IJPSR (2011), Vol. 2, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 January, 2011; received in revised form 21 February, 2011; accepted 22 March, 2011

DESIGN AND CHARACTERIZATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY OF THEOPHYLLINE

Amit Bhat*[1], K. P. R. Chowdary [2], Shobharani R. H. [3] and Lakshmi Narasu [4]

Department of Pharmaceutics, Bharat Institute of Technology (Pharmacy)*[1], Mangalpally (V), Ibrahimpatnam, Hyderabad, Andhra Pradesh, India

Department of Pharmaceutics, University College of Pharmaceutical sciences[2], Andhra University, Visakhapatnam, Andhra Pradesh, India

Department of Pharmacy Practice, Al-ameen College of Pharmacy[3], Hosur Road, Lalbagh Road, Bangalore, Karnataka, India

ISTE, JNTU-H[4], Kukatpally, Hyderabad, Andhra Pradesh, India

Keywords:

Theophylline, Chronotherapeutics, Hydrogel polymers, Nocturnal asthma

Correspondence to Author:

Amit Bhat,

Associate Professor, Department of Pharmaceutics, Bharat Institute of Technology (Pharmacy), Mangalpally (V), Ibrahimpatnam, Hyderabad, Andhra Pradesh, India

ABSTRACT

Chronopharmacokinetic studies have been reported for many drugs in an attempt to explain chronopharmacological phenomena and demonstrate that the time of administration is a possible factor of variation in the pharmacokinetics of a drug. The present study aimed at preparing a novel time dependent pulsed release system containing 'pellets in-capsule' device plugged by biodegradable polymers for the programmed release of theophylline for the treatment of nocturnal asthma. The pellets of theophylline were prepared using direct compression method containing a superdisintegrant. Physical characterization of the plug and pellets used was under taken using a range of experimental technique. Karaya gum, Xanthum gum and cross-povidone XL 10 were used as polymers for making plug which were fitted on to the capsule. Factors studied in design were percentage of drug entrapment, swelling index and the effect of plug position on In-vitro drug release. Dissolution studies of pulsatile capsule device in media with different pH (1.2, 6.8 and 7.4) showed that drug release in colon could be modulated by optimizing the concentration of polymers in the plug and also the position of plug. The study showed that, lag time prior to drug release was highly affected by the plug position. The dissolution data revealed that the plug position and the ratio of polymers are very important to achieve a optimum formulation. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The FTIR, DSC studies pointed out there was no such incompatibility between drug and excipients. Stability study of the optimized formulation indicates no significant difference in release profile after a period of one month.

INTRODUCTION: In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases drug effect can be optimized and side effects can be reduced [1]. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration.

Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount [2-5]. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behaviour; drugs having specific absorption site in GIT, targeting to colon; and cases where night time dosing is required.

For several drugs or therapies, a pulsatile release profile, where the drug is released completely after a defined lag time, is advantageous [6]: for drugs which develop biological tolerance, for drugs with an extensive first pass metabolism, for drugs targeted to a specific site in the intestinal tract, e.g. to the colon, protecting the drug from degradation and for the adaptation of drug needs to circadian rhythms of body functions or diseases [7-9]. With eroding or dissolving systems, a potential problem is the retardation and therefore there is no immediate drug release after the loss of the barrier function or a premature release, seen in particular with highly water-soluble drugs [10-12]. In the present research study, an attempt was made to develop a novel dosage form by using a chronopharmaceutical approach (**fig. 1**).

