

## Research Article

# Development and Evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen

MA Naeem<sup>\*</sup>, A Mahmood, SA Khan and Z Shahiq

Faculty of Pharmacy & Alternative Medicine, The Islamia University of Bahawalpur, Punjab, Pakistan.

## Abstract

**Purpose:** To develop and characterize bilayer tablet formulations of tramadol HCl (TmH) and acetaminophen (AAP) microparticles.

**Methods:** Coacervation via temperature change was the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. The microparticles of the two drugs were prepared separately and then compressed into bilayer tablets. The physicochemical compatibility and stability of the tablets were determined by Fourier transform infrared spectroscopy (FTIR), x-ray diffractometry (XRD), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) while their mechanism and pattern of drug release were assessed by applying Higuchi, Zero order, First order and Korsmeyer-Peppas kinetic models. Bilayer tablets were subjected to accelerated stability studies for three months.

**Results:** FTIR, XRD, DSC and TGA data for the formulations indicate good compatibility and stability. Furthermore, accelerated stability studies confirmed the stability of the formulations. Controlled drug release from the microparticles and bilayer tablets was observed for 8 h and 12 h, respectively. The Higuchi model produced the best fit, with regard to release profile, for both drugs, with correlation coefficient ( $R^2$ ) of 0.966 and 0.960 for AAP and TmH, respectively.

**Conclusion:** Microencapsulated TmH and AAP can be developed into suitable bilayer tablets that are stable and capable of releasing the drugs over 12 h.

**Keywords:** Acetaminophen; Tramadol; Ethyl cellulose; Microparticles; Bilayer tablets; Kinetic models.

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<sup>\*</sup>Corresponding author: **E-mail:** [mna19bwp@yahoo.com](mailto:mna19bwp@yahoo.com); **Tel:** 0092-321-4527428; **Fax:** 0092-62-9255565

## INTRODUCTION

Acetaminophen (AAP) is an odourless, slightly bitter, white crystalline powder. It is soluble in organic solvents such as methanol and ethanol but slightly soluble in water and ether. It is an analgesic and antipyretic drug that is used for the relief of fever, headache, and other moderate aches and pains [1]. AAP reduces production of prostaglandins, which are involved in pain and fever processes, by inhibiting the cyclooxygenase enzyme (COX-3) [2,3].

Tramadol hydrochloride (TmH) is a centrally acting analgesic having both opioid and non-opioid effects. TmH acts as opiate agonists, through selective binding to the  $\mu$ -opioid receptor, and weak inhibition of norepinephrine and serotonin uptake [4]. It is administered when non-steroidal anti-inflammatory drugs fail to mitigate pain. It is readily absorbed after oral administration. Its half-life is 6.3 h [5].

Ethyl cellulose (EC), an ethyl ether of cellulose, is a long chain polymer of  $\beta$ -anhydro-glucose units joined together by acetal linkages. Ethyl cellulose is an inert hydrophobic polymer and is essentially odourless, tasteless, colorless, non-toxic, biocompatible and soluble in a wide range of organic solvents [6, 7].

Although a conventional solid dosage combination of TmH and AAP has been approved by the United States Food and Drug Administration (FDA) for use, patients still have to take the conventional tablets 3 - 4 times a day. To improve patient's compliance, a controlled-released combination was developed and characterized in this study for its physical and chemical stability as well as for release characteristics.

## EXPERIMENTAL

### Materials

Tramadol hydrochloride (Ali Gohar Pharmaceuticals, Pakistan), acetaminophen (Neuro Pharma, Pakistan), methanol (Merck, Germany), ethyl cellulose (22 cP, BDH Chemicals Ltd, Poole, UK), cyclohexane (Merck, Germany) and n-hexane (Merck, Germany) were among the materials used in the study.

