

THE PHARMA INNOVATION

Evaluation and Characterization of Different Polymers Based Drug Theophylline In Pulsatile Drug Delivery System

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Novel Oral Drug Delivery technologies have emerged and expanded into different drug delivery system with different drug release mechanisms. Pulsatile drug delivery system (PDDS) is the most interesting time- and site-specific system as per the patho-physiological need of the disease. Pulsatile drug release profile is characterized by time period of no release (lag time) followed by a rapid and complete drug release. The objective of the present study was to develop an oral pulsatile drug delivery system and evaluating and doing comparative characterization of different polymers used in the formulation of pulsatile drug delivery system. The core tablet was formulated using Drug- Theophylline, polymers- HPMC K4M, XANTHAN GUM and combination of HPMC K4M + XANTHAN GUM. Further Excipients employed were Lactose, Microcrystalline Cellulose, Starch, Sodium Carbonate, Citric Acid, Cross Carmellose Na, Magnesium and Sodium Stereate. The method adopted was Direct Compression Method. Eudragit L-100 in acetone (6%w/v) was enteric coated over the Press Coated tablet to formulate Pulsatile Tablet. From the evaluation and results, we conclude that the drug release from the pulsatile tablet formulated with polymer HPMC K4M+Xanthan gum shows more efficient drug release than pulsatile tablet formulated with only polymer HPMC K4M or tablet formulated with only polymer Xanthan Gum. The reason behind this is that Xanthan Gum is a natural polymer and Xanthan Gum exaggerate the action of HPMC K4M i.e. it has a tendency to imbibe water as well and thereby get swelled to that extent that it hinders the drug release for a definite time. Hence when after the function of gum gets terminated, the drug is released to the desirable organ to show its therapeutic action and therefore Gums shows positive effect when used with POLYMER LIKE HPMC K4M.

Keyword: Pulsatile Release, Chronotherapeutics, Time Controlled System, pH Targeted Release

INTRODUCTION: In recent year, a major goal for the drug delivery research is turned towards the development of efficacious drug

delivery systems with already existing active ingredients in case of new drug discovery.¹ Pulsatile Drug Delivery System are gaining a lot of significance as the drug is released completely after defined lag time. Pulsatile Delivery provides special and temporal relief increasing patient compliance. PDDS is being defined as the rapid and transient release of certain amount of

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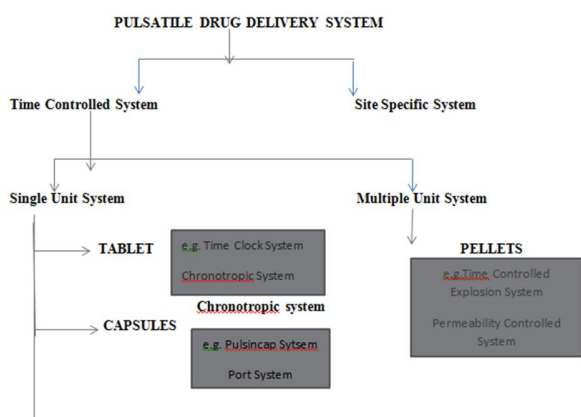
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molecules within short time period after a predetermined lag phase. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time.²

PDDS gaining importance / relevance in following situations:

- 1-Avoidance of the degradation in upper GIT e.g. – proteins and peptides
- 2-Chronopharmacotherapy of diseases showing circadian rhythms in their pathophysiology.
- 3-For drugs which exhibit biological tolerance (which can't be delivered at a constant rate since, the drug effect decreases with time of constant drug level) For drugs with extensive first-pass metabolism.
- 4-For time-programmed / dependent administration of hormones and many drugs such as isosorbide di nitrate .

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM



CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM.³⁻¹⁰

1. Time Controlled
2. Stimuli induced
3. Externally regulated

Time controlled pulsatile release system.

In time controlled drug delivery systems pulsatile release is obtained after specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two

components: One is of immediate release type and other one is a pulsed release type. Various methodologies that can be used for time controlled pulsatile release systems are discussed in following section

Stimuli Induced System

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli (Fig A). These systems are further classified in to temperature induced system and chemical stimuli induced system, on the basis of stimulus.