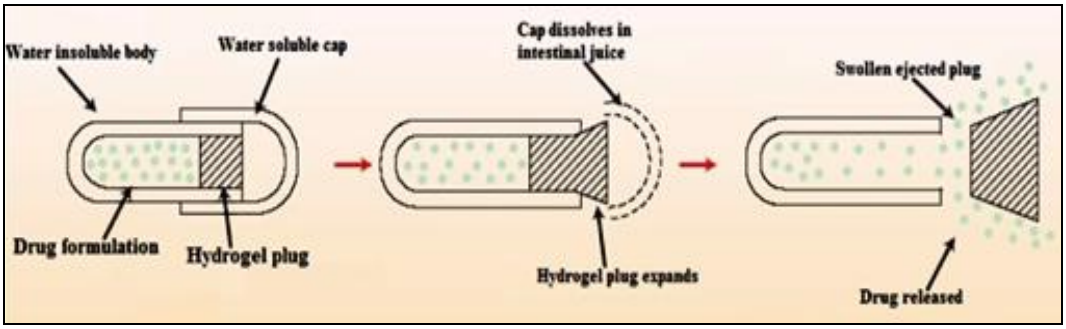

FIG. 1: MECHANISM OF DRUG RELEASE FROM PULSED BASED CHRONOPHARMACEUTICAL DRUG DELIVERY

A pulsatile 'pellet in capsule' dosage form, whose lag time was controlled by polymer plug was taken at bed time with a programmed start of drug release early in morning hours, can prevent a sharp increase in the incidence of asthmatic attacks, during the early morning hours (nocturnal asthma). The objective of this study was to design and characterize pulsatile drug delivery system delivering (400 mg) theophylline. Theophylline was chosen as the model drug because of its high solubility and high permeability pattern throughout the GI tract.

MATERIALS AND METHODS:

Materials: The following chemicals were obtained from commercial suppliers and used as received: Theophylline (Cipla, Bangalore, India), PVP K30 (Dr Reddy's Pvt. Ltd., Hyderabad), Crosspovidone XL-10 (International Specialty Inc, Hyderabad), Ethyl cellulose, Lactose, Formaldehyde solution (Bharat

Institute of Technology-Pharmacy, Hyderabad), Xanthan gum (Al-ameen College of Pharmacy, Bangalore), Karayagum (AP Girijan Cooperative Society), Hard gelatin capsules, Tween 80 (AP Pharma distributors, Hyderabad), Dichloromethane, High density polyethylene, Phosphate buffer saline, Polydimethylsiloxane, Isopropyl alcohol (S D Fine Chemicals ltd, India).

Methods:

Formulation of pulsatile capsule: Theophylline blend was added slowly by spraying the binder made from PVP-water solution. The pellets were then dried in a tray drier at about 45°C-55°C to attain the moisture content less than 2.5%. The drug and excipients were sieved (315µm), blended in a Turbula-mixer for 15 mins. The bodies and caps of formaldehyde treated hard gelatine capsules were separated manually. Pellets equivalent to 400 mg of theophylline were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the pellets were then plugged with various polymers, i.e., Xanthum gum, Crosspovidone XL-10 and Karaya Gum prepared by direct compression method. The compressed plugs (F1-F45) made of various polymers like Xanthum gum; Crosspovidone XL-10 and Karaya gum with dip coating with different compression pressures were placed by hand on top of the pellets in the open end of capsule as shown in **Figure 2**.

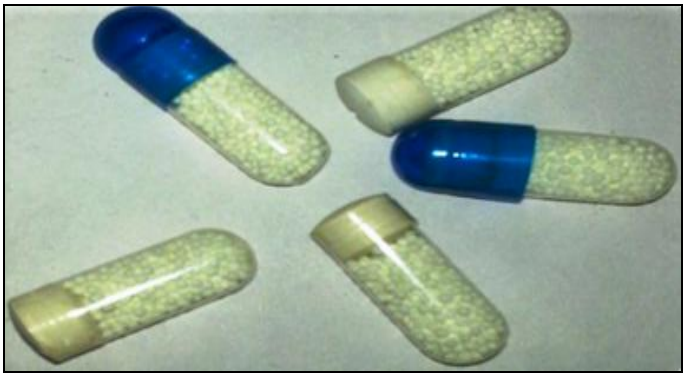

FIG. 2: CHRONOPHARMACEUTICAL BASED PULSATILE CAPSULAR FORMULATIONS OF THEOPHYLLINE

Characterization studies of complete pulsatile system:

Drug- Polymer Compatibility Studies by DSC and FTIR: Physical mixture of the drug theophylline and various polymers were prepared. After powder sieving, the mixture was analysed by DSC and FTIR. For DSC, thermogram was obtained for drug-karaya gum, drug-xanthum gum, drug-Crosspovidone XL-10 and was compared with the thermogram of the pure drug. Accurately weighed samples (10mg) were hermetically sealed in flat bottom aluminium pans. The scanning was carried out at a temperature ranging from 40^0C to 300^0C at a rate of 20^0C/min under an atmosphere of nitrogen.

