Taguchi orthogonal design array to optimize methylcellulose based elementary osmotic pump tablets for the delivery of highly water soluble drugs

Narimane Lammari 1, Hadjira Rabti 1, Jumah M M Salmani 1,2, Eltayeb S Elamin 3, Qineng Ping 1
1 Department of Pharmaceutics, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China.
2 Department of Pharmaceutics, College of pharmacy, Al-Mustansiriya University, Al-Qadisiya District, Baghdad, Iraq.
3 Omdurman Islamic University, faculty of pharmacy, department of pharmaceutics, Khartoum 00249, Sudan.

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Abstract
It is difficult to retard the release of highly water soluble drugs due to their fast dissolution and absorption in gastrointestinal tract. A novel methylcellulose based elementary osmotic pump tablets of metoprolol succinate, which was used as a model drug, has been designed to overcome these drawbacks. Taguchi orthogonal L18 array design with analysis of variance was conducted to optimize the release profile. The results showed that the drug release was inversely proportional to the viscosity and amount of methylcellulose, thickness of semipermeable membrane and amount of dibutylphthalate, while it was directly proportional to the amount of polyethylene glycol 400 and independent to the compacting method and orifice size. The results approved also the reliability of this system to control the release of drug at zero order kinetic for up to 12 hours. The in vivo studies conducted in rabbits using the optimized and marketed formulations revealed that in addition to the enhanced bioavailability, this design maintained a constant therapeutic drug concentration within plasma even up to 24h independently to the pH variations, in conclusion this approach can circumvent all intra and inter subject variations in gastric physiology and serve as promising delivery system for highly water soluble drugs.

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KEY WORDS: Elementary osmotic pump, methylcellulose, Taguchi orthogonal design, zero order kinetic.

1. Introduction
The improvement of patient compliance remains one of the major challenges facing health care professionals, providers and researchers [1]. Many patients with chronic diseases including asthma, hypertension, diabetes and cancer, have difficulty in adhering and complying with their recommended regimens [1, 2]. According to the National Council on Patient Information and Education, “Lack of medication adherence is one of America’s main drug problems [3]. This can lead to undesirable impact on clinical outcomes, reduce patients’ quality of life, and waste health care resources [1, 2]. Non compliance can be related to the complexity of the treatment regimen, the frequency of the dose and the immediacy of adverse effects [1]. Furthermore, multi dose regimen may be the cause of unavoidable fluctuations in drug level which lead to precipitation of side effects especially of a drug with small Therapeutic Index, and of a typical peak-valley plasma concentration time profile which makes attainment of steady state condition difficult. One approach to overcome all these problems is the oral controlled drug delivery system (OCDDS) [4]. By providing drug release at a predetermined, predictable, and controlled rate, these systems could maintain drug concentration within the therapeutic window, enhance the activity of duration for short half-life drugs; minimize side effects, reduce frequency of dose and hence improve patient compliance [5]. Despite all benefits, drug release from conventional controlled release (CR) systems (matrices and reservoirs) is often affected by the pH, gastric motility, and the presence or absence of food [6-9]. Thus, these shortcomings can be circumvented by the introduction of osmotic drug delivery systems which utilize the osmotic pressure as an energy source and driving force for delivery of drugs [6, 8]. Elementary osmotic pump tablets (EOPTs) are one of the several types of osmotic devices already reported [10],
they basically consist of a core surrounded by a semipermeable membrane (SPM) and drilled with a delivery orifice [11, 12]. When they become in contact with the gastrointestinal (GI) fluids, the osmotically driven water enters the system through the SPM, dissolves the soluble contents, which exit through the orifice [13]. Since the SPM is permeable to water and not to ions, the release rate is essentially independent of the environmental pH. Further, the process of drug dissolution takes place inside the delivery system, regardless of the variation in the surrounding environment [14]. In addition, EOPTs can also provide zero order delivery rate [15] and high degree of \textit{in vitro in vivo} correlation. Thus, they have a strong market potential as evident from their simple structure and high efficiency [16].

