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Research Article

Design, Evaluation and Optimization of Albuterol Sulphate and Theophylline Pulsincap drug delivery system for chronotherapy of Asthma

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Abstract

The aim of the current study was to design and develop and evaluate pulsatile drug delivery system of Albuterol Sulphate and Theophylline for the treatment of Asthma. The capsule body was made water insoluble by cross linked with formaldehyde vaopur. The treatment of Formalin was adopted to modify the gelatin capsule solubility. The formalin residue was carried out by quantitative test. The drug-excipient compatibility is done by FTIR and UV . The pulsincap formulation were prepared by using hydrogel plug of various components. The drug content of the formulation of pulsincap was found to be in the general range. The invitro drug release studies in ph1.2 .6.2 and 7.4 buffern was noticed to be zero percent and capsule was stable for 2 hours drug the studyF5 formulation batch was selected which was best and good formulation and promoted maximum drug release of 96.29% percentage at phosphate buffers when compared with other formulation. Pulsincap formulation can be adopted for optimum delivery of pellets in the treatment as per chronotherapy

Keywords: Theophylline, quantitative test, invitro drug release studies, phosphate buffers6.2 and 7.4.

INTRODUCTION

Chronopharmaceutics is the branch of pharmaceutics which is reserved to develop and a design and evaluate the system of drug delivery that promotes the bioactive agent at proper rhythm that delivery clearly fits the actual time of the biological requirement at a given disease condition [1]. The orally controlled are the system which exhibits a different pattern of drug release ,where the drug concentration is controlled within the therapeutic window for the longer period enabling a sustained therapy. But, in fact there are other conditions where this type of release pattern is not matched, where there conditions expect drug release after a lag time. Pulsatile release is the drug release where it is not released during the initial phase of dosage form administration. Pulsatile drug delivery system is the release of drug rapidly with certain amount of drug molecules within the short time period immediately after a predetermined lag time of release period In the drug delivery systems the drug release is controlled by specific circadian rhythm that regulates several body functions in humans[2]. The methods designed and developed with chronotropic system for pulsatile drug release usually are stimuli induced, time controlled pulsatile drug delivery system. Chronobiology is the branch of biology which studies the biological rhythms and their mechanism. Chronotherapeutics is the branch concerned with drug delivery according to internal activity of disease over a certain time interval because due to biochemical, physiological and pathological variation for 24 h period in humans[3]. Pulsatile drug delivery systems functions with the lag time controlled by plug, where it is pushed by swelling and erosion mechanism followed by drug release. As, when the capsule dissolves by dissolution fluid, it starts swelling, after a lag time, the plug itself pushes outside the capsule and the drug is released instantly. By manipulating or changing the dimension and position of plug the lag time can be controlled[4].Pulsatile drug delivery system is designed and developed by different attempts of pulsatile drug delivery like time controlled, stimuli induced or externally regulated pulsatile drug delivery system. These can be developed in various steps of dosage forms like pellets, granules and more[5].

RESEARCH METHODOLOGY

Materials: PVPK-30, Lactose,Aerosil and other chemicals and polymers of analytical grade were procured from SD fine chemicals Mumbai. Theophylline, Albuterol Sulphate was purchased from Yarrow chem. products, Mumbai

Formulation of pulsatile (modified pulsincap) drug delivery system:

Preparation of modified pulsincap

Equivalent to 10 mg drug beads were filled in the capsule

bodies and plugged with hydrogel plug. The treated body and the cap of the capsules were sealed with a small amount of 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with enteric coating (5% CAP) to reduce variability in gastric emptying time, coating was repeated until an expected weight gain of 8-12% was obtained.

Evaluation of modified Pulsincap:

Weight variation:

10 capsules were selected randomly from each batch and weight individually for weight variation.

Thickness of cellulose acetate phthalate coating:

The thickness of coating cellulose acetate phthalate to capsule was measured with screw gauge and expressed in mm [6].

