In Vitro and in Vivo Evaluation of Sustained Release Hydralazine Hydrochloride Tablets Prepared by Thermal Granulation Technique

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Abstract: The aim of this work was to use the thermal granulation technique to formulate hydralazine hydrochloride (HLZ) as sustained release tablets using hydroxypropylmethyl cellulose (HPMC) and polyethylene glycol 6000 (PEG 6000) blend as hydrophilic heterogeneous matrices, the prepared granules and the corresponding tablets were evaluated for their physical properties. The kinetics of drug release was also studied using different models that could describe the release mechanism of the drug. Finally Differential Scanning Calorimetry (DSC) had been used as stability assurance test to indicate there is no incompatibility between the tablet ingredients. Also in this work the bioavailability of HLZ sustained release tablets was investigated and compared to a conventional immediate release tablet (Apresoline®) following oral administration to beagle dogs. From the drug plasma concentration max time profile, pharmacokinetic parameters such as C_{max}, T_{max}, AUC, absorption rate constant, MRT, K_a and t_{1/2} were determined. Statistical analysis showed that there is a statistical significant difference between the prepared tablets and the commercial tablets in MRT and absorption rate constant, on the other hand, C_{max} was not statistically different. In summary, this data provide strong evidence that HLZ tablets prepared by thermal granulation technique provide sustained release drug delivery following oral administration when compared to the immediate release tablets dosage form.

Key words: Hydralazine hydrochloride, Thermal granulation, DSC and Bioavailability

INTRODUCTION

Thermal granulation technique had been the subject of many reports (Gooie et al., 2008; Sandhu et al., 2007; Yang et al., 2007). It is a process in which granulation is obtained through the addition of a binder which melt or soften at a relatively low temperature. After melting, the binder acts as a binding liquid and also coats the powder particles and, upon cooling, granules are formed (Van Melkebeke et al., 2006). The binders normally used for this kind of granulation are polyethylene glycols, different waxes, poloxamer and gelucine 44/14 (Van Melkebeke et al., 2006; Ansari and Stepanek, 2006; Uhumwungho and Okor, 2006; Passerini et al., 2006; Chambin and Janma, 2005). Thermal granulation is advantageous compared with an ordinary wet granulation process, since the liquid addition phase as well as the drying phase of the process are eliminated and consequently, it requires less heat energy (Yang et al., 2007). Thermal granulation technique is useful on granulating solvent sensitive and/or volatile materials. HPMC is a pH independent polymer which is used in preparation of swelling controlled release systems (Khan and Meidan, 2007). In these systems water penetrates the matrix hydrating the polymer chain, which eventually disentangles from matrix (Oehoa et al., 2005; Esaudero et al., 2008). The quick formation of gelatinous viscous layer resulting from hydration is considered to be the first essential step for the release of drug from HPMC matrices (Salsa et al., 1997). HLZ is a potent peripheral vasodilator used in the treatment of hypertension by direct relaxation of arteriolar smooth muscle (Boon et al., 2007). It has a minimal effect on the venous capacitance vessels but has no direct action on the heart (Martelli et al., 1995). HLZ has a relatively short biological half life in human (1-2 hrs.) when administered as a conventional immediate release tablet and used usually three to four times in most patients to maintain the therapeutic serum concentration of the drug throughout the dosing intervals (Kirsten et al., 1998). In this study we attempted to use the thermal granulation technique to formulate HLZ as sustained release tablets using HPMC and PEG 6000 blend as hydrophilic heterogeneous matrices. Development of a sustained release preparation with extended clinical effects may reduce HLZ dosing frequency. The
pharmacokinetic characteristics of the prepared dosage form were examined using beagle dogs as animal model which has been used successfully for HLZ pharmacokinetics studies (Siegmund et al., 1987). Beagle dogs have been chosen because its HLZ pharmacodynamic effect is similar to that reported in humans (Semple et al., 1990).

**Experimental:**

**Materials:**

HLZ commercial tablets Apresoline® (Novartis), HLZ powder, HPMC (4000 cp) and theophylline (Sigma-chemical Co., St. Louis, Mo., U.S.A.), PEG 6000 (J.T. Baker chemical Co. Phillipsburg, NJ., U.S.A.), Talc powder (Riedel-de Haen, AG, Seelze, Hannover, Germany), Magnesium stearate (E. Merck, D-6100, Darmstadt, Germany), acetonitrile (BDH Chemicals Ltd.,Poole, England), heparinized vacutainer (Belliver industrial estate,UK), methanol (chromasoly©), absolute ethanol and sodium acetate (Riedel-de Haen AG, Seelze, Hannover, Germany).