In present time, hydrophilic polymers are widely used in formulating OCDDS as polymeric retarding materials [4]. Upon contact with water, they produce a gel layer which controls water ingress into the tablets and delay the drug release [17]. Among all the hydrophilic polymers used, METHOCEL Premium products hold a major place in the industry due to their excellent consistency and reproducible performance [18], and they are listed as methylcellulose (MC) and hypromellose [19]. MC has been extensively used in oral and topical application and as retarding agent in OCDDS [20].

It is often difficult to retard highly water soluble drugs from CR formulations because they readily dissolve in GI fluids and thus quickly absorbed leading to a sharp increase in the blood drug concentration which could increase the risk of toxicity [4, 21]. The pH dependent solubility would be another problem for CR formulation because of the variation in pH throughout the gastrointestinal tract (GIT) and variation in dissolution rate [21]. In the current work, metoprolol succinate (MET) was used as a model for the highly water soluble drugs. It is widely used for the treatment of hypertension, has short elimination half life (3-4 hours(h)), thus needs frequent administration, usually three to four times daily and if a dose is missed then nocturnal attack may occur [7, 22]. Thus, an attempt was made to combine the retarding property of MC with the unique characteristic of osmotic pump to design a novel MC based EOPT of MET.

The retarding polymer together with osmotic agent, SPM thickness and plasticity and the orifice size were the key parameters that affect this formulation [13, 23]. In order to determine the effects of all these factors on the release rate and establish the optimum formulation, Taguchi orthogonal L18 array design was employed. One of its main features is the insensitivity to the variation of environmental conditions and other noise factors, hence improving optimization of process parameters; it emphasizes a mean performance characteristic value close to the target value rather than a value within certain specification limits, thus improving the product quality [24]. Instead of having to test all possible combinations like the factorial design, the Taguchi design tests pairs of combinations in only few experimental runs, thus saving the time and resources [25].

Further characterization of both \textit{in vitro} and \textit{in vivo} has been applied, for the optimal formulation and compared with the marketed extended release formulation as a reference.

2. Material and methods

2.1. Materials

Metoprolol Succinate was purchased from Apeloa Jiayuan Pharmaceutical Co., Ltd (Zhejiang, China). Cellulose acetate (CA) (Opadry CA 500F190004), METHOCEL Methyl Cellulose A4CP, A15CP and A4MP were gift by Shanghai Colorcon Coating Technology Ltd. (Shanghai, China). Mannitol was from Roquette Co., Ltd. (Shanghai, China). Betaloc® ZOK 100 (MET extended release tablets 95mg) was purchased from local drug store. All others chemicals used were of analytical grade.

2.2. Methods

2.2.1. Experimental design

Taguchi experimental design was used to optimize and develop MET-EOPT. The optimized formulation was obtained by orthogonal array L18 which examined eight factors as shown in Table 1. Except of the compacting method that had two levels, all other factors had three levels. The cumulative percent of drug released (Q %) in 1, 4, 8 and 20 h were considered to be the responses. Table 1 demonstrates also the different responses with their constraints according to the USP 29 requirement for MET release from extended release tablet. Table 2 summarizes the 18 experimental runs of this study.

2.2.2. Preparation of Core Tablets

Each formulation was prepared using 95mg of MET with 15\% of microcrystalline cellulose, 1\% of talc and 1\% of magnesium stearate of the total core weight. Core tablet of MET were prepared by direct compression or wet granulation methods. In direct compression method, the required amount of MET and other excipients were passed through 60- mesh sieve and manually mixed to get the powder blend ready for compression. In wet granulation method, the blend of powders was mixed homogeneously with water in mortar, granulated through 18- mesh sieve and dried in a hot air oven at 60°C for 4 h. The dried granules were passed through 20- mesh sieve and finally blended with the required amount of talc and magnesium stearate to get the final granule blend for compression. The compression step was performed using TDP single Punch Tablet Press (Tianxiang Zhitai, Shanghai, China) with different diameters of round concave punches depending on the weight of the core tablet. The compression force was adjusted to give tablet hardness of 4 - 5 kg/cm².