Externally Regulated System

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. In case of ultrasonically modulated systems, ultrasonic waves causes the erosion of the polymeric matrix thereby modulating drug release

2 -PROCUREMENT OF MATERIALS:

1. Drug Theophylline was obtained as gift sample from Oskar Pharmaceuticals, Yamunanagar, Haryana District, India.
2. Lactose, Microcrystalline cellulose (MCC), citric acid, starch, Sodium and Magnesium Stearate, sodium carbonate were obtained from our Lab in SGRRITS Institute.
3. Xanthan Gum was obtained from Himalayan Pharmaceuticals. And Cross carmellose Na was obtained as gift sample from Cipla, BADDI, HP, India

3-METHOD EMPLOYED: Direct Compression Method
 Procedure In Steps:

- 3.1-Formulation of core Tablet
- 3.2-Formulation of Press coated Tablet
- 3.3-Formulation of Pulsatile Press coated Tablet

Summarization Below:

3.1-Formulation of Core Tablet:

The inner core tablets were prepared by using direct compression method as shown in Table 1. Powder mixtures of Theophylline, microcrystalline cellulose (MCC, Avicel PH-102), citric acid, sodium bicarbonate and crosscarmellosesodium (Ac-Di-Sol) were dry powder for 20 min, followed by addition of magnesium stearate and talc as lubricant. The mixtures were then further blended for 10 min., 300 mg of resultant powder blend was manually compressed using hydraulic press. The inner core tablets were prepared by using direct compression method as shown in Table 1. Powder mixtures of Theophylline, microcrystalline cellulose (MCC, Avicel PH-102), citric acid, sodium bicarbonate and crosscarmellose Na (Ac-Di-Sol) were dry powder for 20 min, followed by addition of magnesium stearate and talc as lubricant. The mixtures were then further blended for 10 min., 300 mg of resultant powder blend was manually compressed using hydraulic press at a pressure of 1 ton, with 8mm punch and die to obtain the core tablet.

3.2 -Formulation of press coated tablet:

All press coated with the various compositions containing HPMCK4M, Ethylcellulose, Xanthan Gum with their compositions individually as well as simultaneously. The formulations Z1, Z2, Z3, Z4, different compositions were weighed dry blended at about 10 min and used as press-coating material to prepare press-coated pulsatile tablets, Z1-Z4, respectively by direct compression method.(70:30)% of the mixture was drawn from top and below the core tablet so

that ratio after placing must equivalent themselves i.e.(50:50)%

3.3-Formulation of Pulsatile Tablet:

Further the above formulations were enteric coated with Eudragit L-100 in acetone (6% w/v) and

the formulations were renamed as F1, F2, F3, F4.

**TABULAR LISTING:
FORMULATION CHART:**

Table1 No. 1: Formulation of Core Tablet of Theophylline

INGREDIENTS	QUANTITY REQUIERD
Theophylline	100
Lactose	45
MCC	95
Sodiumcarbonate: citric acid(1:1)	45
Crosscarmellose Na	09
Magnesium Stearate	03
Talc	03
Total(mg)	300 mg

Table 2: Composition for press coating Tablet:

INGREDIENTS	Z1	Z2	Z3	Z4
HPMC K4M	200	-	-	-
XANTHINE	-	200	-	-
HPMC K4M+XANTHAN GUM	-	-	200	-
Na and Mg Stearate	1:1	1:1	1:1	1:1

TOTAL WEIGHT OF TABLET: 500mg

3.3-Preparation of coating solution:

Coating solution was made using different ratios of material like Eudragit L100.. Required quantity of polymers were dissolved in mixture of solvents and stirred on magnetic stirrer to get homogeneous coating solution. Diethyl Phthalate was added in above solution as plasticizer

(1%w/v). After getting homogeneous coating solution; coating was done on tablets.

Parameter	Value
Inlet Air Temperature	40-450C
Exhaust Temperature	30-350C
Bed Temperature	380C
Atomization (bar)	2
Spray rate (gm/min)	10
Pan RPM	10

Percentage weight gain calculated by following equation1:

$$\text{Percentage Weight Gain} = [(Wt-Wo)/Wo]*100$$

Where,

Wt = Weight of table after coating

Wo = initial weight of tablet

Coating with Eudragit L 100:

Coating was done using Eudragit S100. Three formulations were formulated by varying the weight gain on tablet upon coating. The coated tablets were evaluated for In-vitro drug release profile as shown in table no. 3

Table no.3- coating dispersion of different formulation

INGREDIENTS	A1	A2	A3
Eudragit L 100	25	25	25
Diethyl Pthalate	3	3	3
Acetone	250	250	250

4-EVALUATION PARAMETERS

4.1-Methods of Precompression Studies:

(A)Bulk Density(g/ml): determined by pouring presieved (40 mesh) bulk Drug into a graduated cylinder with a large funnel and a measuring volume and weight.

