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The Influence of Polymer Type and Concentration on the Metoprolol Mass Transfer in Extended-Release Tablet of Metoprolol Succinate

Parissa Khadiv-Parsi [*], Morteza Rafiee-Tehrani, Farid Dorkoosh, Jaber Babaee Darabad, Hedayat Azizpour, Nariman Rezamandi, Nadia Larki

1. School of Chemical Engineering, College of Engineering, University of Tehran, Tehran, Iran. E-mail: kparsi@ut.ac.ir
2. Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. E-mail: rafitehr@ams.ac.ir
3. Medical Biomaterial Research Center, Tehran University of Medical Sciences, Tehran, Iran. E-mail: dorkoosh@tums.ac.ir
4. Shimi Pajohan Sabze Nikan, Tehran, Iran. E-mail: jbabaee@ut.ac.ir
5. School of Chemical Engineering, College of Engineering, University of Tehran, Tehran, Iran. E-mail: h.azizpour@ut.ac.ir
6. Department of Civil, Chemical, Environmental, and Material Engineering (DICAM), Alma Mater Studiorum – University of Bologna, Bologna, Italy. E-mail: nariman.rezamandi@studio.unibo.it
7. School of Chemical Engineering, College of Engineering, University of Tehran, Tehran, Iran. E-mail: larki@ut.ac.ir

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ABSTRACT

Metoprolol has been widely used for controlling high blood pressure, preventing myocardial reinfarction, setting rate changes, setting heart rhythm, treatment of chronic angina, and preventing excessive bleeding during surgery. The purpose of this research is the formulation and manufacture of extended-release tablets of metoprolol succinate that conform to all the in vitro physicochemical US Pharmacopoeia national formulary (USP32). For preparing the tablets, the hydrophilic HPMC(K100M) polymer was used in the direct compression method. The release of metoprolol in phosphate buffer having pH=6.8 (USP32) was measured by HPLC. Also, using experimental correlation of diffusivity in a buffer medium and Gurney-Lurie charts during tablet enlargement with time, diffusion coefficients of drug and partition coefficients were obtained at different time steps. The rate of drug release depends on the type, viscosity, and polymer concentration. Drug release results over 20 hours for polymers of HPMC(K100M), HPMC(K4M), HPMC(K15M), polyethylene oxide, ethyl cellulose, and Eudragit (RL100) were investigated and compared. The results demonstrated that HPMC(K100M) met the standards of USP32 very well and was superior over the other polymers tested.

Introduction

Extended-release medications are types of drugs that are designed in a way to release the therapeutic compound into the body gradually, over a period of time, which is usually between 12 to 24 hours. Using extended-release tablets can be advantageous in several ways such as less

* Corresponding Author: P. Khadiv-Parsi (E-mail address: kparsi@ut.ac.ir)

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doses required, fewer side effects, and fewer fluctuations in drug concentration [1-3]. Due to these advantages, nowadays, many commercial drugs are produced in the extended-release formulation. In the special case of metoprolol, according to the literature, extended-release metoprolol (XR) has several advantages over metoprolol tartrate, including better blood pressure control, better heart rate control, and fewer side effects. Also due to the less solubility, it is often used once per day while tartrate should be taken at least twice a day to ensure adequate effect in 24 hours [4]. According to US Pharmacopeia [4], one of the key factors in selecting the best material for extended release of metoprolol is solubility, which should be ten times lower than tartrate. Table 1 shows the release of metoprolol versus time based on USP32 standards [4]. The amount of tablet solvation must be compliant with this table otherwise it would not be accepted.

Table 1. USP standard for the release of metoprolol XR

Time (hour)	Metoprolol solubilized
1	<25%
4	20-40%
8	40-60%
20	>80%

Shah et al. [5] designed the extended-release metoprolol succinate tablet with the following materials: metoprolol succinate, microcrystalline cellulose, methyl cellulose (15 mPa.s), glycerol, corn starch, ethyl cellulose (100 mPa.s) and magnesium stearate. They tested their tablet in terms of solubility and the results were in the range of USP standard.