**Formulation of HLZ Sustained Release Tablets:**

The tablets were formulated such that each tablet contains 50 mg of HLZ and total weight of 200 mg, containing 25% (w/w), of the drug, 55 % (w/w) HPMC and 20 % (w/w) of PEG 6000, respectively. The tablets were prepared by mixing the calculated amounts of HLZ, HPMC and PEG 6000 in a cube mixer (Type U.G Erweka, Apparatebau, Germany) for 15 minutes, then the mixture was placed in a beaker immersed in a thermostatically controlled water bath at 65°C. It was reported that high yield of granulation was obtained only at a temperature near the melting point of PEG 6000 (Van Melkebeke et al., 2006). A high speed vertical mixer (Kenwood, Hampshire, England) at 3000 rpm was used for mixing the powder blends until dough mass is formed, stirring was continued until fine granules is produced. The beaker was removed from the water bath and left to cool in an ice cooled bath. The formed granules were passed through a one millimeter diameter sieve for size uniformity. Finally the granules was mixed with 1 % (w/w) of both magnesium stearate and talc powder in a cube mixer for 15 minutes, then compressed into tablets using a single punch tablet machine with 10 mm flat faced punch (EKO laboratory model, Korsch, Berlin Germany). The machine was adjusted to produce tablets having 50 mg of HLZ and hardness of about 5-6 kp.

**In-Vitro Evaluation of HLZ Powder, Granules and Tablets:**

**Density of the powder:**

Poured and tapped bulk densities of the powder were measured using a 10 cm³ measuring cylinder. For tapped density, the cylinder was tapped from a height of 2.5 cm on a smooth surface until no further change in volume was observed. The test was repeated three times.

**Carr's Index (Compressibility Index):**

C.I. was calculated using the following equation,

$$C.I._c = \frac{T - U}{T} \times 100\%$$

where, T and U stand for tapped and untapped densities. The granules, kept in a 100 ml cylinder, were tapped from a height of 1 inch on a smooth surface until no further change in volume was observed. Average of 3 observations was taken in consideration.

**Angle of Repose:**

Angle of repose was measured using a protractor for the heap of granules formed by passing 10 grams of the sample through a funnel at a height of 8 cm from the horizontal surface.

**Content uniformity:**

Ten tablets were randomly chosen, weighed and individually assayed, the mean drug content percent, standard deviation and coefficient of variation percent were calculated.

**Uniformity of Weight:**

A representative sample of 20 tablets were weighed individually from each batch, the average weight, standard deviation and coefficient of variation percent were calculated.
Tablets Thickness:
The thickness of each weighed tablet in the uniformity of weight was measured. The mean thickness, standard deviation and coefficient of variation percent were calculated.

Hardness:
Ten tablets were randomly chosen from each batch and tested for hardness using Erweka hardness tester. The mean hardness, standard deviation and coefficient of variation percent were calculated.

Friability:
Twenty tablets were randomly chosen from each batch and tested for the friability, brushed free from adhering dust, accurately weighed and placed in the drum. The drum was allowed to rotate for four minutes (100 rotations). At the end of the time, the tablets were removed from the drum, carefully brushed free from the dust and weighed. The percent loss was taken as a measured of friability. The mean percent friability of three replicates, standard deviation and coefficient of variation percent were calculated.

Tensile Strength Measurements (T):
The diameter compression test devised by Fell and Newton (Fell and Newton, 1970) was applied, the tensile strength (T) being given by the formula: $T = \frac{2P}{\pi Dt}$ where P is the applied stress, D is the diameter of the tablet and t is the tablet hardness.

Dissolution studies:
Dissolution profiles of the prepared tablets were determined using USP II rotating paddle apparatus (VK7000) at 37°C ± 0.5 and a rotating speed of 50 rpm in a 900 ml distilled water. Samples (3 ml) withdrawn after 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 hours were filtered using a 10 mm VanKel filter and assayed for HLZ using Philips UV/VIS/NIR single beam PU 860/50 spectrophotometer at 260 nm. The dissolution experiments were carried out in triplicate. The release of HLZ from conventional tablets (control) was carried out for comparison.