In-vitro release profile:

Dissolution studies of pulsincap were carried out by using USP dissolution apparatus. In order to simulate the pH changes along the GI tract, three dissolution media with phosphate buffer pH 1.2, 7.4, 6.8 were sequentially used. When performing experiments, the pH 1.2 medium was first used for 2h (since the average gastric emptying time is 2hour), then removed and the fresh pH 7.4 phosphate buffer was added. After 3 hours fresh pH6.8 dissolution medium was added for subsequent hrs. in experiment 900 ml of the dissolution medium was used at each time. Rotation speed was 50rpm and temperature was maintained at 37ºC. 5ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 250 nm, UV visible spectrophotometer [7].

Drug Release kinetics data

To investigate the possible mechanisms of release from the prepared pulsincap, the drug release data were fitted to various models such as Higuchi, Zero-order, First-order, Hixson Crowell and Korsmeyer Peppas kinetics. Model fitting was carried out using PCP DISSO. v 2.08 Software.

Coating of Pulsincap: Dip coating method was used for the development of pulsincap. A 5% w/w solution of Cellulose Acetate Phthalate was prepared by using acetone: ethanol (8: 2) as solvent. The capsules were dipped in 5 % CAP solution and dried in room temperature. Coating was repeated until an expected weight gain of 8 - 12% was obtained[9].

Stability Studies: The prepared formulations of pulsincap were monitored as per ICH guidelines up to 45 days at accelerating conditions of temperature and relative humidity (40 ± 2 °C/ 75 % ± 5% RH) to check the stability. Samples were withdrawn at predetermined intervals and determined the drugrelease[10].

Pre-clinical studies

Preclinical and clinical study material and source selection

Experimental animals

White rabbits in good health served as the subjects of in vivo research (1.5–2.2 kg). Prior to research, the rabbits were obtained with Animal Ethical Clearance from CPCSEA to acclimate the animals to laboratory surroundings. The rabbits were divided into three groups (n = 6) at random, each of which was kept in a designated location for a distinct sampling period. All of the animals received access to libido, food, and water.

Experimental design:

For this investigation, a three-way cross-over design was used. Three groups—A, B, and C—were created out of the rabbits. There were six animals per group (n = 6) in(900 ml pH 7.4 phosphate buffer, USP XXIII, 370.5 C). In order to assess swelling in rats, a model polymer called xanthan gum was used.[11]

Pre-compressional studies:

Angle of repose Angle of repose was performed using the funnel method by keeping a funnel vertically in a stand at a specified height above a piece of paper placed on a horizontal surface. The funnel bottom was closed, and 2 grams of powder were filled in the funnel. Then the funnel was opened to release 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 (b) and tapped densities (t) were determined, and thereby the Hausner ratio (HR) and compressibility index were calculated according to the following equation [12]

RESULTS AND DISCUSSION

Preparation of modified pulsincap

The design of Osmotically controlled pulsatile release capsules: includes push, active, and plug tablets which positioned from bottom to top in a hard gelatin capsule for the assembly of the capsular systems. The capsule system was drilled toward the plug side in the cap and covered with a cellulose acetate semi-permeable membrane. The considerable interaction was not found between the excipients and drug. The prepared blend for compression showed good flow properties. The formulations were characterized by DSC and FTIR spectroscopy. No interactions between drug and additives used in the preparation were noted Theophylline's 100 mg normal prompt adult dosage (Dn), its 6-hour half-life (t1/2), and its 24-hour maintenance period (t) were all taken into account while calculating the Dt. For simplicity and practicality, the total dose (Dt) was rounded up to 400 mg/day from thecalculated 377.2 mg/day.