X-Ray Diffraction study: Powder X-ray diffraction patterns where traced employing X-ray diffractometer (Seiferd,Model NO.3000,Germany) for samples, using Ni filtered CuK radiation, a voltage of 40 KV, a current of 30mA radiation scattered in the crystalline regions of the sample was measured . Patterns where obtained by using a step width of 0.04°C with a detector resolution in 2θ (diffraction angle) between 10° and 80° at ambient temperature [25].

Determination of melting point of theophylline: Melting point of theophylline was found by open capillary method as mentioned in pharmacopoeia. 1 mg of finely powdered theophylline was hand filled into capillary tube, whose one end was fused; this capillary was then inserted into the above mentioned instrument.

Determination of calibration curve of theophylline: The UV scanning of drug sample was carried out using a solution of drug dissolved in 6.8 pH phosphate buffer solution. The lambda max was observed at 272nm. The calibration curve of Theophylline was obtained by dissolving the drug in 6.8 pH phosphate buffer solution and the absorbance was measured at 272nm by keeping 6.8

pH phosphate buffer solution as blank. Beers law was obeyed in the concentrations range of 2- 16 µg/ml in 6.8 pH phosphate buffer solution. 100 mg of Theophylline was accurately weighed and taken in 100 ml volumetric flask. Drug was dissolved in 6.8 pH phosphate buffer solution and ultra sonicated for 10 min to ensure complete dissolving of drug, which give a concentration of 1000 µg/ml. From stock I, 10 ml is taken and diluted to 100 ml which give a concentration of 100 µg/ml solution, this is stock II. From the above stock II solution 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml were withdrawn into 10 ml volumetric flasks and diluted up to the volume with 6.8 pH phosphate buffer solution.

Determination of drug content in pellets: In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH 6.8. The flask was shaken for 12 hrs using an orbital shaker incubator. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 272 nm by using UV absorption spectroscopy.

Evaluation of thickness of coating on pulsatile capsule: The thickness of the EC coating was measured using screw gauge and was expressed in mm. 10 capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than 90% or more than 110% of the average

Determination of swelling index of plugs: The plugs prepared with varying compression pressures were tested for swelling index using disintegration apparatus (900 ml pH 7.4 phosphate buffer USP XXIII, 37±0.5^{o}C). Xanthum gum polymer was taken as model polymer in order to determine swelling rate.

Friability test of theophylline pellets: For each pulse dose capsule formulation, the friability was determined using the Roche friabilator (Camp-bell Electronics, Mumbai, India).

Qualitative chemical test for free formaldehyde: Standard formaldehyde solution used is formaldehyde solution (0.002, w/v) and sample solution is formaldehyde treated bodies (about 25 in number) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. In brief, to 1ml of sample solution, 9ml of water was added. One millilitre of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40^{o}C and allowed to stand for 40 min

***In vitro* release profile of pulsatile capsule:** Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method.

When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred millilitres of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5^{o}C. Capsules were tied to paddle with a cotton thread in each dissolution

vessel to prevent floating. Five millilitres of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analysed at 272 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

Stability studies: Stability studies as per ICH guidelines were carried out for optimized formulation from each polymer batch. Storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated.

RESULTS AND DISCUSSION: Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of time-of-day of drug administration on resultant pharmcodynamic and pharmacokinetics parameters. The significance of these day-night variation has not been over looked from the drug delivery perspective and pharmaceutical scientist have displayed considerable ingenuity in the development of time delayed drug delivery systems to address emerging chronotherapeutic formulations.

The colon is a site where both local and systemic delivery of drugs can take place. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Colon-specific systems could also be used in diseases that have diurnal rhythms. In the present study, attempt was made to target the drug to the colon, and intentionally delaying the drug absorption from therapeutic point of view in the treatment of nocturnal asthma, where peak symptoms are observed in the early morning. Prior to formulation, preformulation studies were carried out in order to established compatibility between drug and polymers by IR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of the drug. The IR spectrum of pure drug as shown in **Figure 3** was found to be similar to the reference standard IR spectrum of theophylline given in British pharmacopoeia.

