



<http://www.e-journals.net>



ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
Vol. 5, No. 2, pp.316-322, April 2008

Thermal and Isothermal Methods in Development of Sustained Release Dosage Forms of Ketorolac Tromethamine

DIMPLE CHOPRA*, VIVEK RANJAN SINHA and MANJEET SINGH

Department of Pharmaceutical Sciences and Drug Research
Punjabi University, Patiala –147002

dimplechopra24@yahoo.co.in

Received 30 September 2007; Accepted 20 November 2007

Abstract: Differential scanning calorimetry (DSC) is a rapid and convenient and conclusive method of screening drug-polymer blend during pre-formulation studies as it allows polymer incompatibility to be established instantaneously. Various batches of matrix tablets of ketorolac tromethamine (KTM) with a series of compatible polymers were prepared. Batches of tablets which gave desired sustained release profile were subjected to stability testing according to ICH guidelines. The analysis for drug content was done using high performance liquid chromatography (HPLC) method. The results revealed that there was no statistically significant change in drug content after storage of matrix tablets at elevated temperature of 40 °C and 75% relative humidity. From our study we conclude that with careful selection of different polymers and their combinations, a stable sustained release oral dosage form of ketorolac tromethamine can be achieved.

Keywords: Ketorolac tromethamine, DSC, HPLC, matrix tablets, stability testing.

Introduction

Ketorolac tromethamine (KTM) is a non steroidal anti-inflammatory drug which exhibits potent analgesic, anti-inflammatory and antipyretic¹⁻³ effects. It is administered intramuscularly, intravenously, orally and as ocular⁴ formulation. KTM is a basic salt of a moderately acidic drug (pKa 3.49), with a reasonable solid-state stability. The excipient-mediated decomposition of ketorolac in the solid state depends on salt form of the drug, the type of excipient, moisture content, temperature and oxygen pressure. In solid blends, ketorolac undergoes decarboxylation, oxidation and amidation to form decarboxy analog, 1-keto analog or 1-hydroxy analog and amide of ketorolac⁵ respectively. Several approaches have been identified in literature for improving the stability^{6,7} of ketorolac powder blends. To predict shelf-life of the final dosage form one should know about stability of the active

ingredient and other components of the formulation. Most of the techniques⁸ reported in the literature are labor intensive, time consuming, deal with limited number of variables and have poor predictive values. The studies on the interaction between the drug and the excipients are generally carried out by means of DSC or accelerated stability tests followed by analytical determination⁹ (HPLC and other methods) of the active principle. There are conflicting reports in literature about compatibility of certain excipients and ketorolac tromethamine upon individual application of these two analytical methods. Therefore the present paper stresses upon the need of using both thermal and isothermal methods in development of stable and efficacious drug formulations.

Experimental

Ketorolac tromethamine (Ranbaxy Laboratories Ltd, Gurgaon), Methocel (Colorcon Asia Pvt. Ltd, Mumbai), Xanthan gum USP (Dabur Research Foundation, Sahibabad), Carbopol974P (Noveon, Mumbai) and Eudragit (S. Zhaveri & Co., Mumbai) were obtained as a gift sample. The solvents used for HPLC analysis were purchased from different commercial sources. All the other excipient used were of AR grade. De-ionized water was used throughout the study.

Instruments

WTC binder stability chamber (Germany) was used to carry out stability studies. DSC (DSC 821^o, Metler Toledo) was used for thermal analysis. HPLC was performed on Shimadzu systems fitted with a LC-10 ATVP pumping system, SPD-10AVP UV-Vis detector (at 254 nm) with class VP software and ODS reverse-phase C₁₈ (25 cm X 4.5 mm) column.