(B)Tapped Density(g/ml):determined by placing a graduated cylinder containing known mass of Drug or Formulation on a mechanical tapper apparatus which is operated for a fixed number of taps(=1000) until the powder bed volume has reached a minimum.

(C)True Density(g/ml):determined by suspending drug particles in solvents of various densities and in which the compound is insoluble.after vigorous agitation,the samples are

centrifuged briefly and then left to stand undisturbed until floatation or settling has reached equilibrium.

Flow properties of powder blend:

The flow properties of powder blend were characterized in terms of angle of repose, Compressibility index and Hausner ratio.

- **Angle of repose** was performed using funnel method [by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 2 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured. The tan-1 of the height of the pile radius of its base gave the angle of repose. Bulk density (ρb) and tapped densities (ρt) were determined and thereby hausner ratio (HR) and compressibility index were calculated according to the following equation

$$\tan \theta = h/r$$

- **Compressibility Index:**

The Compressibility Index of the blend was determined by Carr's ,compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TBD-LBD) \times 100]/TBD$$

- **Hausner's Ratio:**

Hausner's Ratio was determined by Following Equation:

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

4.2-Method of Post Compression parameters of Tablet:

Shape and appearance:

Tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light.

Uniformity of thickness:

Thickness and diameter of both core tablets and coated tablets were measured using a calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated.

Weight variation test:

To study weight variation 20 tablets of each pulse dose formulation were weighed separately using a Sartorius electronic balance and the test was performed according to the official method.

Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a validated dial type hardness tester. It is expressed in kg/cm². Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Friability test:

For each pulse dose tablet formulation, the friability of 6 tablets was determined using the Roche friabilator (Camp-bell Electronics, Mumbai, India). Friability can be determined by following equation:

$$F = \left[\frac{W_{t\text{INITIAL}} - W_{t\text{FINAL}}}{W_{t\text{INITIAL}}} \right] * 100$$

Disintegration time of the tablets was determined using a tablet disintegration test apparatus using distilled water as fluid. For drug content (without enteric coating) the tablets was estimated by the spectrophotometrically at 272 nm (Shimadzu 1800, Japan). Tablet disintegration was carried by placing one tablet in each tube of

the basket and top portion of the each tube was closed with disc and run the apparatus containing pH 1.2 SGF (simulated gastric fluid) maintained at 37 ± 2°C as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In vitro drug release of core tablets and enteric coated tablet

In vitro drug release of core tablets

In vitro dissolution studies were carried out using USP Type II (paddle method) apparatus (Electrolab TDT-08L, India). Distilled water was used as dissolution medium. Release pattern was studied by taking sample of 5 mL at the specific time intervals and analyzed at 272 nm using a UV spectrophotometer (Shimadzu 1800, Japan).

In vitro drug release of enteric coated tablets

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus (Electrolab TDT-08L, India). In order to simulate the pH changes along with the gastro intestinal tract (GIT), dissolution media with 0.1 N HCl and phosphate buffer (pH 6.8) were sequentially used. When performing the experiment, 0.1 N HCl medium was used for 2 h (since the average gastric emptying time is 2 h). Then removed and fresh phosphate buffer (pH 6.8) was added for subsequent hours. 900 mL of the dissolution medium was used at each time and stirred at 50 rpm at 37 ± 0.5 °C. 5 mL of dissolution media was withdraw at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at 272 nm using a UV spectrophotometer.

5-RESULT AND DISCUSSION

5.1-PRECOMPRESSION STUDIES:

(A) **Bulk Density** varied between 0.32±0.013 to 0.33±0.009 as shown in table no. 4.

(B) **Tapped Density** varied between 0.37 ± 0.009 to 0.40 ± 0.011 as shown in table no. 4.

(C) **Carrs index** varies between 12.1 ± 0.25 to 17.1 ± 0.11 as shown in table no. 4.

(D) **Hausners Ratio(%)** varies between 1.11 ± 0.011 to 1.19 ± 0.014 as shown in table no.4.

