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FORMULATION AND EVALUATION OF ERODIBLE PULSATILE DRUG DELIVERY SYSTEM OF THEOPHYLLINE FOR NOCTURNAL ASTHMA

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ABSTRACT:

Theophylline, an asthmatic drug is based on the relaxation of bronchi. This drug has a great variability in clearance (elimination t½ 2-6 h, adults 6-12 h) and a narrow therapeutic range (7.5-20 µg/ml). Once or twice daily administration of controlled release preparations in patients with chronic obstructive pulmonary disease (COPD) is recommended for better patient compliance. The commonest side effects are headache, nausea and vomiting, abdominal discomfort and restlessness. There may also be increased acid secretion, gastroesophageal reflux and diuresis. At high concentrations convulsions and cardiac arrhythmias may occur. Hence, in the present investigation, an attempt has been made to fabricate a Formulation and Evaluation of Erodible Pulsatile Drug Delivery System of Theophylline for Nocturnal Asthma. Aim of the present work was to formulate and evaluate an oral, pulsatile drug delivery system to achieve time release of Theophylline, based on chronopharmaceutical approach for the treatment of nocturnal asthma. An asthmatic attack mainly takes place in the early morning at 4 o'clock. Pulsatile delivery system is an ideal approach for delivering drug when and where it required most. The basic design consists of a core tablets prepared by wet granulation method and it containing with an inner swellable polymers like HPMC K100 M& CARBOPOL 971P. The entire device was enteric coated with 5% cellulose acetate phthalate, which overcomes the gastric emptying time. The prepared Pulsatile tablets were evaluated for the drug content, and *in-vitro* release profile and other parameters.

Keywords: cellulose acetate phthalate ,Chronopharmaceutical, Pulsatile Drug Delivery System, Theophylline, Nocturnal Asthma.

INTRODUCTION

Circadian rhythms have been documented throughout plant and animal kingdom at every level of eukaryotic organization. These rhythms are endogenous in nature, driven by oscillation or clocks and persist under free running (e.g. constant darkness) conditions. The genes expressing the biological clock have been identified in various species. The important feature of endogenous biological rhythms is their anticipatory behaviour. Rhythmicity inherent to all living systems allows them to adopt more easily and to better survive under changing environmental conditions during the 24 hours of a day as well as during changing seasons. The science dealing with the phenomenon of rhythmicity in living organisms is called chronobiology. The branch dealing with the pharmacologic aspects of chronobiology is termed chronopharmacology, which may be further subdivided in to chronotherapy, chronopharmacokinetics and chronotoxicity[1].

Biological rhythms

A biological rhythm is a self-sustaining oscillation of endogenous origin. The spectrum of biological rhythms is broad . Short-period rhythms of a second or so are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuro endocrine system are but a few examples. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days.Included in this category are the ultradian (<20 h), circadian (~24h), and infradian (>28 h)

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

rhythms. Finally, long-period rhythms show oscillations of roughly a week, month, and year[2].

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM:

The term pulsatile drug delivery has often been used as a synonym to chronotherapeutic drug delivery. It is based on observation that there is an interdependent relationship between the peak- to-through rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs

NECESSITIES OF PULSATILE DDS:

1. First pass metabolism: Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. Biological tolerance: Drug plasma profiles are often accompanied by a decline in the pharmaco therapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

3. Special chronopharmacological needs: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. Local therapeutic need:

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5. Gastric irritation or drug instability in gastric fluid:

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (eg, peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting[3].

Asthma is one such disease where pulsatile drug where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning,leading to a state of relative hypercoagulability of the blood[4]. Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well exploited. Furthermore diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C- reactive protein and interleukin-6 of patients with rheumatoid arthritis.

Nocturnal asthma

Some biological rhythms come about monthly or even annually, asthma changes fairly predictably on a circadian cycle or 24 hour. Even in normal, lung function differs between day and night. The activity of the lung exhibit a circadian rhythm with a maximum around 4 p.m. and a minimum around 4 a.m. In asthmatic patients, the intensity of variation in lung function is as much as 50% in a day. Bronchial reactivity generally follows the same circadian cycle in asthmatic patients[5]. It can be defined as any sleep-related worsening of reversible airway disease. Shortness of breath or wheezing at night is symptoms generally shown[6].

MATERIALS AND METHODS

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The following materials were used:

Theophylline anhydrous (Darwins pvt Ltd, Vijayawada.),HPMC K100 M (Merck Specialities Pvt.Ltd, Mumbai),Carbopol 971P (Lubrizol Pvt.Ltd, Mumbai),Dicalcium phosphate dehydrate (Finar chemicals),Magnesium stearate (SD-fine chemicals) ,Sodium bicarbonate (SD-fine chemicals),Cellulose acetate pthalate (Sisco research labotratories Pvt.ltd, Mumbai),Acetone (Loba Chemie, Mumbai),Methanol (Loba Chemie, Mumbai), PEG 400 (Loba Chemie, Mumbai), Citric acid (CDH private Ltd,new Delhi), Magnesium stearate (SD-fine chemicals),Talc (SD-fine chemicals) All other reagents of analytical grade were used.