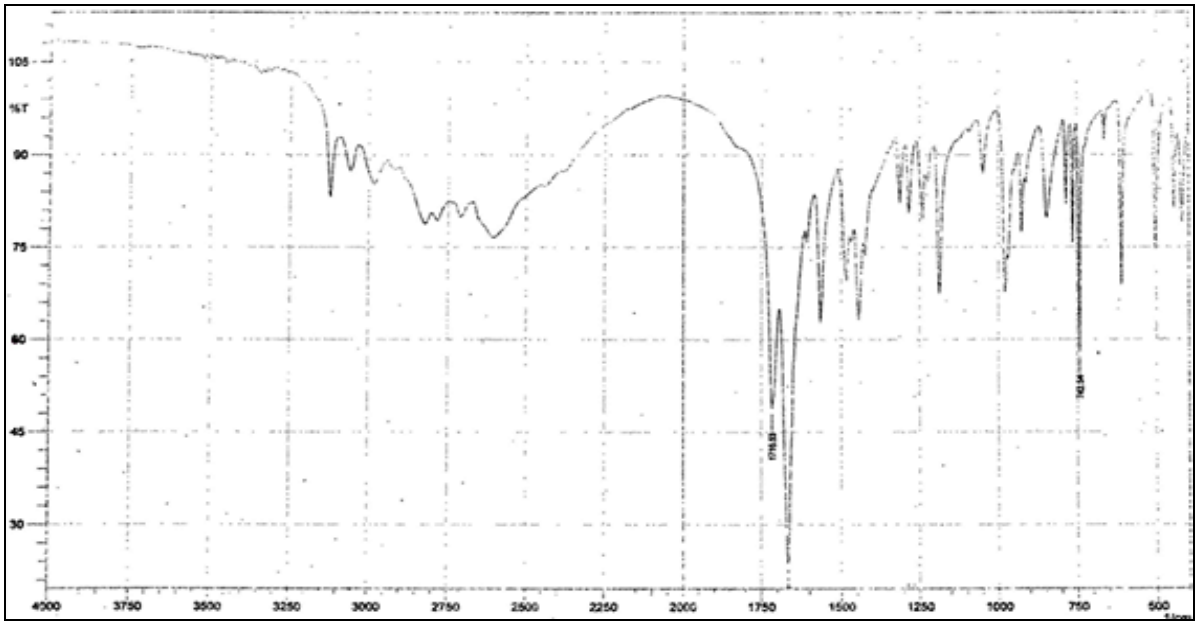

FIG. 3: FTIR GRAPH OF PURE DRUG THEOPHYLLINE

Melting point of theophylline was found to be in the range of 272°C to 274°C as reported in pharmacopoeia, thus indicating purity of the drug sample. The absorbance reading of theophylline standard solution containing 10- 100 µg/ml of drug in pH 1.2, pH 6.8 and pH 7.4 at the maximum wavelength of 272nm. **Figure 4** shows the standard calibration curve for theophylline with slope, intercept and regression co-efficient. The calculations of drug contents and in-vitro drug release study are based on this standard curve.