Hence these value indicated that prepared powders exhibited good to fair flow characteristics.

**BULK CHARACTERIZATION:
FLOW PROPERTIES OF POWDER BLEND:**

Table No.4 : Flow Properties of Powders.

Formulation code	Bulk Density	Tapped Density	Carrs Index(5)	Hausners Ratio(%)	Angle of Repose(θ)
1	0.32 ± 0.013	0.37 ± 0.009	12.1 ± 0.25	1.11 ± 0.011	27.4 ± 1.11
2	0.31 ± 0.019	0.34 ± 0.017	12.3 ± 0.33	1.10 ± 0.017	29.4 ± 0.25
3	0.35 ± 0.025	0.41 ± 0.014	14.74 ± 0.21	1.14 ± 0.019	30.1 ± 0.13
4	0.33 ± 0.009	0.40 ± 0.011	17.1 ± 0.11	1.19 ± 0.014	30.2 ± 0.15

5.2-EVALUATION OF POSTCOMPRESSION STUDIES:

All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, tablet dosage form assay and *in vitro* disintegration time.

Shape and appearance:

Formulations prepared were randomly picked from each batch examined under lens for shape and in presence of light for color. Tablets showed standard concave surfaces with circular shape. Tablets were white in color.

Uniformity of thickness:

Thickness of the tablets was measured using calibrated dial callipers by picking three tablets randomly from all the batches. The results of thickness for tablets are shown in Table No. 28. thickness values lies between 5.45 ± 0.08 to 5.57 ± 0.018 indicating that all formulation are having uniform mass and thickness as shown in table no.5.

Weight variation test:

The weight variation of both the formulations is shown in Table No.28. All the tablets passed the weight variation test, i.e., the average weight of core tablets lies between 294 ± 0.21 to 299 ± 0.17 average percentage weight variation was found within the pharmacopoeial limits of $\pm 10\%$ as shown in table no. 5.

Hardness test:

The hardness of different formulation lies between 4.5 ± 0.054 to 4.7 ± 0.029 indicating all formulation having satisfactory mechanical strength as shown in table no.5.

Friability test:

Friability values lies between 0.59 ± 0.011 to 0.71 ± 0.09 indicating good mechanical resistance of tablet as shown in table no.5.

In vitro drug release of core tablets and enteric coated tablets

In vitro release of Theophylline from core and enteric coated tablets is shown in Fig. 1,2,3. From formulation Z1,Z2,Z3,Z4 (core tablets), Z21

showed faster drug release after 9 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. Based on the above characters formulation, Z1 was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the Theophylline from

enteric coated tablets. The formulation Z3 showed maximum drug release after 7th hr. Time dependent pulsatile drug delivery system has been achieved with 100.12 ± 0.82 drug release which meet demand of chronotherapeutic drug delivery.

Table No.5 : Post Compression parameters of Theophylline core tablet.

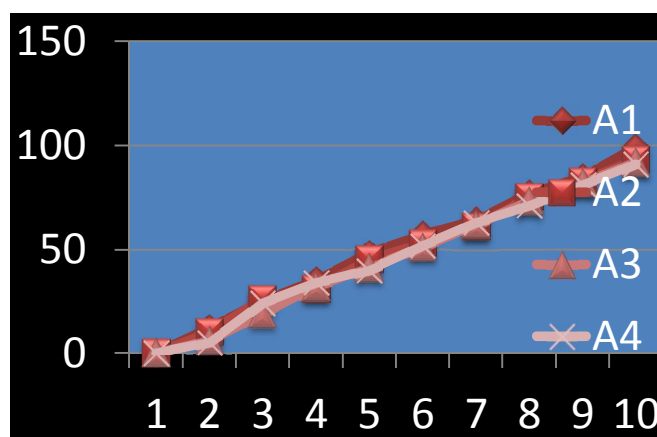
Formulation Code	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Disintegration TIME (sec)	Wt. Variation (%)	Drug Content (%)
Z1	4.5 ±0.054	5.45±0.08	0.59±0.011	53±0.1	294±0.21	99.79±0.19
Z2	4.4±±0.025	5.40±0.020	0.71±0.09	177±0.09	298±0.09	98.93±0.13
Z3	4.5±±0.049	5.42±0.015	0.66±0.014	151±0.09	296±0.13	99.22±0.19
Z4	4.7±±0.029	5.57±0.018	0.68±0.011	180±0.1	299±0.17	99.39±0.19