ANALYTICAL METHOD FOR THE ESTIMATION OF THEOPHYLLINE

A few analytical methods such as HPLC, UV/VIS spectrophotometric methods were reported for the estimation of Theophylline

Method used in the present work

An UV-VIS spectrophotometric method was used for the estimation of Theophylline.A stock solution of Theophylline was prepared in distilled water and the absorbance of Theophylline was measured at 271nm using Elico UV-VIS spectrophotometer SL 150. As the dissolution studies were carried out in 0.1 N HCl and 6.8pH buffer the calibration curves were constructed in these media

Reproducibility of the method

Reproducibility of the method was tested by analyzing six individually weighed samples of Theophylline. The relative standard deviation (RSD) in the estimated absorbance values was less than 1%. These low RSD values indicated the reproducibility of the analytical method

FTIR spectroscopy

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm-1 at a resolution of 1.0 cm- 1. The powder sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra.ATR analysis is less complicated than using KBR pellets, it is fast and a very small amount of the sample is needed. The spectra are shown in Fig 4.1-4.5.

Differential Scanning Calorimetry studies (DSC)

DSC was performed to characterize thermal changes in melthng behaviour of **Theophylline** with other excipients present in different formulations. Thermo grams were obtained by using a differential scanning calorimeter at a heating rate 10ºC /min over a temperature range of 50-45ºC. The sample was hermetically sealed in an aluminium crucible. Nitrogen was purged at the rate of 10 ml/min for maintaining inert atmospheres. The thermo grams were shown in Fig 4.6-4.10.

FORMULATIONS PREPARED BY WET GRANULATION METHOD

In the present investigation core of Theophylline tablets were prepared by wet granulation method and it containing with an inner swellable polymers like HPMC K100 M& CARBOPOL 971P. The entire device was enteric coated with 5% cellulose acetate phthalate, which overcomes the gastric emptying time.

PREPARATION OF TABLETS BY WET GRANULATION METHOD

Core tablets of Theophylline using different polymers were prepared by wet granulation method, as per formulae given in Table 3.5. Accurately weighed quantities of drug, polymer and di calcium phosphate were mixed together. Isopropyl alcohol in which water was previously dissolved was added to the above powder mixture and mixed well to form a coherent mass .Then the coherent mass was passed through sieve no#16 and the granules were dried at 40° $\pm$ 2°C for 2 hours. Dried granules were passed through sieve no#20. After the granules were evaluated, magnesium

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

stearate was added to the granules. Then the lubricated granules were compressed into tablets weighing 300mg using 10mm round punches on single punch tablet press (Cadmach, India) to a hardness of 4 and 5 kg/cm^2. The compressed tablets were dedusted and evaluated for various tablet properties[10].

Table no:01 Formulae of Theophylline core tablets

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Theophylline	200	200	200	200	200	200	200	200	200	200	200	200
HPMCK 100M	75	45	30	22.5	15	-	-	-	-	-	-	-
Carbopol- 971P	-	-	-	-	-	90	75	60	45	30	22.5	15
DCP	15	45	60	67.5	75	-	15	30	45	60	67.5	75
Magnesium stearate	5	5	5	5	3	5	5	5	5	5	3	3
Talc	3	3	3	3	-	3	3	3	3	3	-	-
Total Weight(mg)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Dip coating of optimized Core tablets: (Gayatri C et al.,) The outer polymeric layer consisting of cellulose acetate phthalate (CAP) dispersed in acetone using Poly Ethylene Glycol (PEG) 400 as a plasticizer. The compositions of coating solution are shown in Table 3.6. The outer polymeric layer was incorporated by dip coating method. Selected polymer solution was prepared and the tablets were dipped in the coating solution and simultaneously dried with the help of hot air. The coated tablets were then dried in hot air oven at 40 ºC until the coat is dry. Then dried tablets were weighed and re-coated in the same procedure until expected weight gain was obtained by deep coating. For the CAP coating, coating procedure carried out until the tablets resist disintegration in pH 1.2 buffers for minimum period of two hrs.

Table no: 2 Composition of CAP coating solution

Composition	Quantity
Cellulose acetate phthalate	5%
PEG 400	0.1%
Acetone	100Ml

Preformulation studies:[7]

Preformulation testing is the first step in the rational development of the dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and combined with excipients. The objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

The following Preformulation studies were performed on Theophylline API:

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Determination of densities:[8]

Apparent density (bulk):

Bulk density is the ratio of given mass of powder to its bulk volume. The bulk density, as a measure used to describe packing materials or granules, was determined transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The powder was levelled carefully without compacting and the unsettled apparent volume (Vo) was noted. The bulk density in g/mL was calculated by the formula:

Bulk density = M/Vo

Where M is the weight of the sample taken

Tapped density:

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted, and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula[15].

Tapped density = Weight of sample in grams/tapped volume

Angle of repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane[11].

$$\text{Tan } \Theta = h/r$$

$$\Theta = \text{Tan}^{-1}\, h/r$$

Where, Θ = angle of repose

h = height

r = radius

A funnel was fixed at a height of approximately of 2-4 cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of powder.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Carr's index (compressibility):

The compressibility and Hausner's ratio are the measures of the propensity of a powder to be compressed. As such, these are the measures of relative importance of inter particulate interaction. In a free flowing powder, such interactions are of less significant and the bulk and tapped densities will be closer in value. For poor flowing materials, the bulk and tapped densities will be observed. These differences are reflected in the compressibility index [12]and the Hausner's ratio. Based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula

$$\% \text{ compressibility} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Hausner's ratio:

The ratio of tapped density to the bulk density of the powders is called the Hausner's ratio.

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

EVALUATION OF TABLETS:

Drug content

Five tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 20 mg of Theophylline was transferred to a 100mL volumetric flask, and the Theophylline was extracted into 75mL distilled water. This solution was filtered and collected in to a 100mL volumetric flask and made up to the volume with methanol. The solution was suitably diluted with distilled water and the absorbance was measured at 271nm. The estimations were carried out in triplicate and the results are reported .

