} \times 100$$

Preformulation studies

Melting point

The melting point of etophylline and theophylline was determined using the open capillary method. The drug sample was filled into a capillary and placed in a melting point apparatus. The tube was heated and the temperature at which the drug melted was noted.

Loss on drying

The weighing bottle was dried for 30 minutes in oven then it was allow to cool. The bottle was accurately weighed with cover. Then cover was removed and 100mg of sample was placed in to the bottle and weight. Then sample was heated at 105°C for 3 hour. Then the bottle was removed and it was placed in the desiccators. Then the material was allowed to reach room temperature and weigh and calculate. The difference between successive weights should not be more than 0.5 mg.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

Determination of λ max of drug by UV spectrometer

100mg of etophylline and theophylline was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in an adequate amount of phosphate buffer pH 6.8 and the volume was made up to 100 ml with phosphate buffer pH 6.8 so as to obtain a stock solution of 1000 μ g/ml. A dilution of 6 μ g/ml concentration was made from the above stock solution with the phosphate buffer pH 6.8 and the resulting solution was scanned on a double-beam UV-visible spectrophotometer (Unicam Helios UV 052514) between wavelength ranges of 200 nm to 400 nm.

Calibration curve of etophylline and theophylline in phosphate buffer pH 6.8

A standard curve was prepared in the concentration range of 2-10 μ g/ml. For the preparation of calibration curve, stock solution was prepared by dissolving 50 mg of accurately weighed etophylline and theophylline in 50 ml of phosphate buffer pH 6.8. Further 10ml of this solution was pipette into 100 ml of volumetric and diluted to 100 ml with phosphate buffer pH 6.8. From this 0.2, 0.4, 0.6, 0.8 and 1 ml pipette into a series of 10 ml volumetric and volume was made up to 10 ml with phosphate buffer pH 6.8 to get 2,4,6,8 and 10 μ g/ml of etophylline and theophylline respectively. The optical density values of resulting solutions were measured at 273 nm in UV spectrophotometer

Calibration curve of etophylline and theophylline in water

50 mg of etophylline and theophylline was accurately weighed and transferred to a 50ml volumetric flask. It was dissolved in an adequate amount of water and the volume was made up to 50 ml with water so as to obtain a stock solution of 1000 μ g/ml. 10 ml of this solution was taken and made up to 100 ml with water, which gives 100 mg/ml concentrations (sub-stock solution). From this sub-stock solution, concentration of 2,4,6,8 and 10 μ g/ml in water solutions were prepared. The absorbance of the diluted solution was measured at 273 nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated by linear regression analysis.

Micromeritic properties (Lachman and Lieberman, 2009)

Angle of repose

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface. Angle of repose can be determined by following equation:

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is height of pile; r is radius of

base of the pile.

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula.

Bulk density = Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends was determined using the following formula.

TBD = Total weight of powder/Total volume of tapped Powder.

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 $\pm$ 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume. Carr's compressibility index was calculated using the following formula.

Carr's compressibility index (%) = [(Tapped density-Bulk density) $\times$ 100]/Tapped density.

Hausner's ratio

Hausner's ratio can be determined by the following equation.

Hausner's ratio = TBD / BD

Where, TBD - Tapped bulk densities & BD- bulk densities

Physical Compatibility Studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the pre formulation scientist must generate the needed information. Etophylline & Theophylline mixed

well with the excipients according to the formulas selected for the tableting and kept small portion of this mixed powder in cleaned and dried vial(s) in stability chamber at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75 \pm 5\text{RH}$ and room temperature. Physical observation has been carried out visually for 7 days.

Assay of etophylline and theophylline powder (HPLC method)

Assay or percentage purity of the etophylline and theophylline is done by HPLC method. The HPLC apparatus used for analysis was composed of a Perkin-Elmer 200 (Autosampler) equipped with a UV/VIS dual detector and generated data were analyzed using Total Chrom software. For chromatographic separation Lichrosphere (C-18) Column (250 X 4.6 mm, $5\mu\text{m}$) was applied. The chromatographic analysis was performed at ambient temperature on a RP-C18 analytical column with a mobile phase composed of Acetonitrile: Sodium acetate buffer pH 4.5 with glacial acetic acid (70:30 v/v) and was isocratically eluted at a flow rate of 2 ml/ min. A small sample volume of 20 μl was used for each sample run, being injected into the HPLC system. The chromatogram was monitored with UV detection at a wavelength of 273 nm and total analysis time was 12min for both drugs. The RT of theophylline & etophylline was found to be 6.74 ± 0.5 min and 8.85 ± 0.5 min respectively. The calculation of assay was done with the help of graph obtained and using the formula:

$$\% \text{ purity} = \frac{\text{Ave. sample area}}{\text{Ave. standard area}} \times \frac{\text{Standard dilution}}{\text{Sample dilution}} \times \frac{\text{Standard purity}}{100} \times 100$$