Drug-polymer compatibility studies

Powder blends (50mg) of drug and various polymers *i.e* HPMC, Carbopol 974P, xanthan gum were prepared using geometric dilution method. The ratio of drug to polymer chosen was same as that in the final formulation. DSC was calibrated by using indium as a standard with melting point T_{fus} at 156.63 °C and calibration energy [ΔH_{fus}] of 28.89 J/g. Accurately weighed samples (5mg) were heated in sealed aluminium pans from 25 to 300 °C at a scanning rate of 10 °C/min under nitrogen purging (80mL/min). Differential scanning calorimetry was conducted first with samples of the pure polymers, pure drug and then on prepared drug-polymer blends. The DSC profiles thus obtained were compared for possible drug-polymer interactions.

Stability studies

ICH stability guidelines¹⁰ were strictly followed to carry out stability studies. All the matrix tablets were prepared by direct compression. The general formula for matrix tablets is shown in Table 1. Four batches of hydrophilic matrix tablets containing 80%w/w of polymers *ie* HPMCK4M, Carbopol974P, Carbopol974P:HPMC combinations (1:1 and 1:3) were kept in a screw capped amber coloured glass bottles. All the glass bottles were packed in a black canvas bag and placed in the stability chamber at 40 °C and 75% RH for six months. Samples were withdrawn at periodic time intervals *i.e* 1,2,3 and 6 months and tested for drug content using HPLC method.

Preparation of calibration curve for HPLC analysis

An accurately weighed quantity (100mg) of KTM was transferred to a clean, dry 100 mL volumetric flask. The sample was dissolved in water (50mL) and the final volume was adjusted to 100mL and labelled as stock solution. The stock solution was diluted with mobile phase (water:methanol:acetic acid 40:59:1) to produce solutions with concentration range of 1.0-20.0 mcg/mL. Twenty microlitres of each dilution was injected triplicate into the

chromatographic system. The peak area was used as the response for the preparation of the calibration curve. The method was validated for linearity and accuracy.

Quantitative analysis of the stressed samples

All isothermally stressed samples were analyzed by reported⁶ HPLC method. To an accurately weighed sample of crushed tablets, 15mL of water was added and the mixture was processed ultrasonically for further 10min. This procedure was followed in order to solubilize all the drug and its degradation products (if formed), leaving the insoluble excipients. A 5mL portion of this solution was filtered through a 0.45µm membrane filter. An aliquot of filtrate (1mL) was diluted with the mobile phase (dilution factor 25) and analyzed by HPLC. The percentage of residual KTM was determined using peak area of KTM from the calibration curve.

Table 1. Formulation of ketorolac tromethamine used in the study.

Ingredient	Milligrams per tablet
Ketorolac tromethamine	10
Polymer	160
Spray-dried lactoseUSP	26
Talc	2
Magnesium stearate	2

Results and Discussion

The DSC thermograms of the drug and polymers tested are shown in Figures 1-5. Each of these figures indicates the thermal behavior pattern of the pure drug, polymer and drug-polymer blend. The DSC trace of KTM shows three endothermic peaks at 160.94, 167.85, 196.73 °C. The first peak is associated with the melting of KTM (reported m.p is 160-161 °C). The second and third endothermic peaks are related to the decomposition and evaporation of the drug respectively. In all drug-polymer blend, the melting endotherm of KTM was well preserved with little change in terms of sharpening, broadening or shifting towards a lower temperature. These minor changes in the melting endotherm of the drug may be attributed to mixing process, which lowers the purity of each component in the mixture, thus resulting in slightly lower melting points, but not truly representative of incompatibility. Slight variations in the peak shape and melting point may be also triggered by varying sample geometry¹¹ during mixing. In some cases, the shape of the DSC curve of the pure excipient differed from that of the mixture. This may be due to variations in the quantities of excipient used for the analysis. The peak shape and enthalpy depend on quantity of material used whilst the peak transition temperature^{12,13} associated with complete fusion is independent. Since the amount of polymer present in the corresponding mixture is less than that in the pure substance. The difference in peak shape was apparent. Therefore, peak transition temperatures were taken into account for interpretation of DSC curves. The polymers did not show any characteristic endotherms, instead a broad endotherm was observed below 100 °C. This is attributed to evaporation of absorbed water from the polymers during heating.