Hardness: [9]

Six tablets from each batch were selected and hardness was measured using Monsanto hardness tester (M/s Campbell Electronics, MODEL EIC-66, India). The results were given in Table 4.3.

Friability (%F) :

Six tablets from each batch were selected randomly and weighed. These pre weighed tablets were subjected to friability testing using Roche friabilator (M/s Campbell Electronics, India) for 100 revolutions. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability. The results were given in Table 3.

$$\%F = 1 - (\text{loss in weight} / \text{initial weight}) * 100$$

Weight variation:

Weight variation was calculated as per method descried in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

than the percentage listed in Table and no tablets differ in weight by more than double that percentage. The results were given in Table 3.

Table: 3.9 Weight variations allowed as USPXX- NF XV

Average weight of tablet (mg)	Percentage difference allowed
≤130	10
130-324	7.5
>324	5

In-vitro dissolution studies:

The tablet samples were subjected to *In-vitro* dissolution studies using USP Type II dissolution apparatus at 37±0.5°C and 50 rpm speed. To mimic the Gastrointestinal conditions, as per the official recommendation of USFDA, 900 ml of 0.1 N HCL was used as dissolution medium for initial 2hr and 6.8pH buffer for next 10 hr. Aliquot equal to 5 mL was withdrawn at specific time intervals and replaced with fresh buffer. The aliquots were filtered through using 0.45µ nylon filters, diluted and drug release was determined spectrophotometrically at a wavelength[1] of 271 nm by comparing with the standard calibration curve. Percent of Theophylline dissolved at different time intervals and various dissolution parameters were given in Tables and represented in Fig.

RESULTS AND DISCUSSIONS:

In the present investigation, an attempt has been made to fabricate a Formulation and Evaluation of Erodible Pulsatile Drug Delivery System of Theophylline for Nocturnal Asthma.So, in the present investigation hydrophilic polymers like HPMC K100 M& CARBOPOL 971P have been used as drug release retarding polymers[14]

ANALYTICAL METHOD FOR THE ESTIMATION OF THEOPHYLLINE

The present analytical method obeyed Beer's law in the concentration range of 2-10µg/mL

and is suitable for the estimation of Theophylline from different solutions. The values of R^2

(regression coefficient) for the linear regression equations were found to be in the range of

0.997-0.99 (Figs 1).

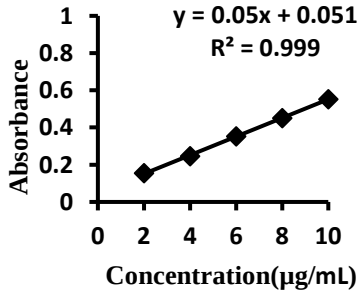


Fig:1 Calibration curve for Theophylline in 0.1 N HCl

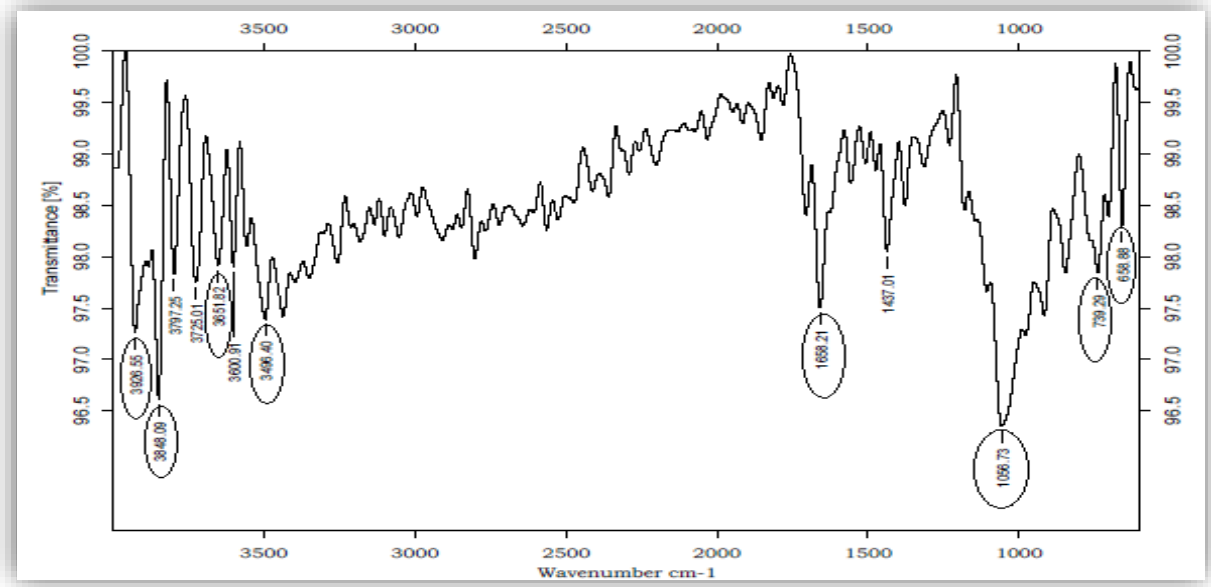
FT-IR STUDIES:

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The FTIR studies were done to characterize the drug. The infra red spectrum for pure drug and polymers are given in Fig.2-3.To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Theophylline and polymers were analyzed over the range 600-4000 cm $^{-1}$.It showed that there was no significant interaction between the drug and polymer and they are compatible with each other .