In-vitro release profile

A three-factor 3-level, face centered CCD was designed to execute the experiments and quadratic polynomial model was generated to predict and assess the independent variables (i.e. lag time, release at 6 h and release at 12 h) with respect to the dependent variables (i.e. push, plug and coat weight). The composition of optimal formulation was determined as weight of push tablet 138 mg (coded value: +0.59), plug tablet 60 mg (coded value: +0.49) and coating weight gain of 8.4 mg (coded value: -0.82). The results showed that the optimal formulation of PRCs had lag time of 4.5 h and release at 6 h and 12 h are 61.95% and 96.29% respectively. There is no release was observed in 0.1N HCl (pH 1.2) for all formulations. However, rapid release from cross linked beads in phosphate buffer, pH 6.8 has been presumed to be due to greater solvent penetration into the calcium alginate network, followed by greater ion exchange between Ca2+/Zn2+ and Na+/K+ ions.

Stability Studies:

To determine the stability, the stability studies were carried on with individual mixtures of albuterol sulphate and theophylline in the ratio of1: 0.5 subjected to 25°C/60 percent relative humidity and 40°C/75 percent relative humidity by incorporating in borosil glass vials for a duration of 4 weeks which gave no major decompositions of formulation with chemical interactions which was found to be suitable and secure for formulation. The improved formulation (DRB 14) did not exhibit any physical changes during the study period, according to the findings of accelerated stability studies completed in accordance with **ICH** recommendations, and the drug content (n=3; mean SD) was

discovered to be over 95% after 6 months (Table 59). Under accelerated storage conditions, there was no discernible change in the lag time and release profile of the beads (Figure 56). This shows that the improved batch showed acceptable potency and good physical stability during accelerated storage for six months.

Drug Release kinetics data

T_{max} was discovered by an in vivo pharmacokinetic investigation of DRBs with an initial lag time of 4 h. Patients suffering with early-morning episodic attacks of asthma and related allergic rhinitis may find this formulation beneficial.

Pre-clinical studies

Experimental design:

Pharmacokinetic study Following oral administration of the commercial tablet, cross- linked beads, and DRBs, the plasma concentration of Drug with time is depicted in Figure 58. Table 65 displays the pharmacokinetic parameter data, which were computed using the concentration-time curves for plasma. There was no significant difference in pharmacokinetic parameters was observed between marketed tablets and crosslinked beads. When compared to DRBs, drug absorption was quick after oral administration of a commercial tablet (T_{max}, 2 hours) (T_{max}, 7 h). Using the PK Solution® programme, the pharmacokinetics parameters, such as areas under concentration-time curves (AUC), SC_{max}, T_{max}, and T1/2, were determined. Unpaired t test was used to statistically test for differences between mean values, a minimal level of 0.05 was set a unique value.

CONCLUSION

Eudragit and ethyl cellulose coated core tablets has revealed pH dependent bursting time whereas ethyl cellulose and HPMC coated tablet has shown no effect of buffer pH on bursting time. At 33.33 percent weight-to-weight (coded value +0.33) HPMC coating composition and a 9.42 percent weight-to-weight (coded value -0.29) coating weight gain were found to be the best formulation. The findings demonstrated that the ideal formulation of TCRTs had a lag time (4.5 h), release at 6 h and 12 h are respectively 84.14 percent and 95.32 percent. The optimized TCRTs (containing BaSO4) were tested *in vivo* in white rabbits for bursting time by X-ray imaging study. It was observed that tablet remained intact for 4 h, and at 5 h tablet was disintegrated. An in vivo investigation showed that the pharmacokinetic characteristics of marketed tablets, core tablets, and TCRTs were comparable, but that the T_{max} for these substances was 2 hours while it was 7 hours for TCRTs. As a result, developed TCRTs were proven to be effective in treating early-morning episodic asthma attacks and related allergic asthma.

