Bioavailability Improvement of Diltiazem Hydrochloride  
Gastroretentive Sustained Release Tablets  

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Abstract: Floating drug delivery system (FDDS) is the greatest interesting endeavors facing the pharmaceutical scientist. FDDS are associated with advantages of improved bioavailability and minimizing the dosing frequency. Diltiazem hydrochloride (DTZ HCl) is a calcium channel blockers, anti-anginal drug and anti-hypertensive which undergo extensive first-pass metabolism and display poor bioavailability about 30-40%. In this research, formulation of DTZ HCl sustained release floating tablets to be taken once was attempted. These tablets were formulated using different release-retarding polymers as; sodium alginate (S ALG), hydroxypropyl methylcellulose K15 (HPMC), and Carpolbol 934 (CP). The prepared tablets were characterized for the assessment of floating, swelling and dissolution behavior. The bioavailability of DTZ HCl from the optimized formulation was evaluated. The obtained results showed that, the prepared formulations show better and significant results for all the evaluated parameters. The floating, swelling and in-vitro release characteristics were found to be a function of the type and ratios of polymer used. Moreover, a combination of HPMC-CP in a ratio of 1.5:1 (F6) exhibited desirable floating, swelling and extended drug release, thereby bioavailability which indicated by higher AUC and relative bioavailability values.

Keywords: Bioavailability, Diltiazem hydrochloride, Floating, Gastroretentive.

I. Introduction

Oral delivery systems are the most advantageous route for the drug delivery systems. Unfortunately, these systems have shown some drawbacks related to short gastrointestinal transit time (8-12 hrs) and so, fast gastric-emptying time, thereby decrease their bioavailability [1, 2]. The real goal in the development of oral drug delivery systems is to increase the residence time of the dosage forms in the upper gastrointestinal tract (GIT) or the stomach until the drug is absorbed completely [3]. Various approaches including floating delivery systems [4], bioadhesive delivery systems [5], swelling and expanding delivery systems [6] and high density delivery systems [7] have been successfully developed to increase the gastric residence time of delivery systems [8]. The main target of gastroretentive delivery systems provides a simple approach to prolong gastric residence time for delivering the drug in a sustained manner [9, 10]. Indeed, gastroretentive delivery systems are potent delivery system in the past few decades.

Floating drug delivery systems are an access to increase gastric residence time, thereby targeting drug release in the upper GIT for systemic or local effects [11]. Therefore, FDDS was developed to improve the gastric retention of drugs that: (i) have a narrow absorption window in GIT; (ii) are locally active in the stomach; (iii) exhibit low solubility at high pH medium; (iv) are unstable in the intestinal or colonic pH [12, 13] or (v) improve their bioavailability that exhibit site-specific absorption [14]. FDDS have been categorized into two types according to the mechanism of buoyancy: 1) effervescent formulations, which produce CO2 gas upon contact with gastric medium, and 2) non-effervescent formulations as; alginate beads, hydrodynamically balanced systems, micro porous systems, and hallow microsphere-micro balloons [7].

Most of floating systems with an initial high density, firstly settle down in the stomach and they are exposed to the hazard of premature emptying even though their density decreases with time [15]. To avoid premature emptying, bioadhesive polymers can be used with these systems to prolong their gastric residence time. Many bioadhesive polymers utilized as; poly (acrylic acid) (PAA), chitosan, S ALG, and HPMC. These polymers are efficient in providing bioadhesion but the maintenance of their bioadhesiveness may be affected by highly hydrated stomach environment [16].

Diltiazem hydrochloride is a calcium channel blocker, commonly used as antihypertensive and anti-angina drug [17]. DTZ HCl undergoes an extensive first pass metabolism which results in less than 4% of its oral dose being excreted unchanged in urine and lower its bioavailability which about 30% - 40% after oral administration [18, 19]. DTZ HCl needs frequent administration to maintain adequate plasma concentrations due to its short biological half-life of 3 to 5 hrs [20]. Subsequently, it is considered as a drug of choice for floating system to retain in the stomach and improve the oral bioavailability of the drug. The objective of this research to formulate DTZ HCl floating tablets using different bioadhesive polymers. Evaluation of the prepared formulations regarding physicochemical properties, swelling ability, floating behavior, and dissolution study was investigated. Moreover, the bioavailability and pharmacokinetic parameters of DTZ HCl from the

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optimized formulation on the basis of good physicochemical properties and acceptable sustained-release profiles were studied.