Table:3 Showing FTIR spectral wave numbers and functional groups of Theophylline

FUNCTIONAL GROUP PRESENT	PEAK OBSERVED AT WAVE NUMBER(cm^{-1})
N-H Stretching	3454.54
C-H Stretching	2915.16
C-O Stretching	1658.20
C-N Stretching	1178.19
C-N-H Bending	845.66
C-H Bending	738.61
C-C=O Bending	640.63



ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Fig 2 FTIR Spectrum of Theophylline+ HPMC K100

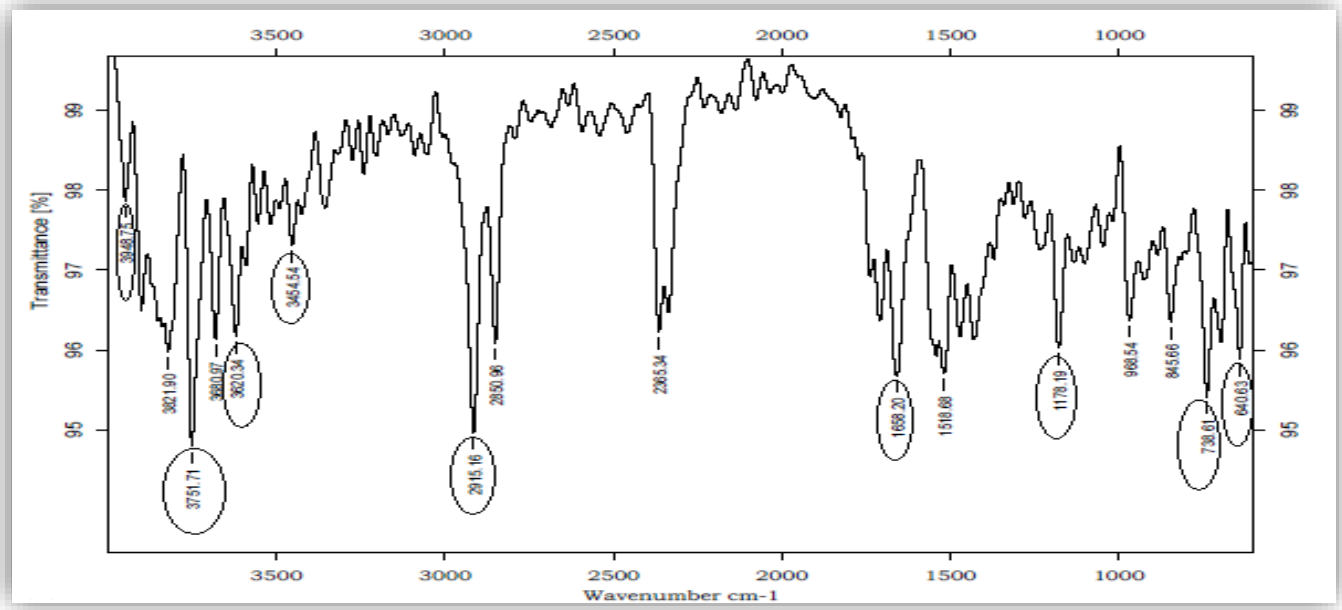


Fig 3 FTIR Spectrum of Theophylline+ Carbopol 971P

DSC Differential scanning calorimetry:

DSC was performed to characterize thermal changes in melting behaviour of Theophylline with other excipients present in different formulations. Thermo grams were obtained by using a differential scanning calorimeter at a heating rate 10^{0}c/min over a temperature range of 50 – 300 ^{0}c.The samples was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 10 ml/min for maintain inert atmosphere. The prominent and sharp endothermic peak at ^{0}c in the pure Theophylline (Fig 4.6) represents the melting point of Theophylline .In all the DSC spectrums the characteristic drug melting point was observed with slight changes in terms of broadening or shifting towards lower temperature. This could be due to mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility. From these results there was no drug excipients interaction. This indicates the choice of excipients used in the formulation of matrix tablets were suitable.

PREPATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF THEOPHYLLINE:

In the present investigation Core tablets of Theophylline using different polymers were prepared by wet granulation method. The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, and compressibility index and hausner ratio.

Evaluation of Tablet formulations:

Pre- compression parameters:

The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner ratio.The angle of repose was found to be $40^{o}10'$ ±0.66 – $30^{o}50'$ ±0.74. It indicates that granules have a good flow property. The bulk density and tapped density was found to be in the range of 1.014±0.03 - 1.414±0.01gm/cc and 0.854±0.04 - 1.678±0.02 gm/cc respectively. The compressibility and hausner ratio was found to be 10.14±2.85 to 15.91±1.78 and 1.11±0.04 to 1.20±0.04 indicating good flow character of the granules (table-4.2). All the results are within the prescribed limits.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table no: 4 Granules flow properties for all the formulations