### Preparation of microparticles

Microencapsulation, based on phase separation by temperature change was employed to formulate separate microparticles of TmH and AAP. In this technique, Ethyl cellulose (EC, 1 g) was first dissolved in cyclohexane (50 ml) by heating the mixture to 80 °C and then TmH (1 g) was dispersed in it using a magnetic stirrer at 700 rpm. Phase separation was achieved through rapid temperature reduction by transferring the flask containing the mixture to an ice-bath with continuous stirring. The resulting microparticles, after washing with distilled water (20 ml) and then with n-hexane (20 ml), were dried at 40 °C in an oven (Mammert, Germany). The dried microparticles were stored in an air-tight, amber-coloured glass container. Microparticles of AAP (EC: AAP ratio, 1:1) were similarly produced and stored.

### Morphological studies

Morphological characteristics of the microparticles were studied by scanning electron microscopy (Hitachi, S 3000H, Japan). The microparticles were dotted on an adhesive tape attached to an aluminum stub and excess microparticles were detached. To render the particles electrically conductive, the stub sputter was coated with gold using a vacuum evaporator. The coated microparticles were viewed at 25 kV.

## Drug loading

TmH content of microparticles was determined by dissolving 41.5 mg of the microparticles in 8 ml of methanol in order to remove the EC coating around the microparticles. Distilled water (20 ml) was added to precipitate EC and heated to evaporate the methanol. The precipitated EC was filtered off and the volume of the drug was made to 100 ml with water. Aliquot of this solution was taken, diluted to 100ml and analyzed by UV-spectrophotometry (Shimadzu 1601, Japan) at 270 nm. The absorbance of standard solutions of the pure drug was also determined, from which the drug loading of the microparticles was derived. The same procedure was adopted for AAP except that absorbance measurements were made at a wavelength of 245 nm.

## Preparation of TmH-AAP bilayer tablets

Bilayer tablets of TmH and AAP (equivalent to 100mg and 500mg, respectively) were prepared by direct compression of their microparticles [8]. The microparticles of each drug were first blended with 0.75 % each of talc and magnesium stearate prior to a double compression process with a single punch tablet machine (Emmay, Pakistan). First AAP microparticles were compressed at low pressure and then TmH microparticles were compressed over them.

## *In-vitro* drug release of microparticles and bilayer tablets

*In-vitro* dissolution tests on TmH and AAP microparticles (165 mg and 531 mg, respectively) were carried out separately using USP apparatus-II (Pharma Test, Germany) at 50 rpm [9]. The dissolution medium (900 ml) consisted of 0.1M hydrochloric acid (pH 1.0) for the first 2 h and then replaced with phosphate buffer (pH 6.8) from the 3<sup>rd</sup> to the 8<sup>th</sup> hour to simulate gastrointestinal conditions. The temperature

of the dissolution media was maintained at  $37 \pm 0.5$  °C while sink conditions were attained by enclosing the microparticles in stainless steel sieves, placed at the bottom of dissolution vessel. A 5 ml sample of the dissolution fluid was collected at regular intervals with an automated sample collector after filtering through a 10 µm sinter filter and replaced with an equal volume of fresh dissolution medium stored at  $37 \pm 0.5$ °C. The withdrawn samples were analyzed at 270 and 245 nm for TmH and AAP, respectively, using a double-beam UV/visible spectrophotometer (Shimadzu 1601, Japan). The apparatus, methodology and specifications adopted for the dissolution test on bilayer tablets were the same as that for microparticles except that the test was extended to 12 h. All the tests were conducted in triplicate.

## Evaluation of tablet hardness, friability and weight variation

The hardness of the tablets was determined with an automatic hardness tester (Curio, Pakistan). Ten tablets were used in each test and the mean hardness was calculated. The friability of the tablets was evaluated with a friabilator (Emmy, Pakistan). Twenty tablets were weighed prior to placing them in the friabilator chamber and at the end of the test, their weight was also recorded. Finally, the loss in weight was calculated. For weight uniformity test, twenty tablets were randomly selected and weighed using a 'Class A' electronic weight balance (Precisa, Switzerland) and weight variation (%) was calculated.