II. Materials And Methods

Diltiazem hydrochloride (DTZ HCl) was purchased from JINLAN Pharm-Drugs Technology Co. LIMITED, Hangzhou, China. Hydroxypropyl methylcellulose K15 (HPMC) and magnesium stearate were obtained from Acros organics, New Jersey, USA. Caropol 934 (CP) and sodium alginate (S ALG) were obtained from Appli Chem GmbH, Germany. Talc powder and sodium bicarbonate (SB) were obtained from El-Gomhourra Co. Egypt. Lactose was supplied from Fisher Chemical, UK. The solvent for HPLC (chloroform, acetonitrile and iso-propanol) were supplied from sigma-Aldrich CO. LLC, St. Louis, Missouri, USA. All other chemicals were of analytical grade; fresh double distilled water was utilized during the study.

2.1. Preparation of DTZ HCl Floating Tablets

Floating tablets containing DTZ HCl (90 mg) were prepared by direct compression methods using release-retarding polymer as; HPMC, S ALG and CP. Additionally, gas generating agent as sodium bicarbonate was used. Individually, all powders were sieved (200 µm), mixed for 10 min, and then 1% w/w magnesium stearate was added as a lubricant. Finally, 350 mg of each blend was weighed and compressed using a tablet compression machine (Type E.K.O, Erweka- Apparatebau, G. m. b. H., Germany), using 10 mm flat faced punches [21]. Tablet hardness was adjusted to give 6-7 Kg/cm².

Table 1: Composition of DTZ HCl floating tablets

<table>
<thead>
<tr>
<th>Formula code</th>
<th>DTZ HCl</th>
<th>HPMC</th>
<th>S ALG</th>
<th>CP</th>
<th>SB</th>
<th>Talc</th>
<th>Lactose</th>
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<tr>
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<td>-</td>
<td>125</td>
<td>75</td>
<td>3.5</td>
<td>53</td>
<td>3.5</td>
</tr>
</tbody>
</table>

DTZ HCl Diltiazem hydrochloride, HPMC hydroxypropyl methylcellulose K15, S ALG sodium alginate, CP Carpol 934, SB sodium bicarbonate.

2.2. Tablet Evaluation

2.2.1. Physicochemical Properties of Floating Tablets

Weight variation, drug content uniformity and friability % of all formulae were examined according to the USP Pharmacopoeia [22].

2.2.2. Buoyancy Behavior

The time required for a tablet to rise over the medium surface and float is Floating Lag Time (FLT), and floating duration (Total Floating Time, TFT) were examined according to the procedure previously adapted [23]. Individually, each tablet was added into the vessel consists of 200 ml of 0.1 N HCl pH 1.2 at 37±0.5 °C. The experiment was conducted in triplicate.

2.2.3. Swelling Ability Study

The swelling ability of all tablets was performed according to the method previously described [23]. The swelling index was examined by adding each weighed tablet (W1) in beaker consists of 200 ml of 0.1 N HCl and maintained at 37±0.5°C in a thermostatically controlled water bath (Grant instrument Cambridge Ltd., England). At a predetermined time intervals, each tablet was withdrawn and carefully removed the excess liquid using filter paper and then weighed (W2). The experiment was done in triplicate, and the swelling index % was determined according to the following equation:

\[
\text{Swelling index} (\%) = \frac{W_2 - W_1}{W_1} \times 100
\]

2.2.4. Dissolution Study

The drug release from each formula was performed using USP paddle apparatus II (Dissolution tester, ABBOTA, New Jersey, USA). The release study was carried out using 900 ml of 0.1N HCl which is maintained at 37±0.5°C and stirring speed 100 rpm for 12 hrs. At a predetermined time intervals up to 12 hrs, aliquots of 5 ml was taken out and replaced by fresh dissolution medium to keep the volume constant. The samples were diluted, filtered using millipore filter (0.45 µm pore size, Berlin, Germany), and analyzed.
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spectrophotometrically at 238 nm using UV/VIS spectrophotometer (V-530, Jasco, Japan). The release was described by plots of percentage drug released versus time.