Table 1: Size and effectiveness of cross-linked beads' encapsulation

Batch No.	Size (mm)	Production yield (%)	Encapsulationefficiency (%)
B 1	1.54 ± 0.13	89.72 ± 5.11	81.25 ± 2.15
B 2	1.75 ± 0.15	92.33 ± 5.02	88.30 ± 3.08
B 3	1.86 ± 0.15	93.11 ± 4.66	87.65 ± 2.53
B 4	1.71 ± 0.18	90.81 ± 5.13	83.17 ± 3.32
B 5	1.76 ± 0.16	92.42 ± 4.63	90.20 ± 2.71
B 6	1.74 ± 0.15	93.10 ± 3.95	88.28 ± 3.82
B 7	1.76 ± 0.14	88.95 ± 4.25	89.37 ± 2.76
B 8	1.73 ± 0.15	88.52 ± 4.59	85.82 ± 5.28
B 9	1.77 ± 0.16	93.05 ± 4.71	88.73 ± 3.67
B 10	1.83 ± 0.15	92.83 ± 3.86	89.31 ± 2.75
B 11	1.85 ± 0.14	93.37 ± 4.71	90.10 ± 3.16
B 12	1.85 ± 0.16	92.13 ± 4.62	88.76 ± 3.62

Table 2: Presentation of measured responses of experimental run in CCD

Batch No.	Experimental	Y1: Lag timerun(h)	2: Releaseat6 h (%)
DRB 1	1	3.5	95.89
DRB 2	2	3.5	92.61
DRB 3	3	4	85.88
DRB 4	4	5.5	41.39
DRB 5	5	5	57.79
DRB 6	6	4	86.88
DRB 7	7	4	92.65
DRB 8	8	3	97.56
DRB 9	9	4	91.63
DRB 10	10	4	94.11
DRB 11	11	4	95.21
DRB 12	12	4	88.80
DRB 13	13	5	49.34

Table 3: Solutions suggested by Design Expert that meet the criteria required forDRBs

BatchNo.	Eud RLPO Coded/Actual	Coat wt. Coded/Actual	Lag time(h)	Release at 6 h (%)	Desirability
DRB 14	-0.66/23.33	-0.08/9.84	4.50	78.18	0.834
DRB 15	-0.71/22.9	-0.13/9.74	4.50	78.20	0.834

Table 4: Comparison of predicted and observed responses for the statistically optimized formulation DRB 14

Batch No.	Response	Experimental(Mean)	Predicted	Relativeerror (%)
DRB 14	Release lag time in h (Y1)	4.50	4.50	0.0
	% drug releaseat 6 h (Y2)	74.90	78.18	4.2

Table 5: Desirability for optimization of DRBs of DRUG

Time (Months)	Drug Content (Mean ± SD)
0	99.27 ± 2.93
3	97.13 ± 3.05
6	95.21 ± 2.91

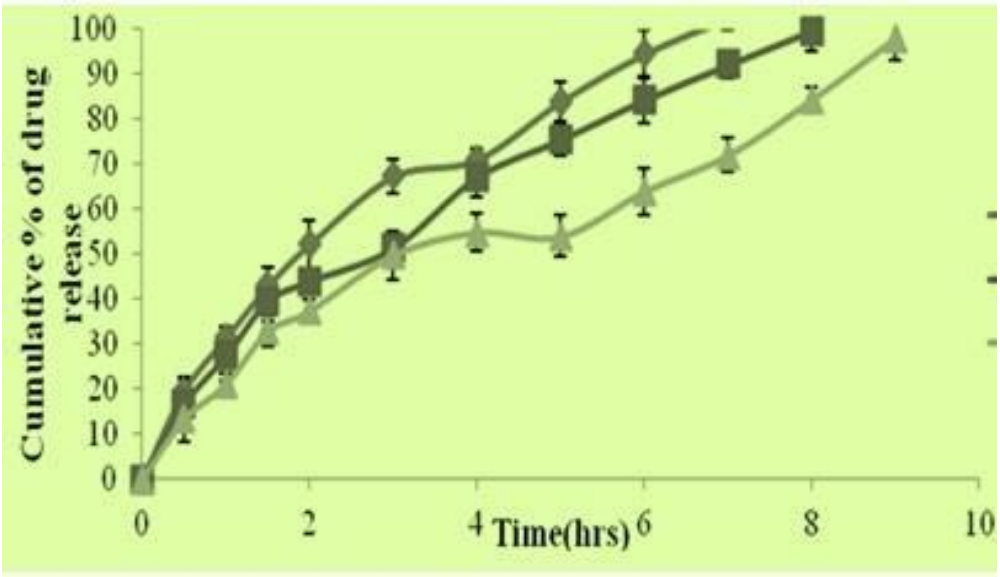

Figure 1: Release profile of optimized formulation (DRB 14) stored ataccelerated stability condition (40 ± 2 °C/75 ± 5% RH)