Stability assuring test using Differential Scanning Calorimetry (DSC):
Samples of 2 - 5 mg of the individual substances and 1:1 physical mixture of HLZ and additives (HPMC and PEG 6000) were accurately weighed, encapsulated and hermetically sealed in flat bottomed aluminum pan with crimped on lid. The pans were positioned on sample pan holder of a Shimadzu DSC 60. The samples were heated in an atmosphere of nitrogen over a temperature range from 30 – 250°C with a constant heating rate of 10°C per minute. Thermograms were obtained by the TA-60WS thermal analyzer program. The transition temperature range, the onset of peak transition and the maximum peak of transition were recorded. At least two replicates were made for each DSC thermogram using an empty sealed aluminum pan as reference and indium as instrument calibration standard.

Animals and Dosing Procedures:
Four male Beagle dogs weighing 19-20 kg were used in the study, animal legs and arms were shaved using electric shaving machine. The dogs were fasted for 24 hrs prior to each experiment and were not allowed any food during the first 6 hrs after dose administration. Both sustained release and conventional HLZ tablets each containing 50 mg were administered by swallowing with dogs’ food, after dose administration the animals were allowed free access to water. Two weeks washout period was allowed between successive administrations. All studies were approved by the institutional animal care and use committee and were conducted in accordance to the NIH guide for care and use of laboratory animals.

Blood Sampling Protocol:
Following dose administration, venous samples (about 3 ml) were obtained from the cephalic and satic veins by a veinupuncture using 18 gauge needle at the following specified time intervals: (0, 10 min, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hrs) and (0, 10 min, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24 and 26 hrs) for conventional and sustained release tablets, respectively. The samples were collected in vacutainer tubes, the plasma was then immediately separated by centrifugation at 5000 rpm for 15 minutes (sorvall RT6000 Refrigerated Centrifuge, Doupont Company Newtown CT06470). Because HLZ is very unstable in plasma (Iwaki et al., 1989) plasma samples were immediately analyzed without storing to prevent drug degradation.
Determination of HLZ in plasma:
The assay is based on a derivatization reaction of HLZ with formaldehyde under acidic conditions (glacial acetic acid) to form s-triazolo (Yang et al., 2007; Van et al., 2007) phthalazine. The latter compound has been shown to be a metabolite of the drug, but its concentration in plasma is generally non-detectable. Reaction of HLZ with formaldehyde to form s-triazolo (Yang et al., 2007; Van et al., 2007) phthalazine was reported to be quantitative (Lessen and Zhao, 1996).

Samples Preparation:
The method of sample preparation was a modification of Proveaux et al., (1979). Briefly, 10 μl of both glacial acetic acid and formaldehyde were added to 0.5 ml plasma. The mixture was vortexed for 30 seconds using a vortex mixer (Scientific Industries INC. N.Y. 11716 U.S.A) at room temperature. A 100 μl of theophylline in methanol - the internal standard solution (10 μg/ml) was added to the plasma samples and vortexed for another 30 seconds and allowed to stand for 20 minutes at room temperature for completion of the reaction. Then, 380 μl of methanol was added to the mixture to precipitate the plasma protein. The precipitated protein was separated by centrifugation for 12 minutes at 4000 rpm (Sigma D-37520 Osterode am Harz, Germany). A 100 μl of the clear supematant solution was directly injected into 50 μl loop for drug plasma determination. The described method was specific, sensitive and applicable to quantitative analysis of HLZ up to 10 ng/ml.

Liquid Chromatography:
A High performance liquid chromatography (Shimadzu, Japan), equipped with solvent delivery pump (LC-10 AD Shimadzu, Japan), 50 μl fixed volume injector (Model 77251), UV variable wave length detector model l0AV was set at 260 nm, μ-Bondapak C_{18} (5 μm) reversed phase column (30 cm x 4 mm I.D, Waters) and model C-R6A chromatopac integrator with a chart speed of 2cm/min were used for the quantitative determination of HLZ. The mobile phase consisted of acetonitrile and 0.01 M sodium acetate buffer in a ratio of 13:87, the pH of the mobile phase was adjusted to 4, filtered through 0.45μm millipore filter prior to use and pumped at a constant rate of 1 ml/min at ambient temperature.