2.2.5. Kinetic Study

To survey the drug release mechanism, the dissolution data were analyzed mathematically depending on the following models: zero-order, first-order and Higuchi model. Additionally, the Korsmeyer–Peppas model was used for more analysis. The model with the highest coefficient of determination (r²) was considered as the best fitting one [24].

2.3. Bioavailability Study

The bioavailability of the optimized formula was investigated. The optimized formula is F6 (HPMC: CP, 1.5:1) based on their desirable physicochemical and dissolution characteristics. This study was conducted on male albino rabbits (each weight 2-2.5 kg). All animal procedures were conducted in accordance to the approved protocol for use of experimental animals set by the standing committee on animal care of the Faculty of Pharmacy, Mansoura University, Egypt. Rabbits were divided into two groups (6 animals per group) as follows: group I, received control tablet (Ct, tablet contains 90 mg drug, SB and lactose) and group II, received the optimized formula, F6. Food was withdrawn before drug administration (12 hrs), until 24 hrs post-dosing, and animals were free access to water during the experiment. Each rabbit was received one tablet using a stomach tube with the assist of double distilled water. Blood samples (2 ml) were withdrawn from ear vein into EDTA disodium salt tubes at time interval of 0, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hrs. All blood samples were centrifuged at 5000 rpm for 10 min to acquire the plasma samples and then were stored at -20°C for further study.

2.3.1. HPLC Analysis

Plasma samples were assayed using HPLC method previously mentioned by Li et al. [25] for the determination of DTZ HCl in plasma after certain modification. The mobile phase consisting of acetone:water using ratio of 50:50 v/v containing 0.35% w/v of triethylamine, the pH was adjusted with orthophosphoric acid to pH 3.0. The internal standard was a solution of 24 μg/ml verapamil hydrochloride prepared in the mobile phase as a solvent. Then, 100 μl of verapamil hydrochloride solution (24μg/ml) as internal standard were added to each of the following calibration solutions; 200, 400, 600, 1000, 2000, 3000 and 6000 ng/ml of DTZ HCl in plasma. After that, 100 μl of sodium carbonate solution in distilled water (1.0 M) was added to each solution and the solutions were mixed well. After mixing, 2.5 ml of hexane–chloroform–isopropanol (60:40:5) was added to the solutions and mixed for 2 min using vortex mixer (Snijders Scientific Tiburg, Holland), then centrifuged for 10 min at 2000 rpm. The organic layer was isolated and then dried at 40°C.

The organic layer residue was then dissolved in 500 μl of the mobile phase and the produced solution was filtered using 0.22 μm nylon filter and 20 μl of the filtrate was injected into the loop of HPLC apparatus (Perkin Elmer, USA). The quantitative analysis of DTZ HCl was done by a reverse phase HPLC system consisting of a reverse phase column (C- 18 column, 5μm, 4.6x250mm, phenomex, USA), pump (LC-20 AD), CBM-20A interface, degasser (DGU-20A5), and UV-VIS spectrophotometric detector (SPD-20A UV-VIS detector). For data processing, LC solution software version 1.3 from shimadzu, Japan was applied. The mobile phase was pumped at a flow rate 0.95 ml/min and the detection wavelength was 239 nm. The peak area ratio of DTZ HCl to verapamil hydrochloride was constructed against the concentration of DTZ HCl in plasma to obtain the standard calibration curve.

The frozen rabbit plasma was thawed at room temperature, then, for each 500 μl of plasma sample, 100 μl of verapamil hydrochloride solution (24μg/ml) were added as an internal standard. The experimental was then completed as mentioned before under construction of calibration curve of DTZ HCl in rabbit’s plasma.