## Kinetic analysis of release data

The dissolution data of the bilayer tablets were fitted to some kinetic models, namely, Zero order, First order, Higuchi [10], and Korsmeyer-Peppas [11,12] in order to determine TmH and AAP release patterns and mechanisms.

### Accelerated stability studies

Bilayer tablets were packed in air-tight amber glass wide-mouth bottles (100 ml) with 25 - 30 tablets in each bottle, and then sealed with aluminum foil. The bottles were kept at  $40 \pm 2$  °C/ $75 \pm 5$  %RH. Twenty one tablets (18 for dissolution and 3 for drug assay) were taken from each bottle at 1, 2 and 3 months, and evaluated for stability by determining *in-vitro* release profile and drug content. Similarity factor ( $f_2$ ) was used to compare the difference of dissolution profile after regular intervals. According to FDA guidelines,  $f_2$ -values between 50 and 100 ensure equivalence of two sets of dissolution data.

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\} \dots (1)$$

where  $R_i$  and  $T_i$  represent dissolution values of the reference and test products, respectively.

### X-ray diffractometry

The crystalline behaviour of TmH and AAP, before and after encapsulation, was evaluated by X-ray powder diffractometer (Bruker D8 Discover, Germany) using a CuK alpha radiation source with Ni-filter. A scanning rate of  $5^\circ \text{ min}^{-1}$ , tube voltage of 35 KV and current of 35 mA over a range of  $8-60^\circ$  were used in measurement.

### Thermal analysis

Differential scanning calorimetry and thermogravimetric analysis of the pure drugs and drug-loaded bilayer tablets were carried out simultaneously with simultaneous DSC/TGA analyzer (model SDT Q600). An amount (4 - 5 mg) of the crushed bilayer tablets was placed in aluminum pans and sealed prior to the test. Measurement was performed at a rate  $20^\circ \text{ C min}^{-1}$  under nitrogen flow of  $25 \text{ ml min}^{-1}$  over a temperature range of 25 to  $180^\circ \text{ C}$ . Indium was used for the calibration of the equipment.

### Fourier transform infrared (FTIR) spectroscopy

Drug-polymer interactions were assessed by FTIR spectroscopy. The spectra were recorded for TmH, AAP and EC singly as well as for the drug-loaded bilayer tablets using FTIR Midac 2000, USA. Samples were prepared in KBr disks and the test was carried out at a resolution of  $2 \text{ cm}^{-1}$  and a scanning range of  $500 - 4000 \text{ cm}^{-1}$ .

### Data analysis

One-way ANOVA Post-Hoc analysis (Duncan and Turkey) was used for regression analysis of drug release data derived from model equations with the aid of SPSS package, version 12.0. Statistical significance was set at  $p \leq 0.05$ . Taking into account the number of independent variables,  $R^2$  was used to determine how well a regression model describes the release data. Mean  $\pm$  SD for drug loading of microparticles and hardness of tablets was calculated by using Microsoft Office Excel 2003.

## RESULTS

### Shape and drug loading of microparticles

Spherical microparticles with a smooth surface were observed. Mean drug loading ( $n = 3$ ) was  $68.0 \pm 1.6$  and  $74.0 \pm 2.3$  % for TmH and AAP, respectively.

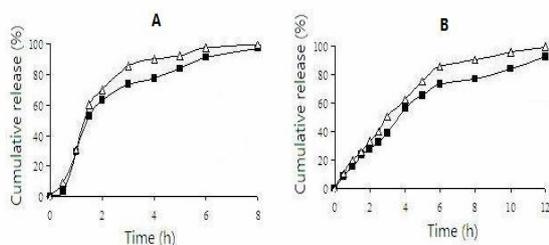
### Tablet hardness, friability and weight variation

Mean hardness, friability and weight variation of the tablets were  $8 \pm 1.19 \text{ kg}$ ,  $\leq 0.05$  % and  $\pm 0.2$  %, respectively.

### *In-vitro* drug release

Fig 1 shows the *in vitro* release profiles of the microparticles. After 8 h, 97.0 and 99.7 % of AAP and TmH, respectively, were released from the microparticles while 92.6 and 99.5 %

of TmH and AAP, respectively, were released from the bilayer tablets after 12 h.