Table 6: Post Compression parameters of Theophylline Press coated tablet

Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Friability %	Wt. variation (%)	Drug Content (%)
Z1	7.45±0.21	8.43±0.16	0.6±0.15	604±0.17	99.20±0.11
Z2	7.65±0.16	8.72±0.21	0.5±0.17	603±.23	98.11±0.18
Z3	7.32±0.17	8.31±0.11	0.4±0.11	599±0.21	100.12±0.82
Z4	7.40±±0.29	8.73±0.12	0.7±0.17	603±0.18	97.13±0.56

5.3- IN VITRO STUDIES OF TABLET:

DRUG RELEASE FROM THE CORE TABLET:



y-axis: Cumulative Percentage of Drug Release

x-axis: Time(minutes)

Fig. 2 :graphical representation of drug release of theophylline Using HPMC k4m.

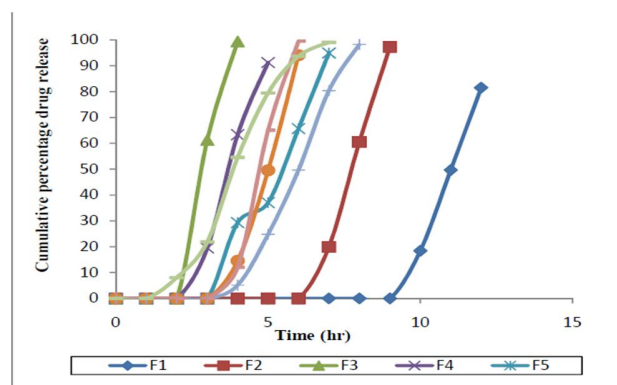
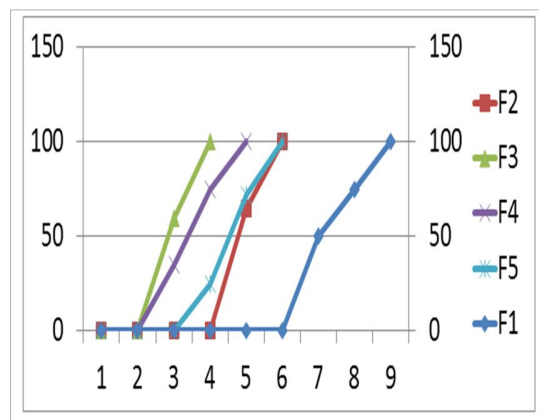


Fig 3 :GRAPHICAL REPRESENTATION OF DRUG RELESAE USING POLYMER HPMCK4M +XANTHAN GUM



y-axis: cumulative percentage drug release

x-axis: time(minutes)

CONCLUSION:

From the above observations, we conclude that the drug release from the pulsatile tablet formulated with polymer HPMC K4M+Xanthan gum shows more efficient drug release than pulsatile tablet formulated with only polymer HPMC K4M or tablet formulated with only polymer Xanthan Gum. The reason behind this is that Xanthan Gum is a natural polymer and Xanthan Gum exaggerate the action of HPMC K4M i.e. it has a tendency to imbibe water as well and thereby get swelled to that extent that it bards the drug release for a definate time. Hence when after the function of gum gets terminated, the drug is released to the desirable organ to show its therapeutic action and therefore Gums shows synergistic effect when used with POLYMER LIKE HPMC K4M.

REFERENCE:

- [1] Yoshida R, Sakai K, Okano T, Sakurai. Pulsatile drug delivery systems using hydrogels. *Advanced Drug Delivery Review* 1993; 11: 85-108.
- [2] Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. *Advanced Drug Delivery Review* 2002; 54: 53-77.
- [3] Gazzaniga A, Maroni A, Sangalli ME, Zema . Time-controlled oral delivery systems for colon targeting. *Expt Opin Drug Del* 2006; 3: 583-597
- [4] Peppas NA, Leobandung W. Stimuli-sensitive hydrogels: ideal carriers for chronobiology and chronotherapy. *J Biomat Sci PolymEd* 2004; 15: 125-144.
- [5] Stubbe BG, De Smedt SC, Demeester J. Programmed polymeric devices for pulsed drug delivery. *Pharm Res* 2004; 21: 1732-1740.