Pharmacokinetic Analysis:
Pharmacokinetic parameters for sustained release and conventional oral HLZ tablet were determined from the plasma concentration time data. The maximum plasma concentrations (C_{max 1} and C_{max 2}) and the corresponding times for maximum plasma concentrations (T_{max 1} and T_{max 2}) were directly obtained from the individual plasma concentration-time data for each animal. The area under plasma concentration time curve (AUC) and the area under the first moment curve (AUMC) were calculated by using trapezoidal rule with extrapolation to infinity. The elimination half life (t_{1/2}), mean residence time (MRT), rate of absorption following oral administration of sustained release and conventional tablets were evaluated, also the relative bioavailability of the two formulations was determined as well.

Statistical Analysis:
Statistical analysis of different pharmacokinetic parameters was performed using unpaired t-test at a significance level of P < 0.05 (Stat 100, version 1.24, Biosoft, 1996)

RESULTS AND DISCUSSION

Granules properties:
The results obtained from studying the physical properties of the powder blends and its corresponding granules indicated that, powder blends of the drug, HPMC and PEG 6000 exhibit bad flowability which in turn affect the die filling leading to weight variation during tablet manufacturing. On the other hands, after thermal granulation the values of Carr's index and angle of repose of powder blends were markedly decreased to be within range of a satisfactory to excellent flowability compared with that of the powder blend. From the obtained results, high bulk density of the granules could be an essential feature during tablet manufacturing since the amount of die filling is limited by the die capacity (Bultmann, 2002). The physical properties of the prepared powders and granules are shown in Table 1.

Tablets properties:
Tablets prepared by thermal granulation showed a coefficient of variation of weight (210 mg with coefficient of variation of 1.25) less than 2% which excellent uniformity of weight according to the reported standards (Saker et al., 1973) these results could be due to the high value bulk density and good flowability
of the granules. The prepared tablets exhibited good mechanical properties as regards both hardness (5.45 kp ± 0.05), friability values (0.52). Also, the prepared tablets showed a tensile strength value of 13.4 kp/cm² and thickness of 2.59 mm ± 0.01, and drug content of 50.03 mg ± 0.97.

**Release Profile:**

In swelling controlled matrix systems, there are two factors which control the rate of drug release from the matrix. One is the rate of aqueous medium infiltration into the matrix followed by the relaxation processes (hydration, gelation or swelling) and the other is the rate of erosion of the matrix. As a result of these simultaneous processes, two fronts are evident, a swelling front (glassy polymer/gel interface) and an eroding front (gel/medium interface). The distance between the two fronts (diffusion layer thickness) depends on the relative rates at which the swelling and eroding is move in relation to each other (Colombo et al., 1995). It has been reported that, the process of drug release from HPMC matrices involves water penetration into the dry matrix, hydration and gelation of the polymer, dissolution of the drug and diffusion of the dissolved drug from the resultant gel layer (Ranga et al., 1988; Sahi et al., 1997; Forni et al., 1990). The results in Figure 1 revealed that, the prepared tablets exhibited good and reliable sustained release profiles. From the release profile of HLZ from conventional commercial tablets (Apresoline®) it is clear that almost 100% of the drug was rapidly released within 50 minutes. Comparing these results with the previously mentioned results of the formulated sustained release HLZ tablets, it can be concluded that HPMC-PEG 6000 matrix has an efficient ability in the formulation of a sustained release dosage forms.

**Kinetics of Drug Release:**

The release data of HLZ from the prepared stained release tablets were fitted to zero order kinetic, first order kinetics and higuchi's equation.

It was observed that swelling and erosion of tablets have occurred. Dissolution and drug release kinetic were also analyzed by applying the empirical exponential equation often used for identifying the release mechanism. In this equation the drug fraction released is related to time according to following equation:

\[ \frac{M_t}{M_\infty} = K t^n \]