Selection of target release profile

The release profile of marketed product of Deriphyllin Retard 300 (German Remedie's Pvt. Ltd.) Tablet is taken as an innovator sample and its release profile is taken as standard profile.

Preparation of tablets

A total number of 10 formulations were prepared by wet granulation method. Required quantity of drug, polymers and diluents were mixed thoroughly and a sufficient quantity of

granulating agent (starch + gelatin) was added slowly to get dough mass. The mass was sieved through 10 mesh and dried at 50° for 2 h. the half dried granules was again pass through 16 no. mess and dried more for 2 h. the dried granules obtained finally were mixed with 2% talc and 1% magnesium stearate. Tablets were compressed using 22 mm * 10 mm caplet concave shaped punches to get tablets with target weight 400 mg on a 16 station automatic Cadmach tablet punching machine, at a compression force of 1.5 ton with hardness of all tablets maintained between 13-15 kg / cm^2 . In all formulations, the amount of the active ingredient is equivalent to 231mg of etophylline and 69mg theophylline. The composition of each tablet is shown in table 1.

Evaluation of tablets (Indian Pharmacopoeia, 1996)

Weight Variation

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeial specification, tablets with an average weight between 80 –250 mg, the percentage deviation should not more than $\pm 7.5\%$ and tablets with an average weight more than 250 mg should not be more than $\pm 5\%$.

Friability Test

Twenty tablets were selected at random; their surfaces cleaned with a hair brush to remove any adhering dust, weighed and placed in the friabilator (Electro Lab USP EF-2). They were then allowed to fall freely 100 times from a height of 6 inch at a speed of 25 rpm for 4 min. The tablets were then dusted and weighed. Any loss in weight due to fracture or abrasion was recorded as a percentage weight loss. The replicate determinations of each formulation were averaged. Friability was calculated by the following formula:

$$F = 100 \left[\frac{W_0 - W}{W} \right]$$

Table 1. Composition of etophylline and theophylline sustained release matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Etophylline	231	231	231	231	231	231	231	231	231	231
Theophylline	69	69	69	69	69	69	69	69	69	69
HPMCK-100	30.36	40.44	50.55	60.66	70.77	-	-	-	-	-
Sod. Alginate	-	-	-	-	-	30.36	40.44	50.55	60.66	70.77
Starch	20	20	20	20	20	20	20	20	20	20
Gelatin	5	5	5	5	5	5	5	5	5	5
Aerosil 200	3.37	3.37	3.37	3.37	3.37	3.37	3.37	3.37	10	10
Mg Stearate	3.37	3.37	3.37	3.37	3.37	3.37	3.37	3.37	3.37	3.37

F = Friability, W = Final weight, W₀ = Initial weight

Hardness Test

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm². Ten tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Uniformity of thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using digital vernier calliper.

In vitro dissolution studies

In vitro drug release studies from the prepared etophylline and theophylline SR matrix tablets were conducted using USP type I (basket) apparatus at 37°C at 50 rpm. Dissolution mediums used were 900 ml of 0.1 N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for first ½ and 1 h and changed to phosphate buffer (pH 6.8) for next 6 h time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV-Visible Spectrophotometer (Unicam Helios UV 052514). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.

Kinetics of drug release (Costa and Lobo, 2001)

The order of drug release can be assessed by graphical treatment of drug release data. A plot of % drug remaining versus time would be linear if the drug release follows zero order (ie. concentration independent release). A plot of log of % remaining drug versus time would be linear, if the drug release follows first order (ie. concentration dependent release).

The linear equation for zero order drug release plot is:

$$C_t = C_0 - Kt$$

Where, C_t = concentration remaining at time t , C_0 = original concentration, t = time, K = release rate

The linear equation for first order release plot is:

$$\log C = \frac{\log C_0 K t}{2.303}$$

A matrix device as the name implies, consists of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior. Obviously, for this

system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Deviation of the mathematical model to describe this system involves the following assumptions.