Aquilante et al. [6] investigated the effect of immediate release metoprolol (IR) and metoprolol XR on the heart rate of patients with chronic heart failure. The experiment was carried out on 13 patients who were taking the same dosage of metoprolol XR and IR for three weeks while their blood pressure, heart electric activity, and electrocardiogram were being monitored constantly. The results demonstrated that metoprolol XR was better at setting the heart rate and blood pressure of patients with heart failure.

Gohel et al. [7] found out that an ideal release mechanism can be created by using hydroxypropyl methylcellulose (HPMC) and Xanthan gum which have gelatin-like properties. Using HPMC makes the matrix structure unified resulting in a good release of active compounds.

In a research study conducted by Sun et al. [8], the internal structure and matrix features of commercial multiple-unit sustained release (MUSR) metoprolol succinate tablet was studied. The results of X-ray imaging revealed that there are an average number of 853 ± 12 spherical pellets inside a tablet. Having studied the changes in pellets during drug release, they found out that the mechanism of sustained drug release is membrane-controlled. In this research, they studied how using HPMC makes matrix structure unified.

Materials and Methods

In this section, information will be provided about the materials, apparatus, and experimental methods used for different formulations of metoprolol tablets. For convenience, tablet formulations are denoted as ‘F’. In all the formulations 95 mg of metoprolol succinate was used as the active compound.

Synthesis of Metoprolol Tablets

7 different formulas were tested to find the polymer with the best properties. The results are listed in section 3.

F1 and F2

Two concentrations of Eudragit RL100 polymer were used for the first two formulations as what is shown in Table 2. Various apparatus used in the experiments are listed in Table 3.

Table 2. Composition of F1 and F2

Material	Role	F1 (mg)	F2 (mg)
metoprolol	Active ingredient	95	95
Eudragit RL100	Binder	3	6
Microcrystalline cellulose (MCC)	Filler	140	137
Povidone-iodine	Binder	10	10
Magnesium stearate	Glidant	5	5
96% alcohol	Solvent (for binders)	1 ml	1 ml

Table 3. Apparatus used for the experiments

Apparatus	Model
Digital weight scale	Acculab (Sartorius group) 0.0001 g precision
Sieve	Mesh number 14 & 20
pH meter	Winlab Germany
Tablet hardness tester	Erweka Germany
Disintegration tester	Erweka Germany
Press	Erweka (AR400) Germany
Solvation	Erweka (DT6)
Liquid chromatography (HPLC)	Agilent Technologies 1260 Infinity
Deionization	Hastaran Teb Co. Iran

Since Eudragit polymers are in the form of big rounded pellets, the direct compression method cannot be used and tablets are manufactured by wet granulation. Ethanol was used as the solvent instead of acetone due to its less toxicity and better availability.

10 metoprolol tablets were produced with the wet granulation method as explained in the following. First, specified concentrations of Eudragit are solved in an alcohol solvent and are added gradually to 95 mg of metoprolol succinate to give a uniform paste. Povidone is also solved in alcohol and is added to the paste and mixed properly. The paste is then filtered through a mesh size of 14. The granule is dried via heating slightly at temperatures below 40 centigrade and then is passed through a sieve with a mesh size of 20. Microcrystalline is then added to the granule and is mixed for 15 minutes. In the last step, magnesium stearate is added and the mixture is stirred for 2 minutes. After that, the mixture is compressed and tablets are produced with a press machine. The tablets are then put inside a dissolution tester with 500 ml of phosphate buffer in pH=6.8 as stated in the USP 32 standard. The mixer is set to 50 rpm and samples will be analyzed in HPLC to measure the concentration of released drug.