Table 6: In-vitro release profile of chronopharmaceutical deliveryof Xanthan Gum

Dissolution Media	Time (mins)	MEAN CUMULATIVE PERCENTAGE RELEASE (CPR%) ± SD								
		CP-1	CP-2	CP-3	CP-4	CP-5	CP -6	CP -7	CP-8	CP-9
pH1.2	15	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0
	60	0	38.45±1.22	77.73±4.47	0	0	0	0	0	0
	120	76.10 ±2.46	81.79 ±4.52	96.33 ±3.26	0	8.42 ± 1.84	86.40 ± 3.39	0	0	0
pH6.8	180	94.65 ±3.47	96.20 ±5.16	-	71.65 ± 4.41	36.20 ± 2.46	94.56 ± 2.19	0	38.12 ±3.26	21.30 ±5.06
	240	-	-	-	97.20 ± 5.33	75.46 ± 3.21	-	16.90 ± 1.47	56.22 ±5.33	46.00 ±1.88
	300	-	-	-	-	93.12 ± 4.11	-	37.11 ± 4.22	81.20 ±1.87	54.33 ±1.52
pH7.4	360	-	-	-	-	-	-	67.33 ± 5.22	98.12 ±4.16	78.14 ±2.10
	480	-	-	-	-	-	-	88.42± 3.61		91.11±3.49
	600	-	-	-	-	-	-	-	-	-
	720	-	-	-	-	-	-	-	-	-
	1200	-	-	-	-	-	-	-	-	-
	1440	-	-	-	-	-	-	-	-	-

Table 7: Summary of physico-chemical properties of bestselected developed formulation (CP-16)

Sr No	Summary of the evaluation parameters of Chronopharmaceutical delivery system(CP16)			
	System	parameters		Results
1	Pellets (P3)	Drug content		98.89 ± 0.11
		In-vitro release profile	pH 1.2	98.34 ± 0.98
			pH 6.8	93.65 ± 2.21
			pH 7.4	92.89 ± 4.21
2	Polymer plug	Pre-compressional properties		
		Angle of repose		28.22 ± 0.98
		Bulk density	UBD	0.377 ± 0.62
			TBD	0.388 ± 0.20
		Post-compressional properties		
		Weight variation (mg)		324 ± 0.11
		Hardness test (KG/Cm^2)		03.7 ± 0.115
		Thickness of coating		0.22 ± 0.022
		Friability test (%)		0.68 ± 0.83
		Disintegration test(minutes)		4.39 ± 0.01
		Swelling rate (minutes)	pH 1.2	189.21 ± 0.08
			pH 6.8	186.32 ± 0.54
			pH 7.4	172.47 ± 1.19
3	Complete chronopharmaceutical Delivery system	In-vitro release profile(%)		97.24 ± 5.21
		Lag time achieved(minutes)		240