The melting endotherm of the drug was well preserved in all cases apart from a considerable shift to a lower temperature in the case of HPMC. The peak corresponding to decomposition of KTM was missing in the blend of KTM with Carbopol 974P and HPMC K4M (1:1) as compared to KTM with Carbopol 974P and HPMC K4M (1:3). This can be very well explained by considering the DSC thermogram of blend of KTM and Carbopol 974P, both the melting and decomposition endotherms are very much suppressed. So as the proportion of Carbopol increases in a drug polymer blend its protective effect on the drug molecule increases. So, KTM is chemically compatible with all these polymers.

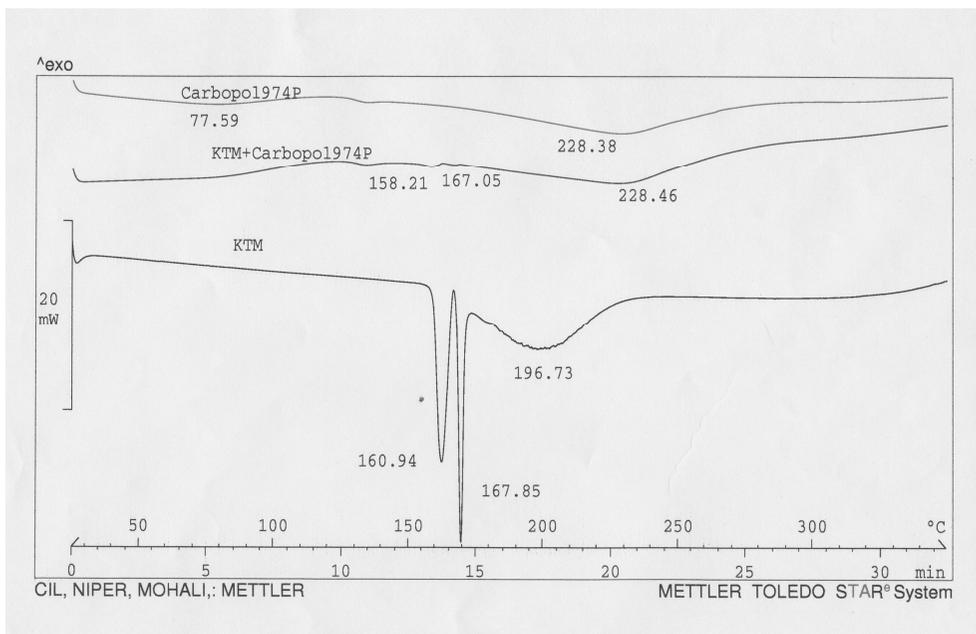


Figure 1. DSC thermograms of KTM with Carbopol 974P

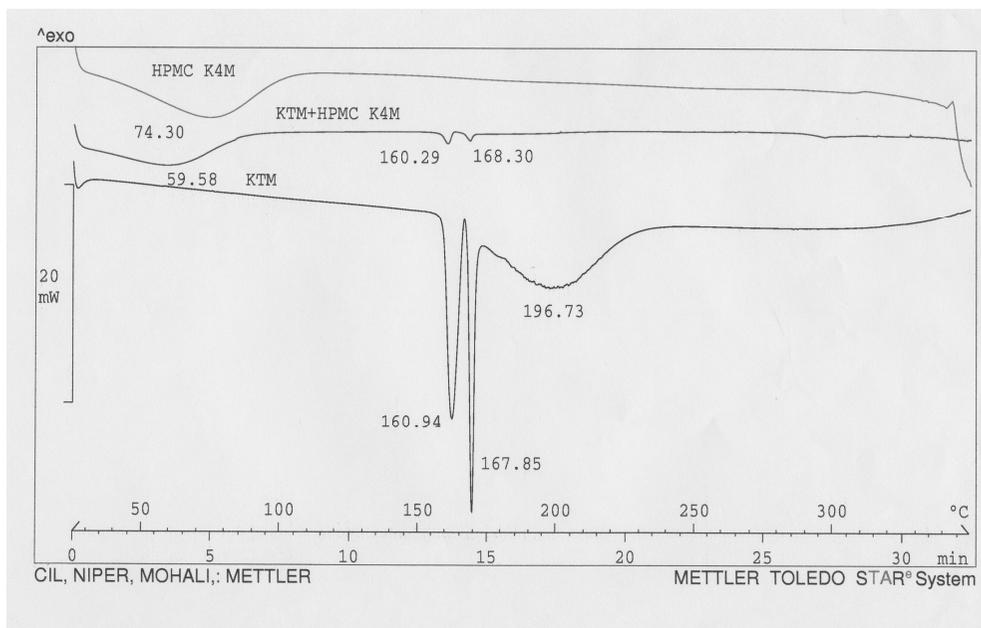


Figure 2. DSC thermograms of KTM with HPMC K4M

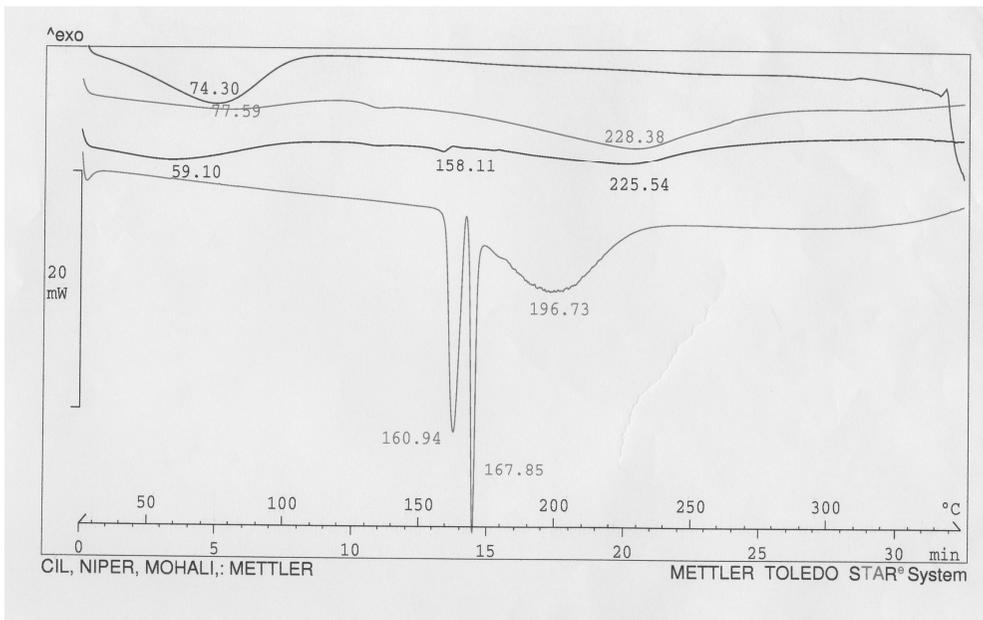


Figure 3. DSC thermograms of KTM with HPMC K4M and Carbopol 974P (1:1)