Parameters / Formulations	Angle of Repose (θ)	Bulk density(ρ_b) (gm/cc)	Tapped density(ρ_t) (gm/cc)	Compressibility index (%)	Hausner's ratio
Pure drug	40.1±0.66	1.414±0.01	1.614±0.01	12.9±1.74	1.17±0.04
F1	30.5±0.74	1.312±0.01	1.513±0.01	11.16±1.66	1.12±0.02
F2	33.8±0.67	1.398±0.01	1.601±0.01	12.34±1.27	1.15±0.02
F3	34±0.62	1.040±0.00	1.392±0.01	10.15±1.86	1.11±0.04
F4	33.2±0.69	1.143±0.01	1.298±0.02	10.14±2.85	1.13±0.03
F5	35±0.77	1.345±0.01	1.539±0.04	13.93±3.51	1.18±0.02
F6	34.8±0.79	1.045±0.02	1.223±0.07	12.21±1.65	1.17±0.05
F7	33.6±0.63	1.014±0.03	1.239±0.06	12.07±1.45	1.15±0.06
F8	35.5±0.62	1.092±0.04	1.208±0.04	15.28±1.89	1.18±0.01
F9	36.4±0.65	1.078±0.02	1.234±0.06	15.91±1.78	1.20±0.04
F10	36±0.74	0.760±0.03	0.854±0.04	10.59±1.86	1.15±0.01
F11	35.5±0.72	1.423±0.04	1.645±0.08	14.42±1.74	1.16±0.04
F12	34.2±0.79	1.420±0.06	1.678±0.02	14.71±1.65	1.14±0.02

Post compression parameters:

The prepared tablets were subjected to various quality control tests like drug content, weight variation, hardness and friability. All the results are within the prescribed limits values are given in Table 5.

Drug content

Drug content of all the formulations were found to be in the range of 98 to 100 % (table-4.3).

Uniformity of weight

The results summarized in Table 5.showed that a good degree of uniformity of weight was achieved for all the batches of tablet formulations prepared. The present deviation did not exceed 5%, indicating excellent uniformity of weight in all batches of tablets.

Mechanical properties

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

All the batches of tablet formulations prepared, exhibited good mechanical properties with regard to both hardness and friability. The values are given in Table 4.3. No significant difference in hardness values within the batches of tablet formulations prepared was observed, in the range of 4-5 kg/cm^2. The friability values of all the batches of tablet formulations prepared are less than 0.5%.

Table no: 5 Post compression parameters of all prepared formulations

Parameters / Formulations	Hardness (kg/cm^2) ± S D	Percent Friability	Weight Variation ± SD	Drug content (mg/tab) ± SD
F1	4.37 ± 0.05	0.25±0.05	300 ± 2.14	200 ± 1.25
F2	5.70 ± 0.10	0.24±0.09	300 ± 1.12	198± 1.98
F3	5.57 ± 0.15	0.30±0.04	300 ±3.15	199 ± 1.67
F4	4.81 ± 0.10	0.23±0.07	300 ± 2.10	200 ± 1.25
F5	5.20 ± 0.10	0.28±0.06	300 ±4.04	200 ± 0.98
F6	5.37 ± 0.12	0.15±0.02	300 ±2.06	200 ± 0.65
F7	4.81 ± 0.08	0.19±0.03	300 ± 3.08	199 ± 0.54
F8	4.53 ± 0.06	0.16±0.05	300 ± 2.04	198 ± 0.78
F9	4.66 ± 0.15	0.26±0.01	300 ± 4.01	200 ± 0.85
F10	5.71 ± 0.12	0.28±0.04	300± 2.02	199 ± 0.97
F11	5.72 ± 0.11	0.26±0.06	300 ± 3.03	198 ± 0.36
F12	5.50 ± 0.10	0.29±0.07	300 ± 3.05	200 ± 0.84

***IN VITRO* DISSOLUTION STUDIES:**

The formulated formulations (coated & un coated) were subjected to *in- vitro* dissolution studies in 900mL of 0.1N HCL buffer for initial 2hr and later in 6.8 buffers for next 10hr to mimic *in- vivo* GI conditions.

Swelling systems consists of hydrophilic polymers and in the presence of water they absorb a significant amount of water and form a gel. As dissolution medium penetrates into the matrix, swelling of polymer material starts and drug molecules begin to move out of the system by diffusion. Swelling therefore modifies the drug release and compared with porous, inert, non-swelling matrix, the porosity and tortuosity of swellable matrix are primarly attributed to the polymer swellability. In swellable systems, the drug release occurs by water absorption matrix swelling and subsequent drug diffusion through the gel layer. In the present investigation swellable polymers like HPMC K100 M and Carbopol 971P were used to to retard the Theophylline release.

The formulations F1-F5 & F6-F12 were formulated by wet granulation method using HPMC K 100 M & CARBOPOL 971P Polymers at a concentration of 25, 15,10,7.5, 5% (W/W) & 30,25, 20,15,10,7.5 ,5% (W/W) respectively with DCP as diluent. In F1 the HPMC K 100 M prolonged the drug release until 12hr, but with less percent of drug release, with about **63.68±0.37**, it may be due to formation of more viscous gel layer around the tablet at high concentration of Polymer, data was given in table 4.4 & shown in fig 4.11. In F2 was formulated by decreasing the concentration of HPMC K 100 M and the release was high when compared to F1 i.e. **70.05±0.23**%

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

data was given in table 4.5& shown in fig 4.12. In F3 & F4 were formulated by the polymer concentration of 10 and 7.5% W/W), release was found to be **80.11±0.12 & 90.57±0.1** respectively data was given in table 4.6-4.7& shown in fig 4.13-4.14. In order to show better prolonged action along with high percent drug release F5 was formulated with 5% (W/W) concentration of HPMC K 100 M. The formulation F5 not only showed prolonged action but also gave high percent drug release at the end of 12hr with about **98.49±0.21**% data was given in table 4.8 & shown in fig 4.15. Among the F1, F2, F3,F4,& F5 formulations F5 showed better prolonged action with high percent drug release at the end of 12 hr. The percent drug release among the formulations was in order of F5 > F4>F3> F2> F1. Based on the above characters F5 was selected as best formulation.