2.3.2. Pharmacokinetics Parameters

The pharmacokinetics parameters were determined for each rabbit. The maximum plasma concentration (Cmax, ng/ml) and the time required to attain Cmax (Tmax, hr) were calculated from the plasma concentration-time curve. Also, the area under plasma concentration-time curve from time 0 to 24 hrs (AUC0-24, ng.hr/ml) was determined using linear trapezoidal rule [26]. The area under plasma concentration-time curve from time 0 to ∞ hrs (AUC∞,ng.hr/ml) was determined regarding to the following equation:

\[ \text{AUC}_{0-\infty} = \text{AUC}_{0-24} + \frac{C_{\text{last}}}{K_e} \]

Where, Clast is the concentration of DTZ HCl in plasma after 24 hrs. The elimination rate constant (Ke) was estimated from the terminal linear phase of the profiles. The elimination half-life (t1/2) was determined as 0.693/Ke. Additionally, the relative bioavailability was decided as the ratio between AUC0-∞ of the optimized formula to that of control.

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2.4. Statistical Analysis
All resulting data are presented as a mean ± S.D. Multiple groups comparisons was conducted using one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test and pairs of groups were compared by performing one-tailed student's t-test at p<0.05. All statistical calculations were done using Graph Pad prism-5 software (Graph Pad software Inc., San Diego, CA, USA).

III. Results And Discussion

3.1. Physicochemical Characterization of DTZ HCl Floating Tablets
All properties of different DTZ HCl formulations are illustrated in Table 2. All the prepared tablets showed desirable physicochemical properties complying with the specifications of USP Pharmacopoeia [22] for weight variation, drug content, and friability %. Tablet weight in a range from 348.6 ± 2.63 to 350.9 ± 0.87 mg. Drug content uniformity results were found to be good for different formulations ranging from 96.7 ± 3.11 to 100.7 ± 2.13 %. The friability % for all prepared tablets was less than 1% that indicates a good mechanical resistance. Hardness of the prepared formulations was ranged from 6 to 7 kg.

<table>
<thead>
<tr>
<th>Formulae code</th>
<th>Tablet weight (mg)</th>
<th>Drug content (%)</th>
<th>Friability (%)</th>
<th>FLT (sec)</th>
<th>TFT (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>350.8±0.725</td>
<td>100.7±2.13</td>
<td>0.536±0.04</td>
<td>18</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F2</td>
<td>349.7±0.812</td>
<td>96.7±3.11</td>
<td>0.746±0.06</td>
<td>20</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F3</td>
<td>350.4±1.04</td>
<td>99.6±1.67</td>
<td>0.681±0.01</td>
<td>23</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F4</td>
<td>349.9±1.61</td>
<td>98.9±2.00</td>
<td>0.480±0.08</td>
<td>11</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F5</td>
<td>349.9±1.54</td>
<td>99.2±3.67</td>
<td>0.392±0.03</td>
<td>10</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F6</td>
<td>350.9±0.87</td>
<td>98.8±1.87</td>
<td>0.457±0.07</td>
<td>8</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F7</td>
<td>348.6±2.63</td>
<td>99.6±3.64</td>
<td>0.583±0.05</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>F8</td>
<td>350.3±2.22</td>
<td>100.0±4.25</td>
<td>0.810±0.09</td>
<td>180</td>
<td>10</td>
</tr>
<tr>
<td>F9</td>
<td>349.2±4.85</td>
<td>99.8±5.22</td>
<td>0.721±0.03</td>
<td>Immediate</td>
<td>5</td>
</tr>
</tbody>
</table>

All values are expressed as a mean ± S.D. (n=3), FLT: Floating Lag Time; TFT: Total Floating Time.