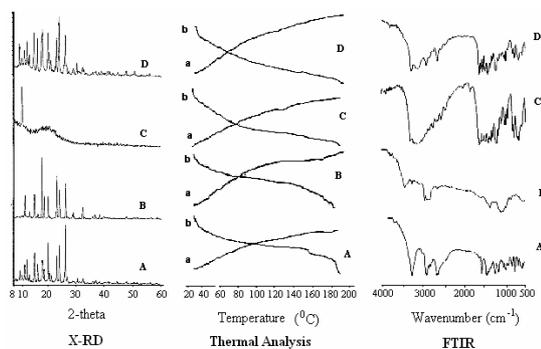


**Figure 1:** Drug release from (A) microparticles and (B) bilayer tablets containing AAP (■) and TmH (△)

## Drug-polymer interaction

### X-ray diffractometry

Fig 2 shows the crystallographic pattern of the drugs, polymer and tablet formulation. Every crystalline substance has a specific XRD pattern, which can be used for its detection, just like fingerprint. EC showed a single characteristic peak while TmH, AAP and bilayer tablets presented multiple peaks.



**Figure 2:** Diffractograms, thermograms and FTIR spectra of TmH (A), AAP (B), EC (C) and bilayer tablets (D). **Note:** For thermal analysis, a = DSC thermogram and b = TGA thermogram

### Thermal analysis

Fig 2 also shows the data obtained by thermal analysis. The DSC thermograms showed endothermic peaks around 181 and 168 °C which indicate the melting point of

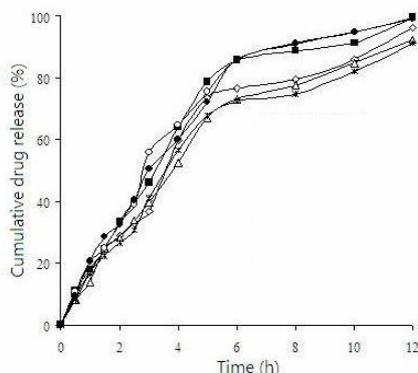
TmH and AAP, respectively. Similarly, an endothermic peak at 129 °C indicates the glass transition temperature ( $T_g$ ) of EC. TGA thermograms of all the components and bilayer tablets showed downward shift which indicated loss of mass (due to both moisture loss and degradation) upon heating.

### FTIR spectroscopy

In the FTIR spectrum of TmH (Fig 2), the characteristic peaks of aromatic ring stretching at 1600  $\text{cm}^{-1}$ , aliphatic CH stretching at 2900  $\text{cm}^{-1}$ , aromatic CH stretching at 3050  $\text{cm}^{-1}$  and OH shoulders at 3300  $\text{cm}^{-1}$ , respectively, were seen. The FTIR spectra of AAP showed C–N amide stretching peaks (1566, 1507 and 1560, 1513  $\text{cm}^{-1}$ ) and C–C aromatic stretching peaks (1614, 1507, 1442 and 1626, 1513, 1453  $\text{cm}^{-1}$ ) [13]. EC displayed two main characteristic peaks, first at 3365  $\text{cm}^{-1}$  due to stretching vibration of OH groups at carbon numbers 2, 3 and 6, and a second peak at 3210  $\text{cm}^{-1}$  due to OH bond at carbon numbers 1 and 4.

### Stability studies

Fig 3 shows the results for accelerated stability studies in terms of their effect on drug release. There was no significant difference ( $p < 0.05$ ) between the release profiles of TmH and AAP after storage for 1, 2 and 3 months.  $f_2$  values were greater than 50 (80.98, 86.45, 86.02 for AAP and 79.56, 84.56 and 85.70 for TmH, after 1, 2 and 3 months, respectively, of stability studies) thus showing that no significant change in release patterns of both drugs occurred over the period of the stability studies. The drug content of the tablets was 100.2, 98.0, 96.8 and 97.4% for TmH, and 101.1, 98.7, 96.5 and 95.8% for AAP after 0, 1, 2 and 3 months, respectively, of stability studies, thus demonstrating that no significant degradation of the drugs took place over the period.