- 1) A pseudo steady state is maintained during drug release.
- 2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
- 3) The bathing solution provides sink conditions at all times and
- 4) The diffusion coefficient of drug in the matrix remains constant (ie. no change occurs in the characteristics of the polymer matrix).

Hydrophilic matrix tablets contain a water swellable polymer. On contact with gastric juices the tablet surface gels, impeding further liquid penetration into the tablet core and providing a rate controlling layer. Dissolution occurs at the gel core interface and drug diffuses out through the gelled layer. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion. The extent to which diffusion or erosion controls release depends on the polymer ratio.

Mechanism of release from erodible matrix has been described by Hopfenberg. A simple expression describing release from erodible is:

$$\left(1 - \frac{M_t}{M}\right)^{1/3} = 1 - Kt$$

Where, M_t = mass of drug release at time t , M = mass release at the infinite time, K = rate of erosion, t = time

Thus a plot of $[1 - M_t / M]^{1/3}$ versus time will be linear. If the release of drug from the matrix is erosion controlled.

In order to ascertain whether the drug release occurs by diffusion or erosion, the drug release data was subjected to following modes of data treatments.

- 1) Amount of drug release versus square root of time (Higuchi Plot).
- 2) $[1 - M_t / M]^{1/3}$ versus time.

Determination of drug content in tablets

Twenty tablets of the sustained formulation were weighed and crushed to fine powder. Powder equivalent to 231 mg etophylline and 69 mg theophylline was weighed and dissolved in 100 ml phosphate buffer (pH 6.8), sonicated for 10 min and filtered through Whatman filter paper No. 42, finally different concentrations of tablet sample were prepared by serial dilution technique. The total amount of

drug for each tablet was analyzed spectrophotometrically by using UV/ Visible spectrophotometer at 273nm and HPLC method. As we have chosen the HPLC so there is no chance of detection of any degradation products.

Accelerated stability studies

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F3), by keeping at $40 \pm 2^\circ\text{C}$, in air tight high density polyethylene bottles for three months, at RH $75 \pm 5\%$. Physical evaluation was carried out in each month.

Gellayer dynamics

When hydrophilic matrix former matrices were hydrated in cobalt (II) thiocyanate solution (6.8 gm cobalt chloride and 4.3 gm ammonium thiocyanate in 100 ml water) is permeated into the tablet along with water. Cobalt (II) thiocyanate gives a pink colour when diluted and forms a blue complex with compounds containing amino groups. Thus a blue colour was developed in the hydrated region of the tablet containing etophylline & theophylline while drug free hydrated region appeared pink due to cobalt (II) thiocyanate. The un-hydrated glassy core of the matrix retained its off- white colour. The junction of these regions mark the different fronts observed in a hydrating matrix and are marked in figure 1.

Figure 1. Hydrophilic matrix containing drug after hydration for 8 hours in cobalt (II) thiocyanate solution. The white region is the unhydrated core, blue region is the hydrated region-containing drug and pink region is the drug free hydrated polymer

Results and discussion

Spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}). The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug and in the physical mixture which confirms the absence of chemical interaction between drug and polymers (Figure 2). Matrix tablets were formulated according to wet granulation method. Granulation is the key process in the production of matrix tablet sustained release dosage form. The properties of granules which should be evaluated to ensure the proper formulation of the tablet dosage form are an important aspect in matrix tablet formulation. Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio (Table 2). All the formulated tablets (F1-F10) containing the active drugs were evaluated to find the physical properties like hardness, thickness, friability and drug contents (Table 3). In a weight variation test, the pharmacopoeial limit of percentage deviation for tablets whose weight is more than 250 mg is $\pm 5\%$. The average percentage deviation of all the tablets was found within the limit which was less than 2%. Hardness of the tablets was found acceptable and uniform from batch to batch variation. The drug content was also found uniform and within the prescribed limit. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. Results of friability test were also has been found within limit. Assay was carried out for finally selected formulation (F3) and the result was found to be 98.0% (etophylline) & 101.1% (theophylline) by HPLC Table 4 & Figure 3. The absorption maximum for drug was found to be 273 nm in pH 6.8 Phosphate buffer and water. The concentrations in range of $2\mu\text{g/ml}$ to $10\mu\text{g/ml}$, Regression coefficient r^2 Values of drug was found to be in water is $r^2 = 0.999$ and in pH 6.8 Phosphate buffer is $r^2 =$