3.2. Buoyancy Behavior
Floating Lag Time (FLT) and Total Floating Time (TFT) are important factors affecting the behavior of effervescent floating systems. To explain the in-vitro buoyancy of DTZ HCl tablets, sodium bicarbonate was used as effervescent gas generating base during tablets preparations. When the formulated tablets were contacted with the dissolution media (0.1N HCl), the acid-base reaction occurs liberating CO₂ gas which is entrapped in the hydrocolloid gel matrix [27]. The porosity of tablet may increase and so it floats over the surface medium for this extended period of time. The results of FLT and TFT for all formulated tablet are summarized in Table 2.

From the obtained results, it was found that immediate floating was observed with CP tablets (F9) upon contact with the test medium possibly due to the entrapment of the resultant CO₂ within the CP gel layer. While, FLT values of HPMC (F7) and S ALG (F8) tablets were 34 and 180 sec, respectively. This could be elucidated with regard to the test medium rate to penetrate into these matrices and thus the time required for CO₂ generation and gel formation. Tablet consists of HPMC (F7) or S ALG (F8) remained buoyant over the media for 10 hrs possibly due to the development of a gel matrix with an excessive strength to trap the air bubbles and

Figure 1: Photographs during in-vitro buoyancy study of formula F6 in 200 ml 0.1N HCl.
maintain buoyancy [29]. However, the tablet containing CP (F9) floated only for 5 hrs since CP has a high tendency to imbibe water and the subsequent increase in density inhibiting the prolonged floating [28, 29]. The formulae containing HPMC-CP in different ratios (F4, F5 and F6) had shorter FLT (11, 10 and 8 sec, respectively) than that of formulae containing HPMC- S ALG in different ratios F1, F2 and F3 (18, 20 and 23 sec, respectively). Regarding HPMC combinations with each of S ALG and CP in different ratios revealed that increasing the TFT longer than 12 hrs possibly due to the CO\textsubscript{2} generated was trapped in the tablets and protected within the gel formed by hydration of polymers and so decrease the tablet density below 1, hence, maintaining tablet buoyant [30]. Figure 1 illustrates the photographs taken during in-vitro buoyancy study of formula F6 in 200 ml 0.1 N HCl at different time intervals.

3.3. Swelling Study

The swelling index characterizes the ability of tablet to water uptake. The ability of polymers to absorb water is attributed to the entity of hydrophilic functional groups that hydrated which lead to entrance of water into the polymer network. The hydration ability of the formulations is very significant because it influences tablet buoyancy and drug dissolution. From the obtained results, it was noticed that the strong differences among HPMC, CP and S ALG tablets regarding percent swelling indices were obtained (Fig. 2a). The swelling of CP tablets (F9) was significantly (p<0.05) higher than that of HPMC and S ALG tablets (F7 and F8, respectively).

CP tablets (F9) exhibited the highest water uptake, so, the swelling index percentage increased till reached the maximum value (399±18.4) after 5 hrs and then followed by a gradual decrease of the swelling index percent till a value of (315±15.3) at 12 hrs which might be due to the dissolution of the gel formed around tablets. It was previously reported that, CP is insoluble in gastric fluid and, its swelling ability is due to the uncharged –COOH group that hydrated by forming hydrogen bonds with the imbibing water and, therefore, extending the polymer chain [31]. Also, S ALG tablets showed higher swelling index which may be related to the high affinity of S ALG- containing matrices to the test medium. Similar results were previously obtained by [21]. While, HPMC tablets exhibited less swelling ability than others with a maximum swelling index 280±10.7 after 5 hrs possibly due to the neutral cellulose groups.

![Swelling profiles of DTZ.HCl floating tablets](attachment:swelling_profiles.png)

**Figure 2:** Swelling profiles of DTZ.HCl floating tablets (a) Individual polymers, (b) HPMC-S ALG combinations and (c) HPMC-CP combinations.
The swelling profiles of F4, F5, and F6 tablets are shown in Fig. 3c. The higher CP content increased the percentage of swelling indices probably due to more carboxylic moieties and more expanded network [32]. Similar behavior was also noticed with HPMC- S ALG matrices (F1, F2, and F3 tablets) as depicted in Fig. 3b. However, the maximum swelling percentage of HPMC -CP formulations was significantly higher (p<0.05) than those of the corresponding HPMC- S ALG formulations that may be explained by the higher swelling capability of CP compared with S ALG.