**Figure 3:** Accelerated stability studies – Drug release pattern of TmH/AAP bilayer tablets after 1 month (◇ = AAP; ■ = TmH), 2 months (△ = AAP; ○ = TmH), and 3 months (× = AAP; ● = TmH)

## DISCUSSION

### Drug release and kinetics

Microparticles are small units and, therefore, drug would readily be released from them due to their large surface area. On the other hand, tablets are large compact masses of particles and sufficient time would be required for medium to penetrate into them because of their much smaller surface area [14]. The hardness of the tablets was kept high and constant in order to prevent disintegration during drug release. Furthermore, the release of both drugs was independent of pH of the dissolution medium used. TmH is a salt of basic drug and is soluble in acidic as well as in basic medium. AAP is unionized in 0.1 M HCl (pH 1.2) and phosphate buffer (pH 6.8).

The release patterns of TmH and AAP were predicted by application of zero-order, first-order and Higuchi models while release mechanism was evaluated by the Korsmeyer-Peppas model. Release constant (k) and regression coefficient ( $R^2$ ) for TmH and AAP release kinetics indicated that their release was best described by the Higuchi model, based on the highest linearity ( $R^2 = 0.966$  for AAP and  $R^2 = 0.960$  for TmH); a close

relationship with zero-order kinetics was also found ( $R^2 = 0.910$  for AAP and  $R^2 = 0.881$  for TmH). Korsmeyer-Peppas plot indicated an  $n$  value of 0.65 for AAP and 0.61 for TmH, both of which are indicative of an anomalous diffusion mechanism i.e., diffusion coupled with erosion. Thus, the release of both drugs was regulated by more than a single process [15,16].

### Drug-polymer interaction

#### X-ray diffractometry

The intensity of the diffraction peaks of TmH and AAP was reduced when the drugs were encapsulated in the polymer (EC), which indicates reduced crystallinity of TmH and AAP. The decrease in crystallinity indicates a change in the physical stability of TmH-AAP-EC combination with the drugs showing increased amorphous nature [17]. The crystalline behavior of TmH and AAP was present in the spectra of bilayer tablets which mean both drugs remained intact and there was no interaction of drugs with polymer.

#### Thermal analysis

For the bilayer tablets, the lowering of  $T_g$  of EC to  $118^\circ\text{C}$  and melting point of TmH  $180^\circ\text{C}$  was observed. This indicates a decrease in the stability of the drug in the tablet form, compared to the pure drug [18,19]. AAP showed no melting peak in the bilayer tablets, probably due to solvation in the solvent. The endothermic peaks of EC and TmH were unchanged in the bilayer tablets, thus indicating compatibility between the two compounds. The continuous downward trend of TGA thermograms suggests that mass loss was due to moisture/residual solvent loss and decomposition of the tablet materials.

#### FTIR spectroscopy

No new bands were detected in the FTIR spectra of bilayer tablets, indicating no chemical interaction between TmH-AAP-EC

combinations. Therefore, both drugs were chemically stable in the tablet formulations. Physical conjugation of the polymer with the drugs was probably responsible for the prolonged-release characteristics of TmH and AAP.

### Stability of the bilayer tablets

The data obtained from drug assay and stability studies, including the values of the similarity factor ( $f_2$ ) [[20] indicate that drug content of, and release from, the tablets were essentially unchanged after 3 months, suggesting that the tablets would be able to tolerate harsh storage conditions.

### CONCLUSION

Coacervation via temperature change method can be employed for the development of bilayer tablet formulations of tramadol/acetaminophen combination, using ethyl cellulose as the encapsulating polymer for retarding drug release from the tableted microparticles. Prolonged release of up to 12 h was achieved thus making it feasible to attain reduced frequency of administration of the drug combination.

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