In F6 formulation drug release was found to be **60.47±0.37%** at 12hr, it may be due to formation of more viscous gel layer around the tablet at high concentration of Polymer (CARBOPOL 971P) i.e 30% (W/W) data was given in table 4.9 & shown in fig4.16.The percent drug release at the end of 12hr for the formulations F7, F8, F9 was **64.36±0.42%,71.27±0.16%&77.23±0.12%** respectively data was given in table 4.10-4.12 & shown in fig 4.17-4.19. The percent drug release at the end of 12hr for the formulations F10,F11,F12 was **85.56±0.13%, 85.56±0.13% & 91.70±0.16 %** respectively data was given in table 4.13-15 & shown in fig 4.20-4.22. Among the F6, F7, F8,F9, F10,F11 & F12 formulations F12 showed better prolonged action with high percent drug release at the end of 12 hr. In order to show better prolonged action along with high percent drug release F12 was formulated with 5% (W/W) concentration of CARBOPOL 971P . The percent drug release among the formulations was in order of F6>F7>F8>F9>F10>F11>F12. Based on the above characters F12was selected as best formulation.

***In vitro* drug release of optimized formulation**

The selected formulations F5 & F12 were enteric coated with cellulose acetate phthalate by dip coating method.

5% w/v CAP solution with 1%v/v PEG 400 as plasticizer was tried initially (F13)with a 5% Coating weight gain and gave Theophylline release of **11.50±0.56%** in pH 1.2 acidic buffer at 2h and **73.47±0.41%** at the end of 10h in pH 6.8 phosphate buffer, data was given in table 4.16 & shown in fig 4.23. In (F14) tried with a 10% coating weight gain and gave Theophylline release of **10.61±0.58%** in pH 1.2 acidic buffer at 2h and **79.67±0.49%** at the end of 10h in pH 6.8 phosphate buffer, data was given in table 4.17& shown in fig 4.24.

Where as, (F15)with a 15% Coating weight gain and gave Theophylline release of **0±0%** in pH 1.2 acidic buffer at 2h and **81.60±0.17%** at the end of 10h in pH 6.8 phosphate buffer, fulfilled the requirements for Pulsatile Drug Delivery System, data was given in table 4.18 & shown in fig 4.25. Further trails were carried out with 15% weight gain of the coating solution. In F16 Theophylline release was found to be **0±0%** in pH 1.2 acidic buffer at 2h and **80.37±0.46%** at the end of 10h in pH 6.8 phosphate buffer**,** data was given in table 4.19 & shown in fig 4.26.

From the results of *in vitro* dissolution study, formulation F15 & F16 were found to be optimized in terms of achieving the drug delivery system, consistent with the requirement of chronopharmaceutical drug delivery, providing drug delivery rate of more than 80% in 10-12h of duration.

Minimal or no release of Theophylline in upper GIT especially in stomach is great interest and can be achieved by enteric coating. Morever, prolonged release in small intestine may enhance the absorption of theophylline and results in improved therapeutic efficacy by shorter onset of action. Hence the developed enteric coated theophylline tablet for will have better therapeutic efficacy and more patient compliance.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

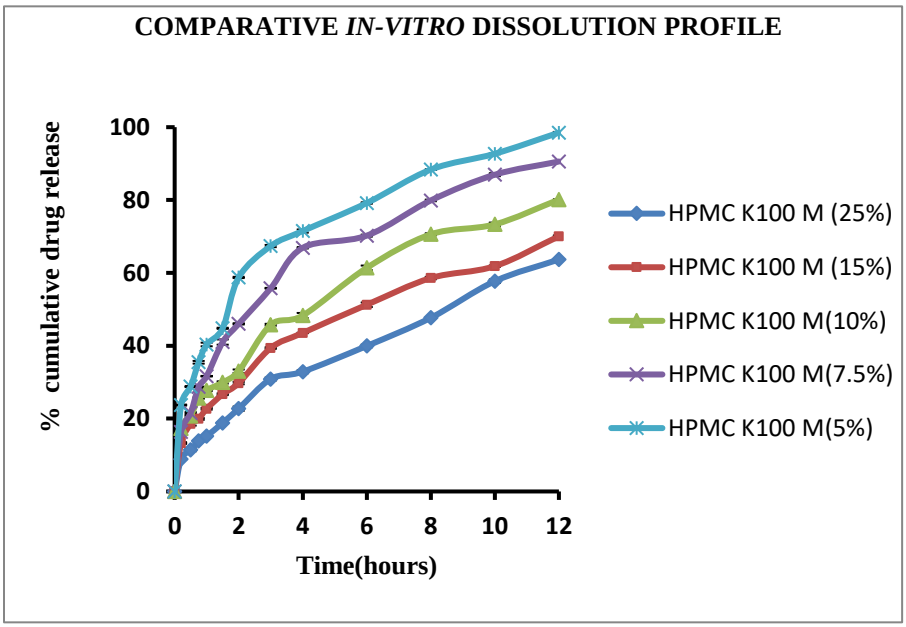


Fig: 4Comparative *in-vitro* dissolute on profile of formulations with HPMC K100M