2.2.3. Coating and drilling

The coating of core tablets was performed on a pan-coating machine (Huanghai Medicine & Drug Testing Instruments Co., Ltd Technology, Shanghai, China) with hot air. The coating solution contained 3% (w/v) of CA in a mixture of acetone: water, 90:10 (v/v), and different amount of polyethylene glycol 400 (PEG 400) and dibutylylphthalate (DBP). Coating conditions were as follows; coating temperature, 40°C; rotation speed of coating pan, 20r/min; spray speed, 3.0 ml/min. The coated tablets were dried at 40°C for 6 h to remove the residual solvent. The SPM thickness was evaluated by measuring orifice was drilled in the center of each coated tablet by a high technical laser beam.
2.2.4. In vitro drug release
During the optimization process the dissolution profile was performed on the basis of USP 29 requirement with some modifications, the release of MET from the coated tablets was performed in 500 ml phosphate buffer solution (pH 6.8) at 37±0.5 °C and rotation speed of 100 rpm using USP Dissolution apparatus Type I, rotating basket (ZRS-8G dissolution tester, Tianda Tianfa Technology Co. Ltd., China). Ten milliliters aliquots were withdrawn and replaced with fresh medium at 1, 2, 4, 8, 12, 20 and 24 h, filtered and analyzed immediately on UV/VIS spectrophotometer (Rayleigh UV 9600, Beijing Ruili Analysis Equipment Co. Ltd. China) at 274nm.

2.2.4.1. Release models and Kinetics
To establish the drug release kinetics, drug release data obtained was applied to different drug release models which are zero-order, first-order and Higuchi given from equations 1 to 3.

\[ Q_t = k_0 \cdot t \]  
\[ \ln Q_t = \ln Q_0 - k_t \cdot t \]  
\[ Q_t = k_H \cdot t^{1/2} \]

Where \( Q_t \) is the amount of drug release in time \( t \), \( Q_0 \) is the initial amount of the drug in tablet and \( k_0 \), \( k_t \) and \( k_H \) are release rate constants for stated model [7, 11]. The criterion for selecting the most appropriate model to apply for the release kinetics is the best fitness to the mentioned equations.

2.2.4.2. In vitro release pattern of optimized formulation
Dissolution profiles of the optimized formulation and the conventional MET extended release tablets 95mg, Betaloc® ZOK 100, marketed by Astra Zeneca, were applied in gradient pH; phosphate buffer pH 1.2 for the first 2 h, pH 4.5 for next 2 h and pH 6.8 for remaining hours, and

**Table 1 Factors and respective levels investigated in L18 design with the responses and their constraints.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Levels investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1: Compacting method</td>
<td>Direct compression</td>
</tr>
<tr>
<td>X2: Type of MC</td>
<td>MC A4MP</td>
</tr>
<tr>
<td>X3: Amount of MC (%drug)</td>
<td>MC A15CP</td>
</tr>
<tr>
<td>X4: Amount of mannitol (%core weight)</td>
<td>Wet granulation</td>
</tr>
<tr>
<td>X5: Amount of DBP (%CA)</td>
<td></td>
</tr>
<tr>
<td>X6: Amount of PEG400 (%CA)</td>
<td></td>
</tr>
<tr>
<td>X7: SPM thickness (%core weight)</td>
<td></td>
</tr>
<tr>
<td>X8: Orifice size (μm)</td>
<td></td>
</tr>
<tr>
<td>Responses: Cumulative % drug released (Q%)</td>
<td>USP 29 requirements for MET extended release tablets</td>
</tr>
<tr>
<td>Y1: Q%1h</td>
<td>Y1 ≤ 25%</td>
</tr>
<tr>
<td>Y2: Q%4h</td>
<td>20% ≤ Y2 ≤ 40%</td>
</tr>
<tr>
<td>Y3: Q%8h</td>
<td>40% ≤ Y3 ≤ 60%</td>
</tr>
<tr>
<td>Y4: Q%20h</td>
<td>Y4 ≥ 80%</td>
</tr>
</tbody>
</table>

**Table 2 L18 orthogonal array design matrix with experimental responses result of preparation of MET-EOPT.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>Q%1h</td>
</tr>
<tr>
<td>X2</td>
<td>Q%4h</td>
</tr>
<tr>
<td>X3</td>
<td>Q%8h</td>
</tr>
<tr>
<td>X4</td>
<td>Q%20h</td>
</tr>
<tr>
<td>X5</td>
<td></td>
</tr>
<tr>
<td>X6</td>
<td></td>
</tr>
<tr>
<td>X7</td>
<td></td>
</tr>
<tr>
<td>X8</td>
<td></td>
</tr>
</tbody>
</table>