3.4. Dissolution Study

Figure 3 illustrates the release characteristics of DTZ HCl from different floating tablets. The obtained results revealed that, the rapid drug release was occurred with control tablet (without any polymers) in 0.1N HCl. It was found that, the drug release rate was about 96.3% ± 4.56 at 60 min. This may be due to the solubility of DTZ HCl in the dissolution media with acidic nature (pH 1.2). Additionally, it is apparent that all tablets were effective in controlling the drug release rate for 12 hrs. The type of polymer and ratios affected the release of the drug from the prepared formulations. As shown in fig. (3a), the percent drug release of formula F8 (containing S ALG only) and F7 (containing HPMC only) was about 97.5±3.67 and 56±5.29 %, respectively, while that of F9 (containing CP only) was about 52.3±2.51%. In fact, formula F9 showed a significantly (p < 0.05) lower rate of drug release than that of other formulae.

The influence of HPMC-S ALG ratio on the drug release from sustained release floating tablets in dissolution medium was illustrated in Fig. (3b). It is clear that, the percent drug release was 87.65±4.65, 80.84±5.34 and 74.77± 3.91% for F3, F2 and F1, respectively. So, the retardation degree of the release rate from these formulae was depending on HPMC-S ALG ratio. HPMC having higher viscosity that would promote the formulation of extensive viscous gels layer around the tablet upon contact with the dissolution medium, which in turn promotes retardation of drug release. Kulkarni and Bhatia [31] suggested that HPMC upon contact with aqueous medium would form gel-like networks surrounding these matrices that produce strong surface barriers that would minimize the eruption drug release.

Figure 3: *In-vitro* drug release profiles of DTZ HCl floating tablets in 0.1 N HCl (pH 1.2) (a) Individual polymers, (b) HPMC-S ALG combinations and (c) HPMC-CP combinations.
The combination of CP alone with sodium bicarbonate as a matrix tablets (F9) would significantly (P<0.05) decreased the drug release rate compared with other HPMC-CP tablets at 12 hrs. This behavior may be dependent on the basis that CP, a cross-linked polymer, has high molecular weight and viscosity, leading to formation of a thick gel structure upon contact with the dissolution media. Moreover, the alkaline microenvironment created by the dissolved sodium bicarbonate within the tablet matrix could enhance this gelling effect of CP, so, further slowing penetration of the dissolution medium [33]. Furthermore, there is an inverse relation between the tablet dimensions and drug release rate, as, the tablet size increase by swelling lead to decrease the drug release. On combining HPMC with CP, the percent drug release was 91.36±3.72, 87.86±2.32 and 82.02±5.32 for F6, F5, and F4, respectively, as depicted in Fig. (3c).

3.5. Drug Release Kinetics

Table 3 illustrates the kinetic parameters of the release data and correlation coefficients (r²) determined for the prepared formulations. The data obtained from dissolution studies were fitted to different kinetics models. It was found that, r² values were ≥ 0.9178 suggesting that the drug release may follow any one of these models.

Further determination using the Korsmeyer-Peppas equation, when n = 0.45, it indicates diffusion-controlled drug release. In case of n = 0.89, it indicates swelling-controlled drug release. While, n value ranged between 0.45 to 0.89 can be regarded as an indicator for both the phenomena (anomalous transport, non-Fickian) [24]. It is clear that all formulae have n values between 0.660 and 0.879 that indicated exhibition of non-Fickian (anomalous) diffusion and a drug release controlled by a coupling of diffusion and erosion.