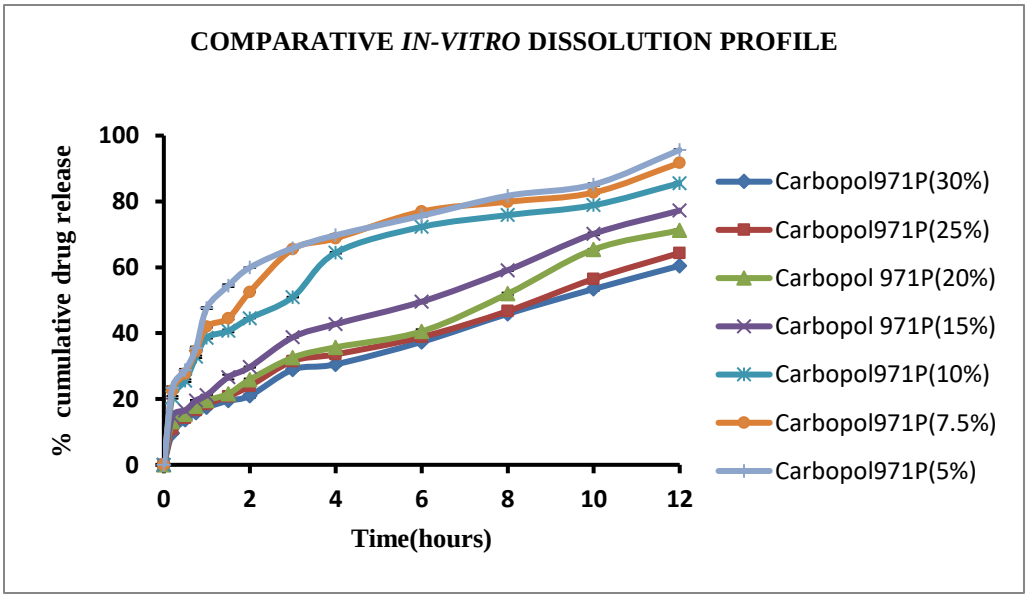


Fig: 5 Comparative *in-vitro* dissolution profile of formulations with carbopol 971P

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

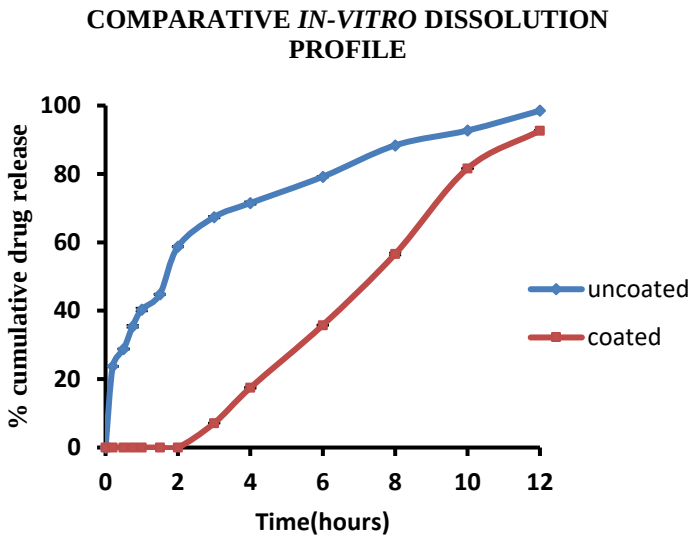


Fig: 6 Comparative *in-vitro* dissolution profile of formulations F5&F15

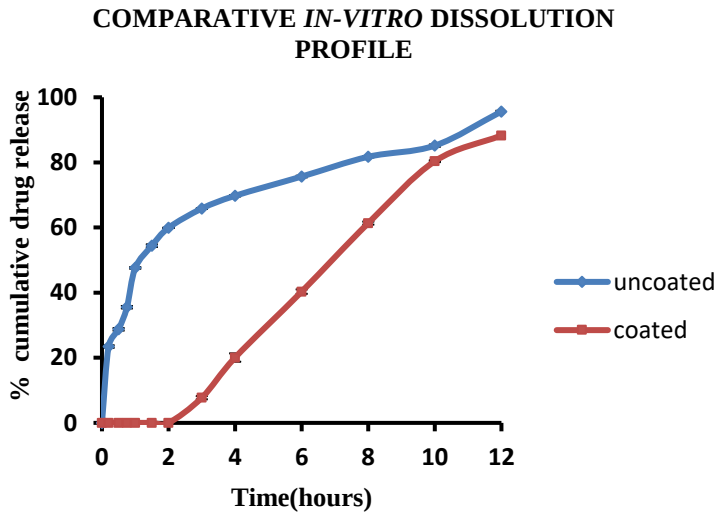


Fig: 7 Comparative *in-vitro* dissolution profile of formulations F12&F16

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Release kinetics and Mechanisms:

Dissolution data of all the formulations of Theophylline release tablets was fitted to zero order model, first order model, higuchi model and koresmeyer peppas model. From the results of the data fitting provided in **table 4.20 And shown in figures 4.29-4.88**, the best linearity was shown by first order models giving value of r^2 with in the range of 0.908-0.986. So the drug release was said to follow first order drug release kinetics. After predicting the order of drug release, mechanism of drug release was determined by value of "n" which was equal to the value of slope given by the equation of line obtained by fitting the data to koresmeyer peppas model. Value of "n" was found to lie between 0.281-0.582 indicating anomalous behavior (also called as non-fickian diffusion) as a mechanism of drug release. This consists of phenomenon of diffusion and erosion of polymer matrix.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table: 6 The Rate Constant and Regression values for all the formulations