(Nanjing Rui Ma Electronic Engineering Technology Co. Ltd, China).
compared to their dissolution profiles at fixed pH 6.8 by calculating the similarity factor $f_2$ defined by the Center for Drug Evaluation and Research (FDA) and by Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA) as follows:

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

(4)

Where R$_i$ and T$_i$ are percent drug dissolved at each time point j from the reference and test products, respectively. The two release profiles were considered to be similar, if the $f_2$ value was between 50 and 100 [26].

2.2.5. Statistical analysis

Design-expert® version 8.0.6 was used to analyze the results and to predict the optimized formulation. All the experiments were analyzed by analysis of variance (ANOVA). Significance level was set at $p$-value of 0.05. The results were further confirmed by calculating the percentage contribution (PC %) of each factor by using the following equation:

$$PC\% = \frac{SS_p}{SS_{total}} \times 100$$

(5)

Where, SS$_p$ is the pure sum of square, SS$_{total}$ is the total sum of square [27]. PC% represents the factor’s contribution to the response. The largest PC% value indicates the largest contribution to the considered response.

2.2.6. In vivo performance of MET-EOPT

2.2.6.1. Pharmacokinetics and bioequivalent study

The pharmacokinetics parameters of MET-EOPT were evaluated in adult rabbits (3-6kg in weight). Rabbits were divided into two groups (n = 6), control and test group, and fasted for 12 h before drug administration. Each rabbit was given a single tablet dose that contains 95mg of MET, either in the form of optimized MET-EOPT or in the form of the reference Betaloc®. The tablet was manually placed deep inside the mouth followed by sufficient quantity of water through feeding needle. 500 μl of blood sample was withdrawn from the marginal ear vein at 0, 1, 2, 3, 4, 5, 6, 8, 10 and 24 h, placed in preheparinized test tube, mixed and centrifuged at 4000 rpm for 10 min. The plasma was then separated and stored in the refrigerator at −20°C before use.

2.2.6.2. Plasma extraction

According to the method proposed by Venkateswarlu et al. [28] with some modifications, 100 μl of the plasma sample was transferred into a vial to which 100μl of internal standard, hydrochlorothiazide (5ug/ml), dissolved in methanol, was added and vortexed for 30 s. Then 1.5 ml of ethyl acetate was added to the sample, vortexed for 10 min, centrifuged at 3000rpm for 5min. The supernatant was transferred into another vial and ethyl acetate layer was evaporated under vacuum at 40 °C. The dried residue was reconstituted with 500μl of the mobile phase and vortexed.

2.2.6.3. HPLC analysis

HPLC analysis was carried in Shimadzu LC10AT supplied with UV-VIS detector, chromatographic separation was performed on an Agilent column (4.6mm × 150 mm, 5 um particle size) at 25°C. The optimized mobile phase was a mixture of acetonitrile and phosphate buffer pH 3 in the ratio of 18:82 (v/v), the flow rate was 1 ml/min. The injection volume was 20μL and the detection wavelength was 223 nm.

3. Results and discussion

3.1. Optimization of MET-EOPT formulation

The effect of each factor on the release responses was demonstrated in Fig. 1. Where, K represents the average response for each factor at each level.

3.1.1. Effect of compacting method

Recently, the complexity and increased time spent in new drug development has induced a rise in costs. According to Saari [29], investments in drug development have increased steadily and have almost doubled, being 17 billion USD in 1996 and 32 billion USD in 2002. In Fig. 1, A, we can realize the negligible effect of the compacting method on the release pattern of MET. And this was in agreement with the previous finding by Unvala, Schwartz and Schnaare [30]. Hence, the direct compression method could be efficiently used to prepare the formulation offering the advantages of using less equipment and participates to a great extent in reducing the total cost and time of the production.