Table 2. Results of physical evaluation of Pre-compression blend

Formulations	Angle of repose (degree $\pm$ SD)	Bulk Density (g/mL $\pm$ SD)	Tapped Density (g/mL $\pm$ SD)	Carr's Index (% $\pm$ SD)	Hausner's ratio (% $\pm$ SD)
F1	27.21 $\pm$ 0.63	0.433 $\pm$ 0.33	0.532 $\pm$ 0.18	18.60 $\pm$ 0.11	1.22 $\pm$ 0.03
F2	26.05 $\pm$ 0.02	0.392 $\pm$ 0.07	0.491 $\pm$ 0.18	20.16 $\pm$ 0.18	1.25 $\pm$ 0.06
F3	26.01 $\pm$ 0.08	0.396 $\pm$ 0.16	0.503 $\pm$ 0.04	21.27 $\pm$ 0.03	1.27 $\pm$ 0.03
F4	26.99 $\pm$ 0.15	0.441 $\pm$ 0.25	0.542 $\pm$ 0.14	18.63 $\pm$ 0.11	1.22 $\pm$ 0.07
F5	27.23 $\pm$ 0.17	0.426 $\pm$ 0.91	0.536 $\pm$ 0.04	20.52 $\pm$ 0.22	1.25 $\pm$ 0.02
F6	27.77 $\pm$ 0.18	0.430 $\pm$ 0.09	0.527 $\pm$ 0.21	18.40 $\pm$ 0.17	1.22 $\pm$ 0.10
F7	26.53 $\pm$ 0.05	0.413 $\pm$ 0.11	0.498 $\pm$ 0.19	17.06 $\pm$ 0.04	1.20 $\pm$ 0.21
F8	26.21 $\pm$ 0.19	0.424 $\pm$ 0.05	0.517 $\pm$ 0.05	17.98 $\pm$ 0.06	1.21 $\pm$ 0.09
F9	27.19 $\pm$ 0.16	0.432 $\pm$ 0.03	0.534 $\pm$ 0.13	19.10 $\pm$ 0.23	1.23 $\pm$ 0.05
F10	26.59 $\pm$ 0.33	0.430 $\pm$ 0.13	0.536 $\pm$ 0.06	19.77 $\pm$ 0.21	1.24 $\pm$ 0.03

Figure 2. IR spectra of A) Pure drug B) Sodium alginate C) HPMC K100 D) Drug + Sodium alginate E) Drug + HPMC K100

Table 3. Physical properties and drug content of SR matrix tablet

F code	Weight Variation (%)n=20	Thickness (mm) n=10	Hardness (kg/cm ²) n=6	Friability (%) n=10	% Drug Content n=3
F1	1.22	5.14±0.12	7.5 ± 0.14	0.38±0.24	98.03 ± 0.12
F2	1.01	4.97±0.24	7.4 ± 0.11	0.47±0.05	97.09 ± 0.12
F3	0.54	5.23±0.26	7.6 ± 0.07	0.37±0.12	99.17 ± 0.03
F4	1.02	5.23±0.33	7.4 ± 0.15	0.51±0.03	98.03 ± 0.12
F5	0.96	4.98±0.54	7.4 ± 0.08	0.47±0.22	97.09 ± 0.12
F6	1.45	4.99±0.09	7.6 ± 0.21	0.39±0.54	94.03 ± 0.12
F7	0.98	5.14±0.07	7.4 ± 0.12	0.47±0.16	101.0 ± 0.12
F8	1.25	5.03±0.06	7.3 ± 0.11	0.59±0.08	97.03 ± 0.12
F9	1.07	5.21±0.52	7.4 ± 0.12	0.55±0.12	98.09 ± 0.12
F10	1.50	5.24±0.50	7.5 ± 0.11	0.49±0.25	98.12 ± 0.12

Table 4. HPLC Chromatographic parameter of pure drug and formulation (F3)

Material	Average area	Height	RT	% Purity
Std. Theophylline	576206	25567	6.73	101.1
Test Sample	552891	25432	6.74	
Std. Etophylline	1716280	60927	8.82	98.0
Test Sample	1716690	64382	8.85	