Formulations	Zero order		First order		Higuchi	Peppas	
	K(mol.L^{-1}h^{-1})	R^2	K(h^{-1})	R^2	R^2	n	R^2
F1	4.794	0.961	0.033	0.986	0.990	0.580	0.992
F2	4.973	0.905	0.038	0.969	0.994	0.454	0.991
F3	5.801	0.905	0.052	0.981	0.990	0.468	0.983
F4	6.141	0.848	0.079	0.964	0.958	0.508	0.933
F5	6.759	0.802	0.121	0.960	0.963	0.401	0.947
F6	6.338	0.785		0.979	0.988	0.520	0.982
F7	4.517	0.734	0.029	0.971	0.986	0.502	0.984
F8	5.128	0.695	0.031	0.972	0.977	0.493	0.977
			0.039				
F9	5.595	0.675	0.047	0.981	0.993	0.507	0.995
F10	5.833	0.840	0.062	0.954	0.965	0.343	0.962
F11	6.020	0.778	0.088	0.915	0.944	0.363	0.972
F12	6.015	0.740	0.087	0.926	0.921	0.281	0.982
F13	7.333	0.902	0.060	0.969	0.927	-	-
F14	8.424	0.812		0.925	0.866	-	-
F15	8.987	0.807	0.084	0.935	0.853	-	-
F16	8.805	0.793	0.097	0.908	0.846	-	-
			0.088				

SUMMARY AND CONCLUSIONS:

The summary of the research work is here under

Selection of polymers

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Drug release retardant polymers are the key performers in the matrix systems. Matrix systems are favoured because of their simplicity, patient compliance etc, than the traditional drug delivery (TDS) which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Hydrophilic polymers are economical, readily available, non-toxic and capable of chemical modifications, potentially biodegradable and biocompatible. Hence in the present research work Hydrophilic polymers were used. After thorough literature review on Theophylline previous works, HPMC K 100 M & CARBOPOL 971P were selected as there were no papers published using these polymers with Theophylline.

Preformulation studies

Before going directly into formulation development, the drug and selected excipients compatibility was tested to ensure that there was no chemical interaction between them. FTIR and DSC studies were carried out on drug and polymers used. The spectra were shown in 2-3. From the obtained spectra it was clear that there was no drug-polymer interaction. Preformulation studies of the API showed that the drug has good flow property. All the formulations were prepared by wet granulation method. The pre-compression parameters were given in Table 5.

Development of matrix enteric coated tablets of Theophylline

Initially, Theophylline core tablet formulations F1-F5 & F6-F12 were formulated by wet granulation method using HPMC K 100 M & CARBOPOL 971P, DCP as diluent. Among all the formulations F5 & F12 were selected as best formulations. The selected formulations F5 & F12 were enteric coated with cellulose acetate phthalate by dip coating method. The prepared tablets were evaluated for post compression parameters as shown in Table. All the parameters like hardness, friability and weight variation were well within the acceptable limits.

***In vitro* drug release studies**

The dissolution studies for all the formulations (coated & uncoated) were carried out in USP-type II apparatus run at a speed of 50rpm and maintained at 37±0.5 ºc. The dissolution medium was 0.1N HCL for 2hr and pH 6.8 buffer for the next 10 hr. The obtained dissolution data was shown in Table 6. The two polymers like HPMC K 100 M & CARBOPOL 971P showed maximum retardation effect because of its more swelling and gelling tendency. The release retardation effect was increased with increasing in the polymer concentration. DCP used as diluent. It is insoluble diluents so it releases the drug slowly.

From the dissolution data ,among all the formulations of Theopylline core tablets F1toF12, formulations F5 & F12 were selected as best formulations. Because of, the drug release was found to be **98.49±0.21**% in F5 & **91.70±0.16** % in F12 respectively at the end of 12hr.

The selected formulations F5 & F12 were enteric coated with cellulose acetate phthalate by dip coating method. 5% w/v CAP solution with 1%v/v PEG 400 as plasticizer was tried initially with a 5% Coating weight gain,10% &15% respectively. 15% Coating weight gain formulations **F15 & F16** were found to be optimized in terms of achieving the drug delivery system, consistent with the requirement of chronopharmaceutical drug delivery, providing drug delivery rate of **81.60±0.17%** & **80.37±0.46%** respectively at the end of 10h of duration.

Release kinetics and Mechanisms:

Dissolution data of all the formulations of pulsatile release tablets was fitted to zero order model, first order model, higuchi model and koresmeyer peppas model. From the results of the data fitting provided in **table 4.20**, the drug release was said to follow first order drug release kinetics. Mechanism of drug release was found to be anomalous behavior (also called as non-fickian diffusion). This consists of phenomenon of diffusion and erosion of polymer matrix. **CONCLUSION:**

In accordance with chronotherapeutic model for nocturnal asthma, symptoms typically occur between midnight and especially around 4 am to 6 am because of increased airway responsiveness and worsening of lung function. Thus this study attempts to design and evaluate a chronomodulated drug delivery system of Theophylline, a bronchodilator for the treatment of asthma. To achieve this, Theophylline core tablets were prepared with composition of hydrophilic polymers by wet granulation method and were further coated with an enteric coating polymer (cellulose acetate phthalate). This coat has enabled us to achieve definite non-release lag phase. The pulsatile enteric coated Theophylline tablets were designed to prevent drug release in stomach and release drug

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

rapidly after predetermined lag time in the intestinal tract when pH is above 6. The system was found to be satisfactory in terms of release of the drug after a predetermined lag time when the greatest need of drug in early morning to treat the disease.

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