Dissolution Studies on Pentoxifylline Sustained Release Tablets Influence of Storage

M. SRIPAL REDDY*[1], Y. S. R. KRISHNIAH, T. RAMA RAO AND S. SATYANARAYANA
Department of Pharmaceutical Sciences, College of Engineering, Andhra University, Visakhapatnam-530 003
[1]University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 009

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Dissolution studies were carried out using the USP dissolution apparatus-I in the presence and absence of rat caecal contents and apparatus-II. The formulation taken for the analysis is Kinetal - 400 SR tablets, which contain 400mg of pentoxifylline, sampled at different storage periods (first month, first year, second year and last month of the shelf life). The studies indicates that there was no significant change ($P>0.001$) in dissolution pattern of the drug from, Kinetal-400 products on storage. USP dissolution apparatus-I showed quicker dissolution of products compared to apparatus-II. Adding rat caecal contents did not improve dissolution of products indicating that the tablet coating is unaffected by clonic bacterial enzymes.

The assurance of quality of pharma-ceutical products is very important since these are life saving in times of illness. The quality is usually determined by subjecting the products to various quality control tests during preformulation and formulation stages. Accelerated stability analysis is carried out by subjecting the drug/ formulation to various elevated temperatures and then predicting its stability at room temperature to determine its shelf life during a specified period. Effects of the storage period on vitamin stability were studied by various authors[1-4]. There may be retardation of the dissolution rate of formulations upon storage periods[5,6]. It is quiet common that the quality of a marketed product is determined during the shelf- life by manufacturers. During marketing, the products are subjected to varied temperature conditions in transport and storage , which may not be exactly similar to the conditions were they are manufactured and tested. Therefore we attempted to study the effect of shelf life on the pentoxifylline tablets (Kinetal-400) sampled at different storage periods from a pharmacy.

The formulation selected for the dissolution studies are Kinetal-400 sustained Release (SR) tablets manufactured by Cipla labs, Mumbai that were sampled at first month (FM,Batch No: K80345, Dec.1998), first year (FY, Batch No: K80160, June 1998),second year (SY, Batch No.:K70171,July 1997) and last month (LM, Batch No:K60051, April 1996) of the shelf life. USP XXIII dissolution apparatus type-I and type-II with rpm 100 and 50 respectively was used for the dissolution studies. Dissolution studies were carried out by using a basket-type assembly at 100 rpm stirrer speed. Tablets in triplicate were taken from different storage periods in to the basket, dissolution was carried out in the presence of 900 ml of gasatric fluid for 1 h in the same way, paddle type assembly with a setting of 50 rpm stirrer speed by taking FM and LM. Only two storages periods were taken in case of paddle type because it takes longer time for dissolution. The samples were collected at different time intervals and absorbances of the pentoxifylline was measured using a UV-VIS spectrometer at 272 nm wavelength. Cumultative percent pentoxifylline release at different time points was plotted.

For the preparation of caecal contents male rats (supplied by M/S Gosh Enterprises, Culcutta, India) weighing 150-200 g maintained on normal diet (soaked Bengal gram) were used through out the study. Thirty minutes before the commencement of drug release studies, four rats were sacrificed by cervical dislocation. Abdomen was cut open and caecum was traced, ligated at both ends, dissected and immediately transferred in to pH 6.8 phosphate buffered saline (PBS), previously bubbled with CO_2. The caecal bags were opened; their contents were individually weighed, pooled and then

*For correspondence
E-mail : sripal.r@usa.net

suspended in PBS to give required caecal dilution (2-4% w/v). As the caecum is naturally anaerobic all these operations were carried out under CO_2.

The release studies were carried out using USP dissolution rate test apparatus (apparatus-I, 100 rpm, 37°) with slight modification. A beaker (capacity 150 ml) containing 100 ml of dissolution medium was immersed in water containing in a 1000 ml vessel, which was in turn placed in the water bath of apparatus. The tablets were placed in the basket and immersed in the dissolution medium containing rat caecal contents. The experiment was carried out with continuous bubbling of CO_2 through the medium to simulate the anaerobic environment of caecum. One millimeter of sample was withdrawn at different timings and same volume was replaced with fresh PBS bubbled with CO_2 and the experiment was continued up to 24 h (usual colonic transit time is 20-30 h[7]). The volume was made upto 10 ml with PBS and centrifuged, the supernant was filtered through a bacterial proof filter (G-5, Borosil) and the filtrate was analyzed for pentoxifylline content at 272 nm using single beam UV spectrophotometer as described earlier (Shimadzu-UV-150-02).

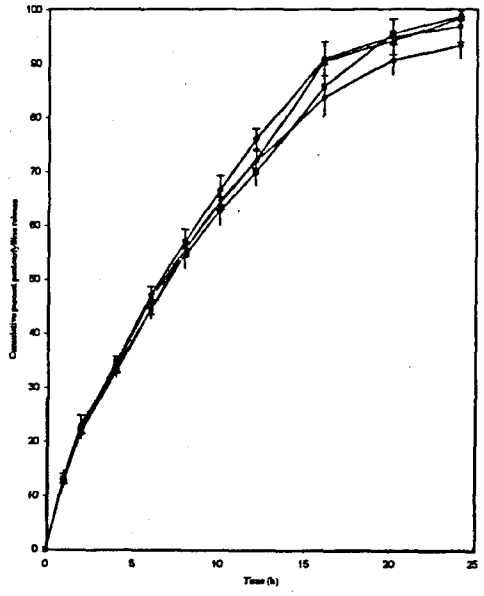

Fig. 1: USP apparatus I and release of pentoxifylline

Cumulative percent release of pentoxifylline was determined using USP dissolution apparatus I from pentoxifylline tablets collected in the first month (-◆-), first year (-□-), second year (-▲-) and lastmonth (-○-) of the storage period