3.1.2. Effect of MC

Regarding the type and amount of MC they were clearly affecting the release but only during the first four hours, as shown in Fig. 1, B. The release of MET was faster using MC A4CP as retarding polymer compared to MC A15CP and MC A4MP. The polymers showed an efficiency of release retardation with the following viscosities order MC A4MP (400cp) > MC A15CP (1500cp) > MC A4CP (400cp) [20]. Clearly the highly viscous polymer the more retarding activity it exerts. As recently reported by Brindha et al. [15], when they studied the effect of three polymers on the release of amitryptiline from EOPT, they found that an increase in the viscosity led to an increase in the gel layer formed after imbibitions of water and hence a decrease in the release rate. Fig. 1, B also demonstrates that the release rate was dependent on the concentration of retarding polymer. When the polymer concentration was increased, the swelling rate and viscosity in the core increased and water entry into the core was retarded. Consequently, the release rate was decreased. Similar results were obtained from osmotic devices of captopril, when the level of the retarding polymer was increased the rate of drug release was decreased [31].

Due to the fact that the used polymers are hydrophilic, the formation of the gel layer into the core is faster and may require few hours to establish the gel network. Thus, the swelling pressure reaches to a balance and the effect after that will be insignificant.

Thus, the current work highlights the reliability of a safe [19], non-allergic, edible, non toxic [32] and inexpensive polymer [33] to prepare a new perspective of EOPT to control the release of highly water-soluble drugs. In addition, MC meets the requirements of U.S., Japanese, and European Pharmacopoeias, Food Chemicals Codex, the International Codex Alimentarius [18].

3.1.3. Effect of mannitol

From Fig. 1, C, it is clear that the mannitol amount had a remarkable effect on the release rate of MET. As the amount of mannitol was increased from 5% to 30%, there was an enhancement in the release rate during all the study. This is related to the increase of the osmotic pressure inside
Figure 1 Process and formulation variables and their average (k) of each level for different responses.

The drug release was independent to the compacting method and orifice size, directly proportional to the amount of PEG400, and inversely proportional to the viscosity and amount of MC, thickness of SPM and amount of DBP. The tablets and so the release rate. Similar results have been already documented [13, 34, 35]. However, when the concentration was increased above 30%, limited drug release was observed after 4 h. Preethi et al. [12] stated that the difference in osmotic pressure between inside and outside of EOPT causes water penetration into the core until equilibrium. This may explain the reduced drug release observed after 4 h where fast equilibrium of osmotic pressure with concomitant release of drug/mannitol occurred.

Another assumption was related to the formation of thick gel layer into the core. On exposure to aqueous fluid, mannitol enhances water diffusion and the polymer starts hydrating to form a gel layer at core periphery. Concomitantly, as the gel layer was not completely formed, an initial high drug release was observed during the first 4 h due to fast water imbibition caused by high osmotic pressure exerted by mannitol. As reported, METHOCEL products are highly affected by the excipients added to the dosage formulations [19]. Lindgren [36] stated that mannitol enhances water diffusion to matrix systems and enhances both rate and extent gelation of polymer. Therefore high level of mannitol led to deeper water penetration, extensive swelling and consequently provided for thick gel-layer formation and as SPM was not expandable [10], the gel layer may block
some pores which may hindered drug release. In conclusion, it is not necessarily always true that increasing the concentration of osmotic agent promotes an increase in drug release, in the present study we showed that this effect is limited to certain extent; hence, we recommend keeping the amount of mannitol in the optimal limits for a better enhancement in drug release. Furthermore, Mannitol in the current approach have extra advantages over the conventionally used osmotic agent (sodium chloride) by minimizing the side effects that may arise from the use of salts especially for patients with hypertension [37].

3.1.4. Effect of SPM plasticity and thickness

The membrane represents the key parameter in the formulation by separating the whole system from the surrounding environment. If CA-acetone solution alone is used for coating the core, the SPM will be easily ruptured over the course of drug release. Plasticizers were added to modify the physical properties and improve film-forming characteristics of coating solution. Meanwhile, it can improve the membrane’s adherence to the core and mechanical character [31]. As plasticizers will also affect the permeability of the polymers films, thus, it is mandatory to investigate their effects on drug release [13]. The amounts of PEG 400 and DBP have a marked effect to the release throughout the study, as shown in Fig. 1. D. The release rate decreased as the amount of DBP was increased, which is related to the hydrophobicity of this agent, when incorporated in the SPM, will resist the leaching out upon contact with water and prevent the formation of pores and reduce the permeability of the membrane. Therefore, an increase in the amount of DBP in the SPM would result in a decline in the released amount of MET [31]. On the other hand, the release rate increased as the amount of PEG400 was increased. Owing to its high water solubility, PEG400 when incorporated into the membrane increases its permeability by increasing the number of pores upon dissolution, allowing a high imbibition of water and dissolution of MET. Similar results were already documented [31, 38].