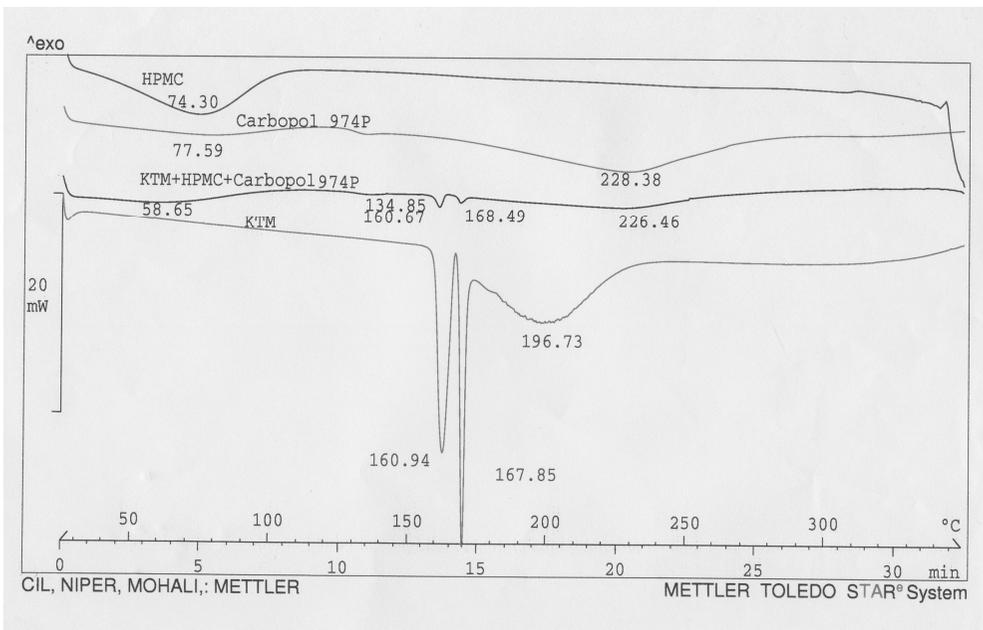


Figure 4. DSC thermograms of KTM with HPMC K4M and Carbopol 974P (1:3)

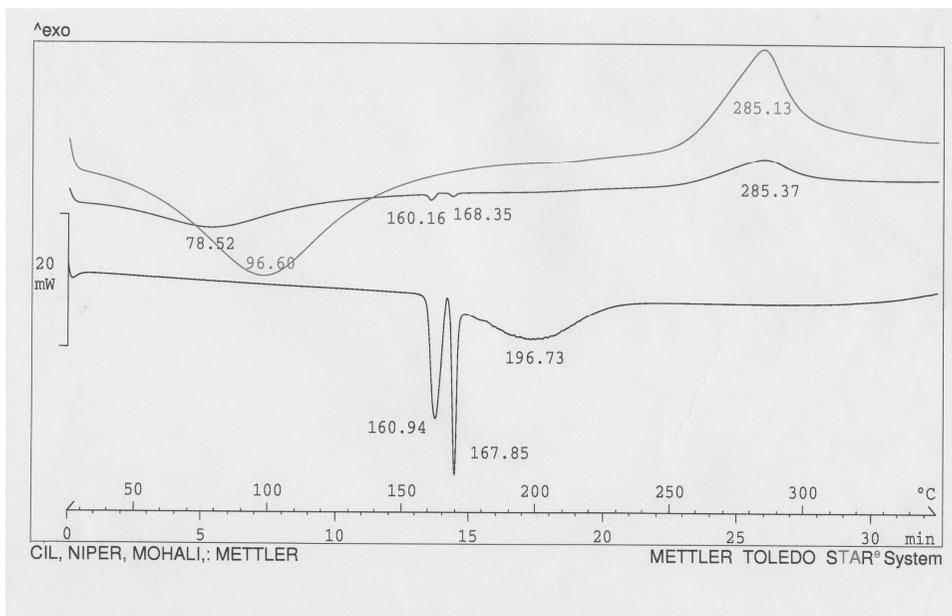


Figure 5. DSC thermograms of KTM with xanthan gum

From the typical chromatogram of KTM as shown in Figure 6, it was found that the retention time was 8.296 min. A good linear relationship ($r = 0.9850$) was observed between the concentration range of 1.0-20.0 mcg/mL. The absence of additional peaks in the chromatogram indicates non-interference of the common excipients used in the tablets. This demonstrates that the HPLC method used is simple, linear, accurate, sensitive and reproducible. The summary of analytical results of stressed samples is given in Table 2. In all the stressed samples, the percentage drug recovered was more than 94% after a period of one month. These polymers are Class I type excipients, which are known to exhibit negligible chemical compatibility and stability problems. Even after exposure to stressed conditions for a period of 6 months the drug content in all the samples was above 90%. This shows that KTM is chemically compatible with various excipients used in the formulation. The results of DSC and HPLC were in consonance for all the drug-polymer blends used in the study. This confirmed the utility of DSC as a rapid and convenient method for screening various excipients during preformulation stage. Further, quantitative assessment⁹ can be made using isothermal methods like HPLC. DSC can also be combined with spectral techniques (diffused reflectance spectroscopy, FTIR) to elucidate^{12,13} degradation mechanisms.