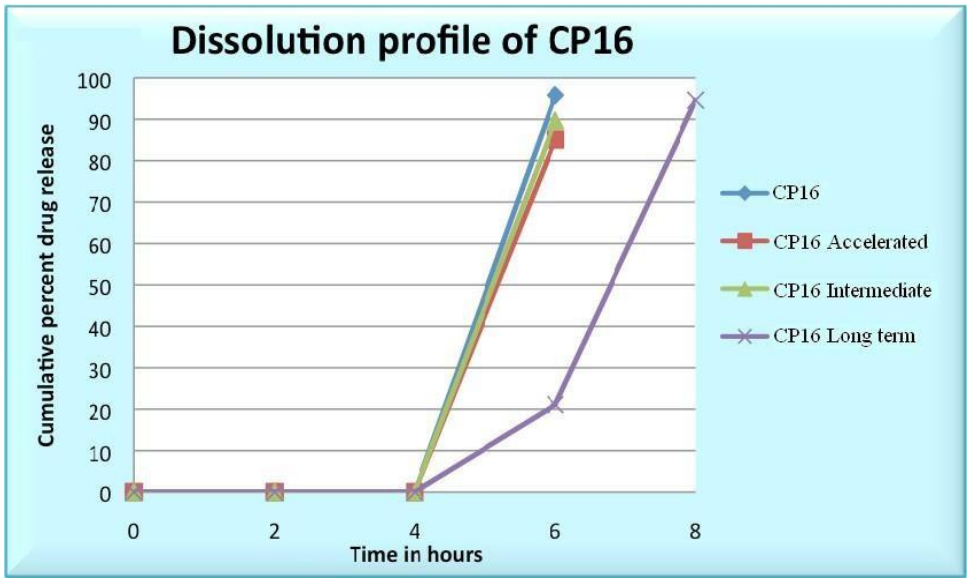

Figure 2: Stability study of CP16 at 0month

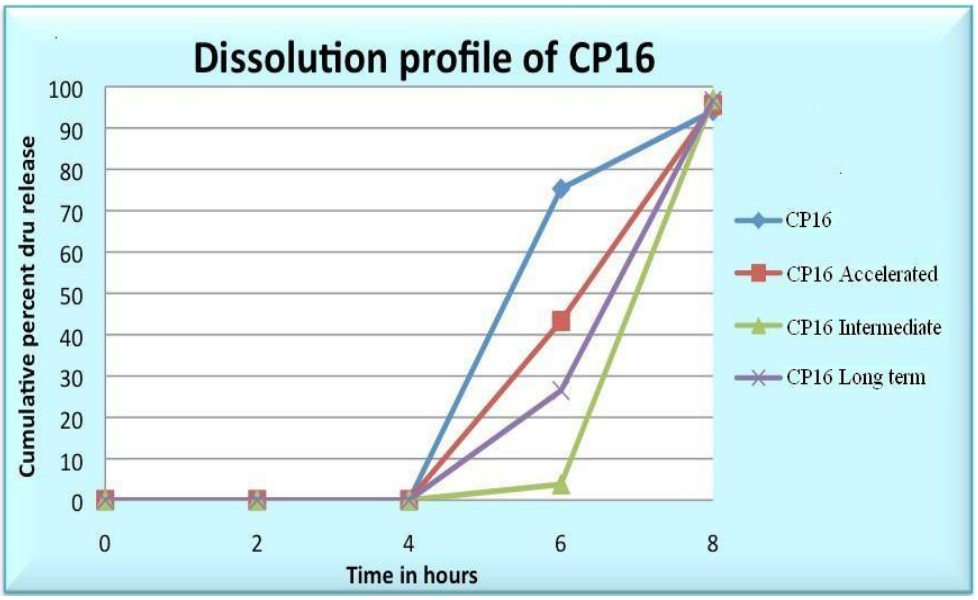

Figure 3: Stability study of CP16 at 3rd month

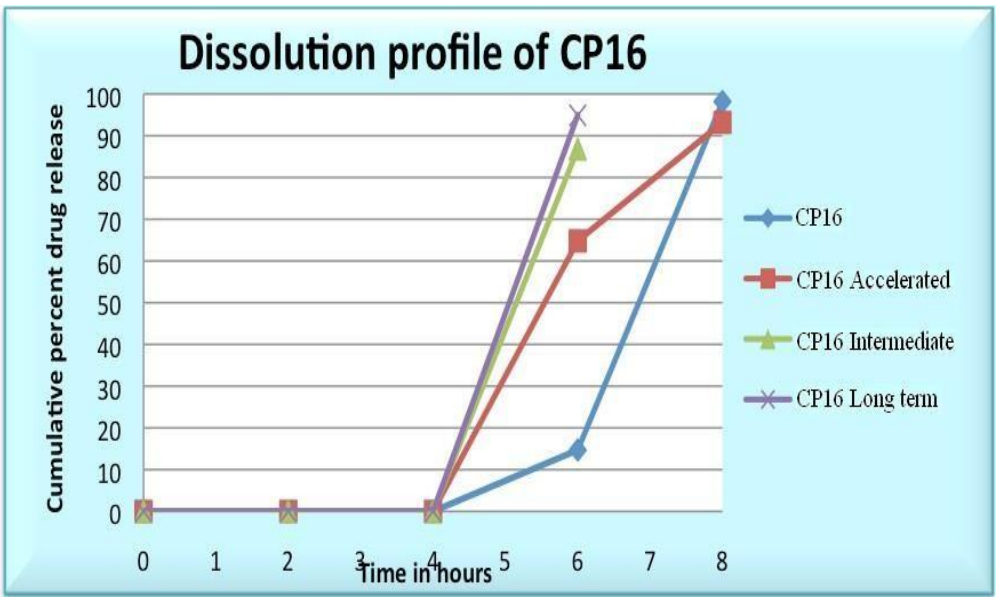

Figure 4: Stability study of CP16 at 6thmonth

Table 8: Physicochemical Characterization of marketed Formulation of Theophylline

Sr no	Appearance	Mean hardness (Kg/cm^2) ± S.D	Mean Wt Variation (%) ± S.D	Mean Drug Content (%) ± S.D	Mean Friability (%) ± S.D	Mean Thickness (mm) ± S.D
1	M	4.4 ±0.05	600.1 ±0.01	99.8 ± 0.35	0.76±0.008	3.9± 0.06

Table 9: Summary of PK parameters derived from Plasma-drugconcentration of Albino rabbits

SUMMARY OF PHARMACOKINETIC PARAMETERS			
PK PARAMETERS	ANIMAL STUDY GROUPS		
	Group A	Group B	Group C
AUC_{0-24} (ng/ml/min)	13472079.23 ± 4.21	12488625.20 ± 5.57	22756283.4 ± 5.87
$AUC_{0-\infty}$ (ng/ml/min)	13472104.63 ± 2.53	12488625.21 ± 3.31	22758470.5 ± 2.27