F3 and F4

The amount of Eudragit (RL100) is reduced to 25 and 40 mg but other compounds are similar to F1 and F2 so that the effect of polymer concentration can be determined. The process of granulation is also carried out similarly. The name of compounds present in F3 and F4 formulations and their composition are given in Table 4:

Table 4. Composition of F3 and F4

Material	Role	F3 (mg)	F4 (mg)
Metoprolol	Active ingredient	95	95
Eudragit RL100	Binder	25	40
Microcrystalline cellulose (MCC)	Filler	115	100
Povidone-iodine	Binder	10	10
Magnesium stearate	Glidant	5	5
96% alcohol	Solvent (for binders)	1 ml	1 ml

The apparatus used are also the same as the ones used for F1 and F2.

F5

Formulation number 5 is produced as what is shown in Table 5. Eudragit is dissolved in alcohol, then added to the solution, and mixed properly. Dissolved povidone is then added drop by drop to the mixture and then it is passed through a mesh size 14. The mixture is then dried and passed through another sieve with a size of 20. After that magnesium stearate is added and the mixture is mixed for 2 minutes. Tablets are then produced with a press machine and tested.

Table 5. Composition of F5

Material	Role	F5 (mg)
Metoprolol	Active ingredient	95
Eudragit RL100	Binder	40
Lactose monohydrate	Filler	100
Povidone-iodine	Binder	10
Magnesium stearate	Glidant	5
96% alcohol	Solvent (for binders)	1 ml

F6

The composition of the F6 formulation is shown in Table 6:

Table 6. Composition of F6

Material	Role	F6 (mg)
Metoprolol	Active ingredient	95
Ethyl cellulose	Binder	6
Microcrystalline cellulose	Filler	134
Povidone-iodine	Binder	10
Magnesium stearate	Glidant	5
96% alcohol	Solvent (for binders)	1 ml

The procedure for producing the tablet is identical to the description for F1 and F2 except that the ethyl cellulose was used instead of Eudragit as the binder.

F7

Since HPMC (K4M) polymer is often used in the matrixes of slow-release tablets, it was used combined with ethyl cellulose as the binder in Formulation 7 (the same granulation method was used). The composition is given in Table 7:

Table 7. Composition of F7

Material	Role	F7 (mg)
Metoprolol	Active ingredient	95
Ethyl cellulose	Binder	40
HPMC (K4M)	Binder	30
Microcrystalline cellulose	Filler	70
Povidone-iodine	Binder	10
Magnesium stearate	Glidant	5
96% alcohol	Solvent (for binders)	1 ml

The procedure is the same as F6 except that HPMC is also dissolved in alcohol and is combined with ethyl cellulose to act as the binder.

Design of Experiment

Since HPMC (K4M) polymer in the F7 formulation has made the drug release slower, Poly ethylene oxide (PEO 10860) and Hydroxypropyl methylcellulose (HPMC K100M) was used in the Box-Behnken experiment design. The kind of polymer, the concentration of polymer, and kind of filler was set as variables. Three kinds of polymer considered were PEO (number 1), HPMC(K100M) (number 2), and HPMC and PEO mixture with a ratio of 1:2. Concentration of polymer was constrained between 250 and 300 mg. Kind of fillers used were povidone (number 1), lactose (number 2), microcrystalline cellulose (number 3). The experiment was designed in 17 runs which is shown in Table below.

Table 8. Box-Behnken experiment design

Run	Factor 1 A: Kind of Polymer	Factor 2 B: Conc. Of Polymer mg/mg	Factor 3 C: Kind of Filler	Response 1 Release% in 1 hr	Response 2 Release %in 4 hr	Response 3 Release %in 8 hr	Response 4 Release %in 20hr
1	3.00	275.00	1.00	16.7	37.67	57.45	**98.78**
2	1.00	300.00	2.00	10.702	14.48	34.8	**98.24**
3	2.00	275.00	2.00	17.72	37.97	58.47	**103**
4	2.00	275.00	2.00	18.36	41.1	66.5	**103**
5	2.00	300.00	1.00	14.22	33.71	52.12	**88.33**
6	2.00	250.00	3.00	24.21	36.21	51.22	**88.6**
7	3.00	300.00	2.00	16.7	37.67	57.45	**98.87**
8	2.00	300.00	3.00	17.11	38.77	61.3	**97.37**
9	3.00	275.00	3.00	17.44	46.9	80.66	**101.1**
10	2.00	275.00	2.00	17.2	38.43	60.1	**91.79**
11	2.00	275.00	2.00	17.2	38.43	60.1	**91.79**
12	3.00	250.00	2.00	18.49	48.31	70.5	**101.1**
13	2.00	250.00	1.00	19.2	39.3	57.9	**98.5**
14	1.00	275.00	1.00	10.7	14.48	34.8	**100**
15	2.00	275.00	2.00	17.2	38.23	59.8	**91.3**
16	1.00	250.00	2.00	16.2	20	57.9	**100**
17	1.00	275.00	3.00	8.7	16	33	**100**