It can be concluded that a good hydrophilic/lipophilic balance in SPM structure is essential to achieve a desirable release profile of the drug from EOPT [13].

The SPM thickness is inversely proportional to the release rate of MET as shown in Fig. 1. E. The increase in coating weight gain led to an increased resistance of SPM to water diffusion, causing a decrease of dissolution of drug in the core, and consequently resulted in a decline in MET release. This is in line with the finding of previous research in the same field [39–42]. Therefore, an optimization of the thickness was necessary in order to make sure the pressure produced during swelling does not lead to rupture of the system and also provide enough water in the tablet core in the preferred period of time.

3.1.5. Effect of the orifice size

Fig. 1. F shows that the drug release did not change with varying the size of orifice in the tablet. It has previously suggested that the orifice size must be in appropriate range; smaller, than the maximum limit to minimize the diffusion of drug and larger than the minimum size to minimize hydrostatic pressure inside the system [43]. However, Shokri et al. [13] stated that the optimum aperture size of the osmotic devices containing moderately soluble drugs is significantly smaller than those containing poor soluble or practically insoluble drugs. In our design the effect of orifice size was found insignificant which reflects the fact that it plays no role in the mechanism of release of the drug, which confirm our explanation for the proposed zero order drug release mechanism through the osmotically derived force regardless the orifice size.

3.2. Statistical analysis

The results of p-value and PC% confirm that the SPM thickness, PEG% and DBP% have the largest influence on drug release during all the study, as shown in Table 3, and this may confirm the potential effect of SPM in controlling drug release.

The effect of type and amount of MC are statistically significant to release responses only during the first four hours because the gel network formation was achieved in this time, as described in section 3.1.2.

However, the amount of mannitol was found to be less significant as compared to SPM components due to the fact that the highly water-soluble drugs may create considerable osmotic pressures [16], so the effect of osmotic agent is less pronounced as compared to poorly soluble drugs. Whereas, both the compacting method and the orifice size have no significant effect on the release which further confirm our results.

3.3. Selection of optimized formulation

The constraints listed in Table 1 were used for numerical optimization of MET-EOPT to achieve the desired responses by using the design expert program. The optimized formulation was characterized to check the usefulness of the design.

As shown in Table 4, there was no significant difference (p > 0.05) between the predicted and obtained values of the considered responses which confirm the validity of the design.

3.4. Drug release kinetics

To describe the kinetics of drug release, dissolution data of the optimized formulation was treated according to first-order, zero-order and Higuchi model using regression analysis. The formulation showed a comparatively good linearity with zero order equation, its regression value was 0.9979 much higher as compared to first order and Higuchi plot, which have R² values of 0.8895 and 0.9878 respectively. Thus, this novel of MC based EOPT serves as a promising approach to deliver the drug at zero order kinetic up to 12h.

3.5. In vitro release pattern of the optimized formulation

To evaluate the performance of the optimized formulation, release profile was compared with a marketed product Betaloc® at fixed and gradient pH.

As shown in Fig. 2, the release of MET from the optimized formulation did not change with varying the pH medium, f2 value was found to be 64 between MET- EOPT at fixed and gradient pH. However, the release from the commercial tablets was highly affected by pH variation with prominent high release at low pH values, and f2 was found to be 39. These results significantly confirm that the release of MET...
from the osmotic pump tablets was independent on the pH of the surrounding media.