Where, \( M_t \) is the amount of drug released at time \( t \), \( M_\infty \) is the amount of drug released at infinity time, \( K \) is a constant incorporating the structural and geometric characteristics of dosage form (% hr⁻¹) and \( n \) is diffusional exponent indicative of release mechanism. According to \( n \) values, the mechanism of diffusional release from swellable controlled release system was deduced. The kinetic studies of the drug release for the prepared tablets revealed that, the values of correlation coefficient (\( r \)) for different mechanisms were found to be close to zero order and diffusion (the value of \( r \) for zero order is 0.987, for first order is 0.920 and for diffusion mechanism is 0.999), it is clear that the value of \( r \) is slightly deviated from first order. This could be attributed to the rapid swelling of the HPMC matrix in the beginning of the release, which became constant by time (Saker et al., 1973), as well as the slow erosion rate of the used medium molecular weight HPMC polymer (Sajja-Areevath et al., 1998). However, it is expected to be an anomalous in swellable systems (Colombo et al., 1990), which was confirmed by the values of \( n \) (0.658). According to many investigators, if 0.50 < \( n \) < 1.0 this indicate an anomalous (non-Fickian or coupled diffusion/relaxation) drug release (Saker et al., 1973; Sajja-Areevath et al., 1998; Colombo et al., 1995; Bayomi et al., 1994). In a trial to explain the mechanism of HLZ release from the prepared sustained release tablets, the release data were divided into two main phases, which are corresponding to the swelling phase (from the beginning to the maximum swelling) and to the diffusion-erosion phase (after the maximum swelling to \( M_\infty \) below 70%). Dividing of the data to two cases depend on the mathematical values of the correlation coefficients phase. The \( n \) values of the swelling phase value which is far from 0.5 (0.753), while the diffusion-erosion phase are close to it (0.553). These results indicate that after the maximum swelling of the matrix the main release kinetics of HLZ from HPMC follows case I Fickian diffusion.

**Stability Assuring Test Using Differential Scanning Calorimetry (DSC):**

The thermograms of the individual tablets ingredients and 1:1 physical mixture of HLZ and additives (HPMC and PEG 6000) in a ratio of 1:1 is shown in figure 2. HLZ shows a characteristic peak at 162.2 °C. From the figure it is clear that the physical mixture of HLZ and HPMC and PEG 6000 at a ratio of 1:1 indicate no chemical interaction or incompatibility between. The reduction in peak intensity is a consequence of less overall HLZ present in the mixture as compared to HLZ alone.
Bioavailability Study Results:

Following oral administration of HLZ sustained release and conventional tablets (Apresoline®), HLZ plasma levels could be measured in all samples. In a few cases the level of HLZ was close to the limit of the quantitation at the last sampling time. The plasma concentrations time curves (Figure 4) of both sustained release and conventional tablets in the four beagle dogs had the same general pattern. This pattern was characterized by the occurrence of double peaks, these double peaks may suggest that HLZ undergoes enterohepatic recirculation which is in good agreement with reported publications (Semple et al., 1990; Chen et al., 2008; Zhang et al., 2007). Another explanation for the double peaks could be that the rate of HLZ absorption varies along the gastrointestinal tract as reported by Shephered et al., (Ludden et al., 1980). Following oral administration of both HLZ sustained release and conventional tablets, the peak plasma concentration of HLZ conventional tablet becomes faster than that observed from the sustained release formulation, this is due to the higher rate of absorption of the conventional tablet than that of sustained release one, as the conventional become immediately accessible for absorption. In addition, plasma levels of HLZ were detectable for 26 hours and 8 hours for both sustained release and conventional tablets, respectively. This is considered a good indication of sustained release drug delivery since the area under the plasma concentration
The AUC curve is the measure of the amount of the drug absorbed, the areas AUC\text{c,\ldots} were calculated for both formulations. The mean AUC\text{c,\ldots} values for the prepared sustained release formulation and conventional HLZ tablets (Apresoline®) were 1435.2 and 376.4 ng.h/ml respectively. There was statistically significant difference between AUC\text{c,\ldots} values for the two formulations. It is interesting to observe that the sustained release characteristic of the prepared HLZ tablets was correlated to the in vitro release study. The results of in vitro dissolution showed that 76% of the drug released in 8 hours while the drug release of the conventional HLZ tablets was 98% in about 1.3 hours. Relative bioavailability of the prepared sustained release tablets was calculated to be 381.3\% ± 51 (mean ± SD). This high value is attributed to the over estimation of AUC\text{c,\ldots} for the sustained release formulation. The reason for this AUC\text{c,\ldots} overestimation is that, the presence of the secondary peaks which are much larger in magnitude in case of the sustained release formulation. Also, sustained release formulation was characterized by an increase in elimination half-life, decrease in elimination rate constant and a decrease in absorption rate values compared to the conventional tablets. This data shows a clear case of the phenomenon commonly referred to in the literature as the flip-flop phenomenon (Chen, 2007; Sintow and Botner, 2006). This phenomenon is often associated with sustained release formulations where absorption of drug from the formulation is the process that determines prolonged plasma concentration and subsequently the apparent increase in elimination half-life and decrease in elimination rate constant. Therefore, the over estimation of elimination rate constant (k\text{e}) leads to the over estimation of AUC\text{c,\ldots}. There was no statistically significant difference in C\text{max} values which showed values of 210.1 ± 26.7 and 180.8 ± 59.1 ng/ml for the prepared formulation and conventional HLZ tablets respectively. A good evidence of sustained release drug delivery of the prepared tablets is the shift in time for maximum blood concentration (T\text{max}). The T\text{max} for prepared tablets was significantly higher than that of the conventional tablets (0.5 hr versus 0.25 hr for conventional tablets). The T\text{max} is the parameter taken as one measure of the rate of absorption of HLZ and this parameter provides strong indication of sustained drug delivery by the prepared tablets. Another indication of sustained drug delivery of the prepared tablets is the mean residence time (MRT) and absorption rate (C\text{max}/AUC\text{c,\ldots}). The MRT was significantly higher for prepared tablets (12.1 ± 1.8 hrs versus 4.8 ± 1.6 hrs for conventional tablets) and absorption rate was also significantly lower for the prepared HLZ tablets (0.15 hr\text{t} vs. 0.5 hr\text{t} for the conventional tablets). The absorption rate calculated as the ratio between C\text{max} and AUC\text{c,\ldots} is considered a good parameter for evaluation of sustained release properties of pharmaceutical formulations (Sehall and Luss, 1992; Lacey et al., 1997).