Four responses were considered for the tests that were the percentage of drug release in 1, 4, 8, and 20 hours. All the formulations in Table 7 were produced using direct compression method and had 95 mg of metoprolol succinate in them.

Final Formulation (F_T)

After comparing the results of experiments, the final formulation was made from the following materials: metoprolol (from Cipla, India), HPMC (K100M), povidone, lactose monohydrate, and magnesium stearate.

Tablet Erosion Test

20 tablets are weighed and put in the test machine. The experiment will go on for 4 minutes at 25 rpm. After that tablets are weighed again. The decrease in weight should be less than one percent.

FT Tablet Chemical Tests

The drug release of tablets is tested to evaluate the extended release of metoprolol according to the USP32 standards. The chemicals required for the test are shown in Table 9.

Table 9. Chemicals used for solvation tests

Manufacturer	Compound
Merck	Monobasic potassium phosphate (0.2M)
Merck	Sodium hydroxide (0.2M)
Merck	Phosphoric acid (1M)
Merck	Sodium dihydrogen phosphate
Merck	Acetonitrile

The solution is 500 ml of phosphate buffer with pH=6.8. The tablets are inserted into the solution and samples are extracted from the solution after 1, 4, 8, and 20 hours. The concentration of metoprolol in the samples is then specified with HPLC analysis.

Results and Discussions

F1-7 results

The percentages of metoprolol release for different formulations are shown in Table 10. As can be seen, F1 and F2 show a very fast release of drug in the solution which should be altered by using more polymer in the formulation. The formulations which had Eudragit polymer as the binder do not show a slow release of the drug in the test, so a better polymer should be used. Moreover, 25 ml of alcohol is required to solve 0.75 g of Eudragit RL100 in the lab. This means that 1333 L alcohol is required for the production of 1 million tablets, which is not economical.

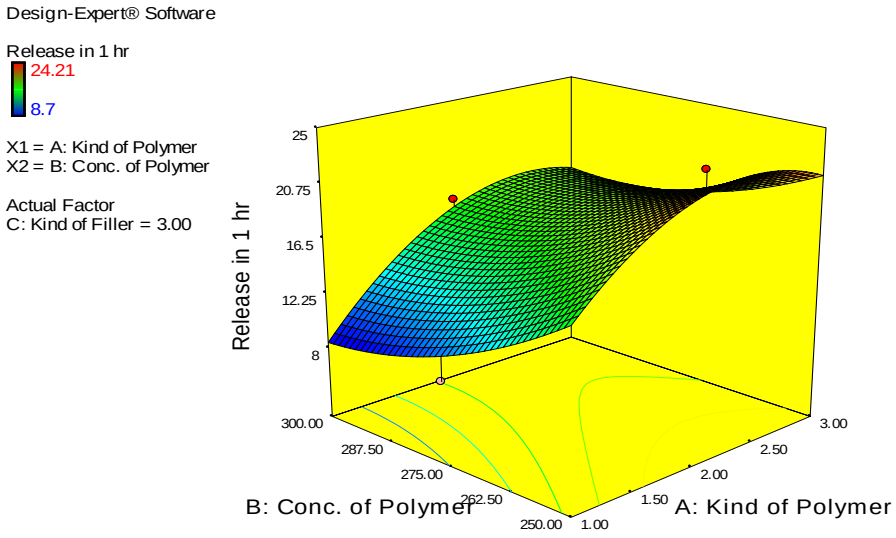
Table 10. In-vitro drug release of different formulations