3.6. In vivo performance of MET-EOPT

3.6.1. Pharmacokinetics and bioavailability study

Herein, a comparative pharmacokinetic study in rabbits was carried out for MET-EOPT and the commercial formulation Betaloc® (used as a reference). Table 5 summarizes the main pharmacokinetic parameters expressed as the mean ± SD. The commercial formulation reaches its T\text{max} in only 1h compared to 3h for MET-EOPT and the difference was significant (p=0.002). As previously documented, the gastric emptying rate of rabbits is slower than human; accordingly, the tablets will remain longer in the gastric pH, which is about 1-2 in adult rabbits [44]. This fact can lead to a conclusion that MET release from the commercial formulation at the first few hours occurred at high rate as compared to the osmotic pump tablets due to the effect of low pH as previously confirmed by the in vitro release study shown in Fig. 2. While the MET-EOPT showed the same level of release independent on the media and its pH, this difference in the initial release led to the this noticeable difference in T\text{max}, and hence further confirms the zero order release pattern of the MET-EOPT. Although there was no significant difference in C\text{max} value of both of the formulations, MET-EOPT significantly had higher relative bioavailability (AUC total), half life, and mean residence time (MRT) than Betaloc® as shown in Table 5. At acidic pH, Betaloc® formulation initially releases high portion of the drug at relatively high rate, however, MET-EOPT releases the drug at zero order kinetic, reserving the drug and controlling the release for longer period of time, which improves the bioavailability about 142% compared to the reference. This can be clearly seen in Fig. 3 where the plasma-MET concentration vs. time profile of EOPT maintained a constant therapeutic concentration even up to 24h. The appearance of secondary peak in the two curves may be related to the enterohepatic recirculation [45].

Taking in consideration different food habit between different populations, we cannot guarantee stable gastric emptying rate which would definitely cause some fluctuation in the drug release in case of using conventional sustained release tablets. Generally, gastric emptying rate can be affected by different physiological factors; solid,
Figure 2 Dissolution profiles of MET – EOPT and commercial Betaloc formulation at fixed and gradient pH. By varying the pH medium, the release from the commercial formulation was highly affected; however, the release from EOPT was not changed.

Figure 3 Plasma profiles of MET following administration of EOPT in comparison to Betaloc formulation. The curves showed the appearance of a secondary peak; however, MET-EOPT showed higher T<sub>max</sub> and higher relative bioavailability compared to the commercial formulation.

Acidic and fatty food; pathological factors; pain, pyloric stenosis, intestinal obstruction, alcohol and pharmacological factors such as; opioid analgesics and anticholinergic drugs [46, 47]. Furthermore, some patients suffer from inflammatory bowel diseases where low pH was noticed in the intestine [48], so the tablet will remain at low pH in almost all the GIT. Hence, to maintain a constant therapeutic drug concentration within plasma even up to 24h there is a need for a novel formulation with constant release rate independent on the media here comes the beneficial effects of the novel MC based EOPT that have the ability to overcome all of these obstacles and maintain a constant drug release.

4. Conclusion

Recently, EOPT have been received regulatory approval for marketing due to their pharmaceutical superiority and clinical benefits over the sustained release and immediate release formulations due to their reliability and ability to deliver the contents at a predetermined rate for prolonged periods independently to the hydrodynamic conditions of GIT. In this work, a novel MC based EOPT of MET (used as model for highly water soluble drug) was prepared and optimized by taguchi orthogonal design. The promising results suggest that an appropriate balancing between type and amount of MC with other parameters that could affect drug release may contribute to deliver MET at zero order kinetic up to 12h. Following in vivo studies, we can conclude that this novel of MC based EOPT promises to be a potential approach to overcome all variation in gastric physiology such as; pH and gastric motility and serve to deliver the drug at a constant rate regardless the physiological and the pathological inter and intra subject variations.

Abbreviation

Oral controlled drug delivery system (OCDDS)
Controlled release (CR)
Elementary osmotic pump tablets (EOPT)
Semipermeable membrane (SPM)
Gastrointestinal (GI)
Methylcellulose (MC)
Gastro intestinal tract (GIT)
Metoprolol succinate (MET)
Hour (h)
Cellulose acetate (CA)
Cumulative percent drug released (Q %)
Polyethylene glycol (PEG)
Dibutylphtalate (DBP)
Food and drug administration (FDA)
Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA)
Analysis of variance (ANOVA)
Percentage contribution (PC %)
Area under the curve (AUC)
Mean residence time (MRT)

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