$AUMC_{0-24}$ ($ng/ml/min^2$)	2721846888.25 ±3.75	1265597754.8 ±1.87	13178330960 ±2.21
Cmax (ng/ml)	56699.52 ± 1.98	58734.61 ± 4.056	54632.23 ± 3.65
t_{max} (hrs)	3 ± 0.85	2 ± 2. 067	8 ± 3. 57
Ke (hrs^{-1})	-0.40 ± 0.73	-0.38 ± 0. 034	-0.29 ± 0. 87
MRT (hrs)	3.36 ± 0. 62	1.68 ± 1.76	9.65 ± 2. 055
$t_{1/2e}$ (hrs)	1.75 ± 1.01	1.83 ± 0. 93	2.43 ± 0. 88
C0 (ng)	354200 ± 2.24	268000 ± 2.09	605600 ± 1.56
Vd (litres)	0.465 ± 0.65	0.614 ± 0.029	0.272 ± 0.009
Ka (hrs^{-1})	0.4 ± 0. 88	1.35 ± 0.47	0.33 ± 0.74
$t_{1/2a}$ (hrs)	1.74 ± 1. 66	0.51 ± 1. 98	2.10 ± 2.89
Tlag (hrs)	0.29 ± 2. 45	0.18 ± 3. 36	1.90 ± 1.74

Table 10: Final Theophylline concentration ofspiked plasma

Final Theophylline Concentration Spiked Plasma	
ıylline Stock(µg/ml)	Theophylline Spiked (ng/ml)
50.6206	5062.063
40.4965	4049.650
24.2979	2429.790
12.1490	1214.859
5.0418	504.181
2.5209	252.091
1.0084	100.836
0.5042	50.418

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