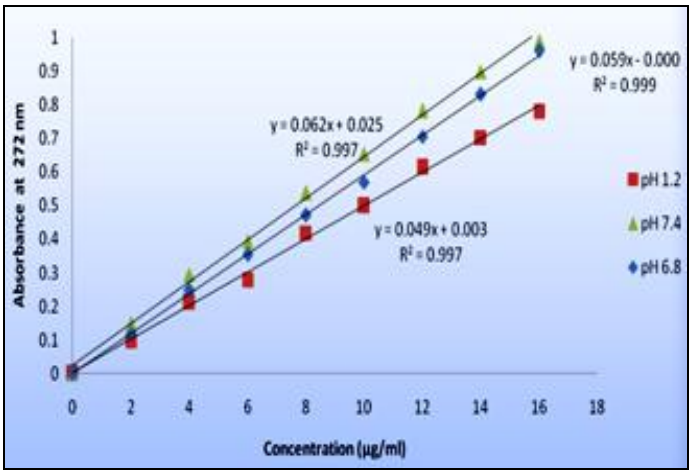

FIG. 4: STANDARD GRAPH OF THEOPHYLLINE IN pH 1.2, pH 6.8 AND pH 7.4

The polymer plugs were formed by direct compression method with a single punch press with varying compression pressures. Theophylline pellets were prepared by direct compression method followed by placing the pellets in the capsule body by hand filling and placing the plug on the capsule opening. A tight fit between the plug and the impermeable capsule was very important in order to prevent water penetration to the capsule content and drug release prior to complete erosion of the plug material. In order to identify proper plug materials, they were tested for swelling index using disintegration apparatus. DSC studies were performed on the pure drug and drug- polymers in order to study the interaction between pure drug and polymers. The DSC thermograms of pure drug and the physical and co-ground mixtures showed two endothermic peaks. First broad endothermic peak in the range of 500c-1300c corresponds to polymeric endothermic peak; second endothermic peak represents the melting temperature of drug in mixtures. X-Ray diffraction studies were undertaken to consolidated DSC data indicating reduction of crystallinity of theophylline with other polymers). The percentage drug content was found to be in the range of 92.6 to 97.6 %.

From the *in-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours. Small amount of drug release was observed in simulated intestinal fluid (pH 6.8 phosphate buffer). Burst effect was found in colonic medium (pH 7.4 phosphate buffer). *In vitro* release profiles were found to have very good sustaining efficacy. After coating thickness of the plug was increased up to 2-3mm all the designed pulsatile capsules were found to be in the limit of weight variation test.

The formulations containing karaya gum showed a lag time of about 8 hrs while the lag time of formulations containing crosspovidone XL 10 was decreased to 6 hrs because of less amount of polymer in the plug on the other hand lag time of formulation containing Xanthum gum was further decreased to 4 hrs this might be probably due to the effect of high content of filler and less amount of polymer in the plug. The 2.5% ethyl cellulose coating on polymer plugs has shown an increase in lag time about 2 hrs.

On the other side 5% ethyl cellulose coating further increased the lag time and the plugs were ejected at the end of 12, 16 and 20 hrs. Cumulative percentage release of about 76.2%, 97.5% was observed overall. Increase in the polymer content (% coating and ratio) resulted in a reduction in release of theophylline. The obtained results

showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting. From the accelerated stability studies, it was observed that there were no significant change in the drug content and % release of drug; therefore the formulations are quite stable (**table 1**).

TABLE 1: DRUG AND POLYMER STABILITY STUDIES

Drug and Excipients	Initial Physical Description	25°C / 60% RH & 40°C / 75% RH (Closed)		
		1st Week	2nd Week	4th Week
Theophylline	White crystalline powder	*	*	*
Theophylline + Sugar spheres	Off-white powder contain spherical pellets	*	*	*
Theophylline + Aerosil	Off-white powder	*	*	*
Theophylline + PVP K30	Off-White powder	*	*	*
Theophylline + Xanthum gum	white powder contain crystalline material	*	*	*
Theophylline + Crosspovidone XL-10	Off-white powder	*	*	*
Theophylline + Karaya gum	White-brownish powder	*	*	*
Theophylline + Ethyl cellulose N 50	Off-white powder	*	*	*
Theophylline + lactose	Off-white powder	*	*	*
Theophylline + Sugar spheres + Aerosil + PVP K30 + EC N-50 + Lactose + Xanthum gum	Off-white powder containing lumps	*	*	*
Theophylline + Sugar spheres + Aerosil + PVP K30 + EC N-50 + Lactose + Crosspovidone XL-10	Off-white powder containing lumps	*	*	*
Theophylline + Sugar spheres + Aerosil + PVP K30 + EC N-50 + Lactose + Karaya gum	Off-white powder containing lumps	*	*	*

(*) indicates that there is no interaction between drug and excipients at 25°C/60% RH, 40°c/75% RH

CONCLUSION: In conclusion, results suggested that lag time is dependent on the nature of the materials employed in plug preparation and found that position of the plug in the capsule body significantly affects lag time. It is evident that an increase in the filler concentration in the plug results in a decrease in lag time. Finally, it is possible to release a drug over a predetermined period of time with specific release rates by manipulating the polymers used to prepare plugs.