Fig. 3: A representative chromatogram of HLZ and internal standard theophylline in Beagle dogs plasma.
Table 1: Physical properties of HLZ sustained release powder and granules

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Powder</th>
<th>Granules</th>
</tr>
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<tbody>
<tr>
<td>Bulk Density (g/ml) ±SD</td>
<td>0.471±0.002</td>
<td>0.641±0.003</td>
</tr>
<tr>
<td>Tapped Density (g/ml) ±SD</td>
<td>0.688±0.003</td>
<td>0.716±0.002</td>
</tr>
<tr>
<td>Carr's Index</td>
<td>31.54</td>
<td>10.48</td>
</tr>
<tr>
<td>Angle of Repose ±SD</td>
<td>45.58±0.987</td>
<td>23.75±0.662</td>
</tr>
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</table>

Table 2: Pharmacokinetic parameters of HLZ sustained release and conventional tablets after single oral dose administration

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Sustained release</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>1435.2±202.7</td>
<td>376.4±31.2</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>210.1±26.7</td>
<td>180.8±59.1</td>
</tr>
<tr>
<td>T_max (hr)</td>
<td>0.5±0.0</td>
<td>0.25±0.0</td>
</tr>
<tr>
<td>C_k (ng/ml)</td>
<td>99.8±15.5</td>
<td>139.8±76.6</td>
</tr>
<tr>
<td>T_k1 (hr)</td>
<td>6.0±0.0</td>
<td>1.25±0.61</td>
</tr>
<tr>
<td>T_k2 (hr)</td>
<td>5.7±1.7</td>
<td>3.46±1.46</td>
</tr>
<tr>
<td>K_1 (hr^-1)</td>
<td>0.13±0.04</td>
<td>0.22±0.07</td>
</tr>
<tr>
<td>MRT</td>
<td>12.1±1.7</td>
<td>4.8±1.6</td>
</tr>
<tr>
<td>K_ab (hr^-1)</td>
<td>0.15±0.04</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td>Relative bioavailability, %</td>
<td>381.3±51</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusion:

In conclusion, melt granulation technique improved the physical properties of HLZ, HPMC and PEG 6000 powder blends. The granules were successively used in the preparation of sustained release HLZ tablets with good physical and mechanical properties. The release studies revealed that the prepared tablets exhibited good and reliable sustained release profiles. Stability assurance testing using DSC indicated that there is no incompatibility occurs between the prepared tablets ingredients. It seemed that the kinetics of the drug release from HPMC matrix are complex, because of the micro and macrostructure of the polymer and did not follow a single release mechanism. The biopharmaceutical evaluation of HLZ sustained release tablets provides strong evidence that the tablets show sustained drug delivery following oral administration.

REFERENCES