Table 5. % Drug release of marketed formulation

Time (hours)	Limit (% drug release)	Observed value
0.5	5-15	13.16
01	10-30	24.18
02	20-50	39.43
04	30-65	55.96
06	60-90	87.74

Figure 3. Representative chromatogram of (A) Standard Drug (B) Formulation

0.995 Figure 4. The drug Release profiles for marketed formulation (Deriphyline 300) was generated in phosphate buffer 6.8 pH using USP Apparatus I at 50 rpm. The same conditions have been used for dissolution studies on prototype formulations (Table 5 & Figure 5). In vitro releases profile of etophylline & theophylline from different batches of formulated matrix tablets were illustrated in Table 6. The results of in-vitro drug release revealed that the etophylline & theophylline was

Figure 4. UV Graph of pure drug (A), calibration curve of drug in water (B), calibration curve of drug in phosphate buffer pH 6.8

Table 6 Data of In-Vitro drug release studies of sustained-release matrix tablets of etophylline & theophylline

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	24.8	18.14	13.37	15.9	17.19	35.94	30.08	21.64	20.68	14.96
1	37.8	33.08	13.37	18.79	24.50	55.64	52.46	41.34	33.08	25.77
2	56.28	44.20	38.80	38.16	34.98	86.47	81.06	75.03	68.67	63.27
4	84.56	76.93	55.96	57.23	53.42	90.92	97.27	94.41	91.23	80.43
6	100.45	94.09	81.70	75.66	70.58	103.31	105.5	104.58	101.72	96.00

Table 7 Summary of drug release kinetics of formulations (F3)

Time (hr)	$\sqrt{\text{Time}}$	Cumulative % release	Amount of drug release	% of drug remained	Log % of drug remained	$\left(1 - \frac{M_t}{M}\right)^{1/3}$
0.5	0.707	13.3	40.1	259.9	2.41	0.288
1	1	28.9	86.8	213.2	2.32	0.237
2	1.414	38.8	116.4	183.6	2.26	0.204
4	2.0	55.9	167.8	132.2	2.12	0.146
6	2.449	81.7	245.1	54.9	1.34	0.051

Figure 5. Release profile of market tablet (Deriphyllin SR 300 mg) **Figure 7.** Comparison of dissolution data of stability samples at room temperature by UV **Figure 6.** Comparison of dissolution data of stability samples at accelerated condition by UV

released in a controlled manner from all the formulations. The dissolution profile for both the formulations was found to be different from batch to batch. But the formulation of F3 was found to be the most desired release profile for the formulation. The release of formula F3 was most consistent, accurate and complete in comparison to that of the innovator sample of Deriphylline SR 300 mg tablet. After the evaluation of dissolution study it can be concluded that the F3 formulation for the matrix tablet containing HPMC K 100 possesses excellent drug release kinetics table 7. The mechanism of drug release from matrix tablet is through diffusion due to soluble nature of drug. The formulation of F3 also possesses good micromeritic and physical properties. The F3 formulation was selected for further

experiment. Stability studies were carried out by keeping the tablets at room temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \pm 5\%$ RH) and at accelerated temperature ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \pm 5\%$ RH) in stability chamber for 90 days. The result of stability studies conducted on F-3 revealed no change in physical appearance, hardness, drug content and in vitro distribution profile whereas IR spectrum attained exhibits no incompatibility. Hence F-3 formulation was found to be stable at tested temperature figures 6 & 7.

Conclusion

The sustained release matrix tablets of etophylline and theophylline were prepared by Wet granulation technique. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers. Etophylline and theophylline SR matrix tablets were formulated with different grades of Polymers. Among 10 formulations, F-3 is optimized based on the cumulative % drug release is 81.7 % in 6 hrs as compared to marketed formulation. The *in vitro* drug release data was plotted for various kinetic models and study showed formulation F3 were well suited to be extended release formulation. Final selected formulations were found to be nearly zero to zero order drug release, governed by diffusion through swollen matrix and erosion of the matrix, showing anomalous diffusion of nonfiction transport. From the results obtained, it can be concluded that formulation F-3 has achieved the objective of sustained drug release, patient convenience and cost effectiveness as a single daily dose of the drug and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

Conflicts of interest

The authors report no conflicts of interest

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