ACKNOWLEDGEMENTS: The authors convey their sincere thanks to, Al-Ameen College of Pharmacy, Bangalore for providing materials and equipments for conducting experimental work. The authors are also very grateful to Jawaharlal Nehru Technological University (JNTU-H), Hyderabad and Department of Pharmaceutics, University College of Pharmaceutical Sciences, Andhra University for providing valuable suggestions for design of the work. One of the authors would also like to express his gratitude to Mrs. Sabiha Banu, Department of Pharmaceutics, Al-Ameen college of Pharmacy, Bangalore for helping in literature survey for the project.

REFERENCES:

1. Peter X. M, Xiaohua Liua, Glenda J. Pettway, Laurie K. McCauley, Pulsatile release of parathyroid hormone from an implantable delivery system, Biomaterials 28 (2007) 4124–4131.
2. Janjira Intra, Justin M. Glasgow, Hoang Q. Mai, Aliasger K. Salem, Pulsatile release of biomolecules from polydimethylsiloxane (PDMS) chips with hydrolytically degradable seals, Journal of Controlled Release 127 (2008) 280–287.

3. Essayan DM. (2001). "Cyclic nucleotide phosphodiesterases." J Allergy Clin Immunol. 108 (5): 67180.Doi:10.1067/mai.2001.119555. PMID 11692087.
4. Daly JW, Jacobson KA, Ukena D. (1987). "Adenosine receptors: development of selective agonists and antagonists."*Prog Clin Biol Res.* 230 (1):41–63. PMID 3588607.
5. Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. Clinical Allergy. 1988; 18:143-50.
6. Lesko LJ. Dose-dependent elimination kinetics of theophylline. Clin Pharmacokinetics 1979; 4:449-459.
7. Grygiel JJ, Birkett DJ,. Cigarette smoking and theophylline clearance and metabolism. Clinical Pharmacology and Therapeutics. 1981; 30:491-6.
8. Vozeh S, Kewitz G, Perruchoud A et al. Theophylline serum concentration and therapeutic effect in severe acute bronchial obstruction: the optimal use of intravenously administered aminophylline. American Review of Respiratory Disease. 1982; 125:181-4.
9. Stein GE, et al. Conversion from intravenous to oral dosing using sustained-release theophylline tablets. DICP 1982; 16: 772-774.
10. Dunn G, Rybak MJ. Nonlinear theophylline kinetics (letter). DICP 1984; 18:155.
11. Coleman RW, Hedberg RL. Comparison of three methods for estimating theophylline pharmacokinetics. Clin Pharm 1983; 2:148-52.
12. Mungall DE, et al. Individualizing theophylline therapy: the impact of a clinical pharmacotherapeutics on patient outcome: Ther Drug Monit 1983; 5:95-101.
13. Jonkman JHG, Upton RA. Pharmacokinetic drug interactions with theophylline. Clinical Pharmacology. 1984;9:309-34
14. Jenne JW. Theophylline use in asthma: some current issues. Clinics in Chest Medicine. 1984; 5:645-58.
15. Hendeles L, Weinberger M. Theophylline: a state of the art review. Pharmacotherapy 1983: 3:2-44.
16. Hendeles L, et al. update on pharmacodynamics and pharmacokinetics of theophylline. Chest 1985; 88:10S-111S.
17. Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. Clinical Allergy. 1988; 18:143-50.
18. Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. Clinical Allergy. 1988; 18:143-50.
19. Nassif EG, Weinberger M, Thompson R, Huntly W. The value of maintenance theophylline in steroid-dependent asthma. New England Journal of Medicine. 1981; 304:71-5.
20. Weinberger M, Hendeles L. Slow-release theophylline: rationale and basis for product selection. New England Journal of Medicine. 1983; 308:760-4.
21. Pharmaceutical Excipients, Edited by: Raymond C Rowe, Paul J Sheskey and Siân C Owen.
22. Handbook of Pharmaceutical excipients, 2009, sixth edition, edited by: Raymond C Rowe, Paul J Sheskey and Marian E Quinn.

****