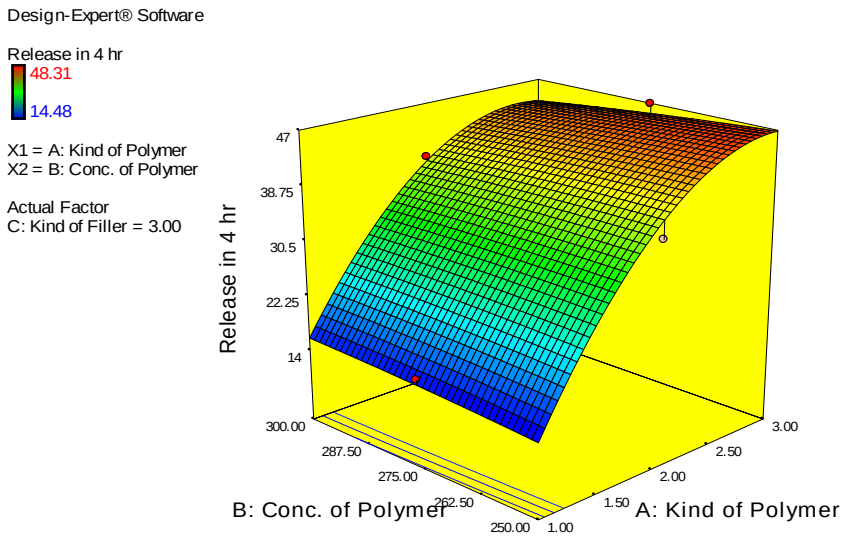
Time (hr)	Drug release (%)						
	F1	F2	F3	F4	F5	F6	F7
1	87.5	84.6	61.5	52.74	46.83	80.1	40.8
4	100	100	90.84	87.88	87.1	100	81.7
8	100	100	100	100	100	100	100
20	100	100	100	100	100	100	100

Design of Experiment Results

The drug release of the different formulations after 1, 4, 8, and 20 hours is given in three-dimensional plots in Fig. 1. Numbers between 1 to 3 on the x-axis represent different polymers

(1=PEO, 2=HPMC K100M, 3=Microcrystalline cellulose). As can be seen, after one hour, as we go from number 1 (PEO) to number 2 (HPMC), the drug release increases, and as we go near number 3, the drug release decreases. The left axis of the cube shows the polymer concentration which if increased, will slow the drug release mechanism. In four hours, the drug release of PEO is lower than HPMC; however, it is less than the minimum concentration specified by the USP32 standard. Thus, the HPMC is preferred. In the 4-hour plot, polymer number 3 has a smaller reduction in release compared to the others, which indicates that although the PEO has a slow release at first, its release will pace up as time goes on. This is especially evident in the 20-hour plot, which shows that the PEO cannot retain the active compound in longer time frames.