Table 2. Summary of HPLC assay of isothermally stressed samples of KTM with various polymers

Polymer(s) used	Percentage drug recovered			
	1 month	2 months	3 months	6 months
Carbopol 974P	98.4	96.7	95.0	94.0
HPMC K4M	97.3	94.7	94.3	93.2
Carbopol:HPMC(1:1)	97.6	95.0	94.6	93.8
Carbopol:HPMC(1:3)	96.5	95.0	94.6	90.7
Xanthan gum	99.9	97.8	95.1	95

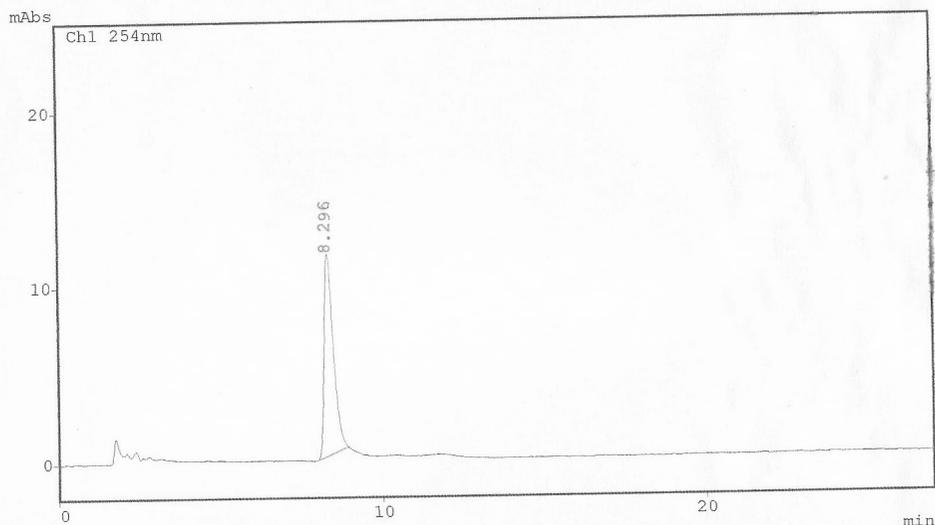


Figure 6. Typical Chromatogram of KTM by HPLC

References

1. Buckley MM and Brogden RN, *Drugs*, 1990, **39**, 86-109.
2. Brocks DR and Jamali F, *Clin. Pharmacokinet.*, 1992, **23**, 415-427.
3. Cho YA and Gwak HS, *Drug Dev. Ind. Pharm.* 2004, **30**, 87-194.
4. Sinha VR and Trehan A, *Drug Deliv.*, 2005, **12**, 133-139.
5. Gu L, Chiang HS and Becker A, *Int. J. Pharm.*, 1998, **41**, 95-104.
6. Brandl M, Magill A, Rudraraju V and Gordon M S, *J. Pharm. Sci.*, 1995, **84**, 1151.
7. Brandl M, Conley D and Johnson D, *J. Pharm. Sci.*, 1995, **84**, 1045- 1048.
8. Marini A, Berbenni V, Bruni G, Cofrancesco P, Giordano F and Villa M, *Curr. Med. Chem.* 2003, **2**, 303-321.
9. Ceschel GC, Badiello R, Ronchi C and Maffei P, *J. Pharm. Biomed. Anal.*, 2003, **32**, 1067-1072.
10. Singh S, *Pharm. Technol.* 1999, **23**, 68-88.
11. Kandrapu R, Grover V, Chawla HPS and Garg S, *S.T.P. Pharm. Sci.*, 2001, **11**, 449.
12. Mura P, Faucci M T, Manderioli A, Furlanetto S and Pinzauti S, *Drug Dev. Ind. Pharm.*, 1998, **24**, 747-756.
13. Swarbrick J and Boylan J C, *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, New York, 1996, 1-79.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