<table>
<thead>
<tr>
<th>Formula Code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi model</th>
<th>Korsmeyer-Peppas</th>
<th>Drug transport mechanism</th>
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<td>0.4241</td>
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<tr>
<td>F9</td>
<td>0.9657</td>
<td>0.9381</td>
<td>0.9366</td>
<td>0.916</td>
<td>0.826</td>
</tr>
</tbody>
</table>

n = diffusional exponent

3.6. Bioavailability Study

The mean plasma concentration of DTZ HCl versus time curve of tested formulations and the pharmacokinetic parameters are illustrated in Figure 4 and Table 4. It's clearly evident that, there was a significant difference between the mean plasma concentrations as a function of time for DTZ HCl after oral administration of the optimized formula (F6) compared to the Ct tablet at all-time intervals. From the results of pharmacokinetic parameters, it was found that, the absorption of DTZ HCl from Ct tablets was rapid and reached to its Cmax in 2 hrs with t 1/2 (1.65±0.23 hr) whereas, following administration of optimized formula F6, the mean Tmax was 4 hrs with t 1/2 (2.34±0.15 hr). These results indicated the sustained release effect of F6 tablet compared to the Ct tablets. The mean plasma concentration (Cmax) was 2700±158 (ng/ml) for F6 compared to 3300±203 (ng/ml) for the Ct tablets.

This prolonged effect agreed with the in-vitro drug release results that may be due to the swelling capability and floating behavior of this formula and hence, extended the gastric residence time [34]. DTZ HCl in optimized formula showed a high AUC0-24 (18814 ± 3468 ng.hr/ml) compared to that of Ct tablet (14438 ± 2361 ng.hr/ml) indicating the greater extent of drug absorption from this formula. These results indicated the more suitability of F6 as sustained-release tablet. These findings confirm the target of sustained release concept which has been estimated in reducing Cmax, prolong Tmax, increasing values of AUC0-24 and AUC0→∞ and finally increasing the bioavailability of the drug. Also, it is apparent that, the Cmax, Tmax, AUC0-24 and AUC0→∞ of F6 tablet were significantly difference (p<0.05) to that of Ct tablet.

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Table 4: Pharmacokinetics parameters of tablets containing DTZ HCl

<table>
<thead>
<tr>
<th>Pharmacokinetics parameters</th>
<th>Optimized formula (F6)</th>
<th>Control formula (Ct)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>2700±158</td>
<td>3300±203</td>
</tr>
<tr>
<td>T_{max} (hr)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>AUC_{0-24} (ng.hr/ml)</td>
<td>18814±3468</td>
<td>14438±2361</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng.hr/ml)</td>
<td>19625.08±3952</td>
<td>14509.49±2536</td>
</tr>
<tr>
<td>K_e (hr⁻¹)</td>
<td>0.2959±0.03</td>
<td>0.4196±0.05</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>2.34±0.15</td>
<td>1.65±0.23</td>
</tr>
<tr>
<td>Relative bioavailability %</td>
<td>135.25±3.45</td>
<td>--------</td>
</tr>
</tbody>
</table>

Each value is expressed as means ± S.D. (n=6), C_{max} (peak plasma concentration), T_{max} (time required to reach the maximum plasma concentration); AUC_{0-24} (the area under plasma concentration time curve from 0-24 hr), AUC_{0-∞} (the area under plasma concentration time curve from 0-∞), K_e (the elimination rate constant) and t_{1/2} (the biological half-life).

Figure 4: Mean plasma concentration of DTZ HCl of the optimized formula F6 and control (Ct).

IV. Conclusion

This research was investigated to formulate the sustained-release floating tablet of DTZ HCl by direct compression technique utilizing different bioadhesive polymers as; HPMC, S ALG and CP in various ratios. All the prepared tablets have uniform drug content, weight variation, and friability % that complied with the USP official requirement. The dissolution rate of DTZ HCl from the prepared tablets was significantly influenced by the type and the ratios of the polymer used. The non-Fickian release behavior obtained, suggests that, the release of the drug is controlled by a diffusion mechanism. Tablet containing a combination of HPMC-CP in ratio of 1.5:1 (F6) showed desirable results regards to FLT, TFT, swelling ability, and extended drug release up to 12 hrs. The in-vivo study proved the superiority of F6 formula over control tablet, that attributed to prolong gastric residence time.

References


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