The dissolution profiles of Kinetal-400 SR tablets using USP dissolution apparatus-I are given in the fig. 1 and apparatus-II are given in fig. 2. This dissolution pattern of the tablets in the presence of rat caecal contents in

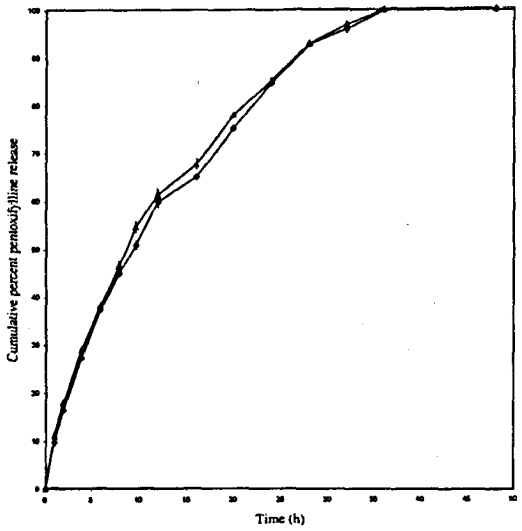

Fig. 2: USP apparatus II and release of pentoxifylline

Cumulative percent release of pentoxifylline was determined using USP dissolution apparatus II from pentoxifylline tablets collected in the first month (-▲-), and last month (-◆-) of the storage period

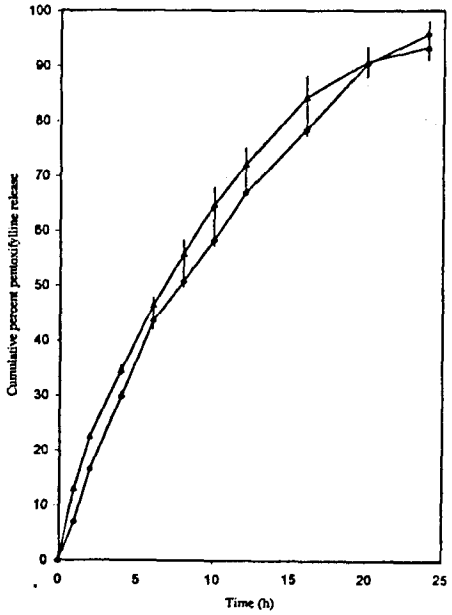

Fig. 3: Influence of caecal contents on the release of pentoxifylline

Comulative percent release of pentoxifylline was determined using USP dissolution apparatus II from Pentoxifylline tablets collected in the first month of the storage period in the presence (-▲-) and absence (-◆-) of rat caecal contents

TABLE 1: DISSOLUTION PARAMETERS USING USP DISSOLUTION APPARATUS-I

Dissolution Parameters	FM	FY	SY	LM	Level of Significance
Commulative Precent Release	93.2±2.2	98.6±1.3	98.2±0.3	96.7±2.9	NS
$T_{50\%}$(h)	6.8±0.2	7.1±0.3	6.8±0.2	6.4±0.2	NS
C_{4th}(mg/ml)	24.6±0.9	33.1±1.4	33.6±1.0	35.0±1.0	NS

Commercial tablets, Kinetial sampled at first month after manufacturing (FM), first year after manufacturing (FY), second year after manufacturing (SY) and last month of their shelf life (LM), NS indicates not significant at P>0.001

TABLE 2: DISSOLUTION PARAMETERS USING USP DISSOLUTION APPARATUS-II

Dissolution Parameters	FM	LM	Level of Significance
Cummulative Percent Release	99.9±.05	99.5±0.4	NS
$T_{50\%}$(h)	9.4±0.3	8.6±0.2	NS
C_{4th}(mg/ml)	27.4±0.3	29.1±0.7	NS

Commercial tablets, Kinetial sampled at first month after manufacturing (FM), and last month of their shelf life (LM), NS indicates not significant at P>0.001

comparison with dissolution in the absence of caecal contents, using USP dissolution apparatus-I with modifications is given in fig. 3 . The time period necessary for 50% release of pentoxifylline from the tablets , the cumulative percentage of the drug released after 24 h and the amount released after 4 h using apparatus-I is shown in Table 1.

By using USP dissolution apparatus-II the time required for the 50%release of the drug from the products was found to be 9.4 and 8.6 h for FM and LM respectively. (Table 2) indicating that the dissolution was increased to a minor extent on storage. The dissolution pattern of the product was also studied using apparatus-I to find whether the total duration of experiment can be reduced. The time required for the 50% of the drug release is 6.8, 7.1, 6.8 and 6.4 h for FM, FY, SY and LM respectively. There might be some degree physical change in the membrane character on storage and it might be responsible for a slight increase in the drug release pattern from the product on storage. Studies using rat caecal contents did not improve the dissolution pattern further indicating that the coating material was unaffected by clonic bacterial enzymes. All the above dissolution studies revealed that the products show drug release character that is excepted for sustained release preparations.

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