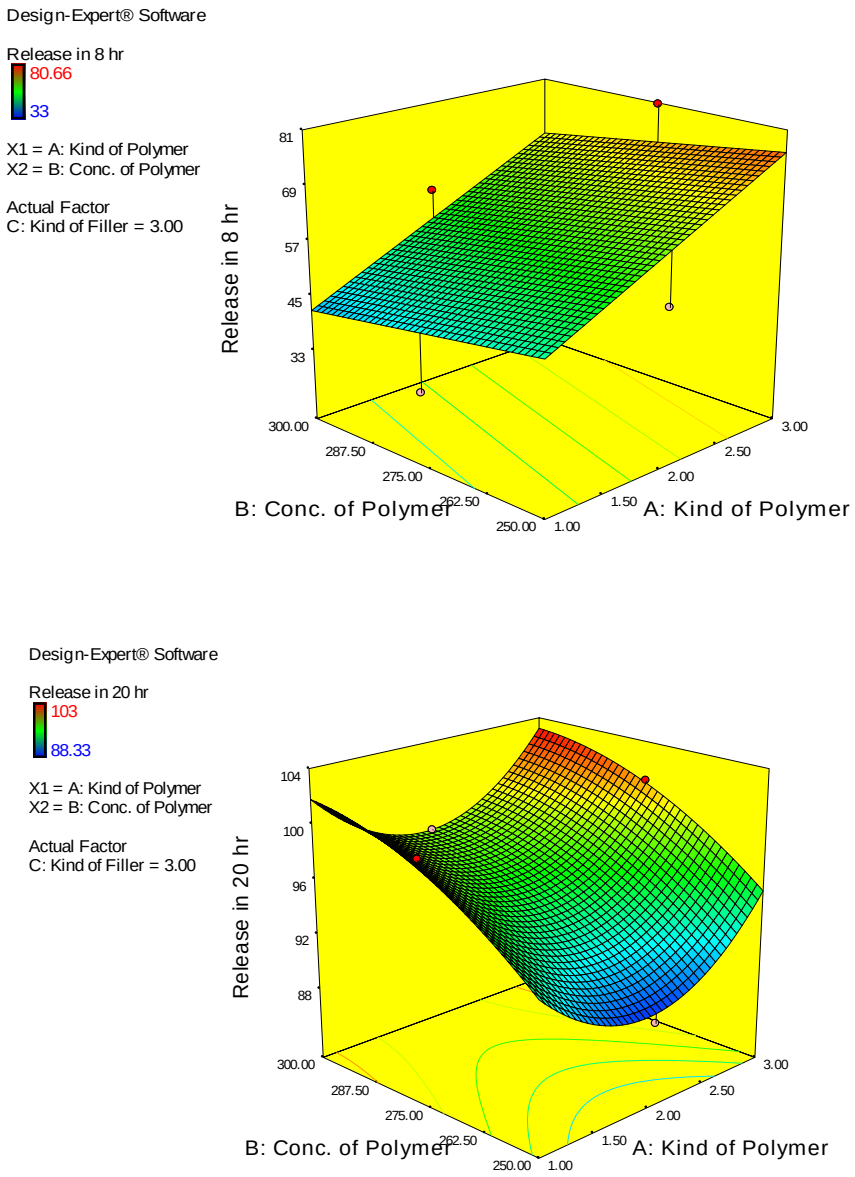


Fig. 1. Drug release of different formulations in 1 hour (a), 4 hours (b), 8 hours (c), and 20 hours (d)

Physical Properties of the Metoprolol Tablet with Final Formulation (F_T)

The dimensions of the tablet were measured with a digital caliper and are shown in Table 11.

Table 11. Dimensions of the metoprolol tablet

Dimensions	Size (mm)
R	5.15
H (flat height)	3.9
h (curved height)	1.8
D	10.3

Tablets were also tested in terms of hardness and erosion to see how resistant the tablet matrix is against mechanical stress. Table 12 shows the hardness number and erosion percentage for the 6 produced samples, as well as the average values.

Table 12. Hardness and erosion tests

	Tablet weight (mg)	Thickness (mm)	Hardness (n)	Erosion (%)
1	440	5.55	6.0	0.3
2	440	5.57	6.0	0.4
3	440	5.7	5.5	0.35
4	440	5.7	5.5	0.45
5	440	5.65	6.0	0.4
6	440	5.7	5.5	0.3
Average	440	5.64	5.75	0.37

Drug Release Test of the Final Formulation (F_T)

Finally, the drug release of the F_T was tested and the results were compared with USP32 standards and a commercial tablet from HEXAL (Germany). As indicated in Fig. 2, the results are similar to the commercial tablet and are in the acceptable range of USP32 standards. The amount of drug release for the F_T formulation and the commercial tablet after 1, 4, 8, and 20 hours are given in Table 13. Similar results have also been reported by other studies that investigated the release rate of metoprolol from polymer-base extended-release tablets [9-11].

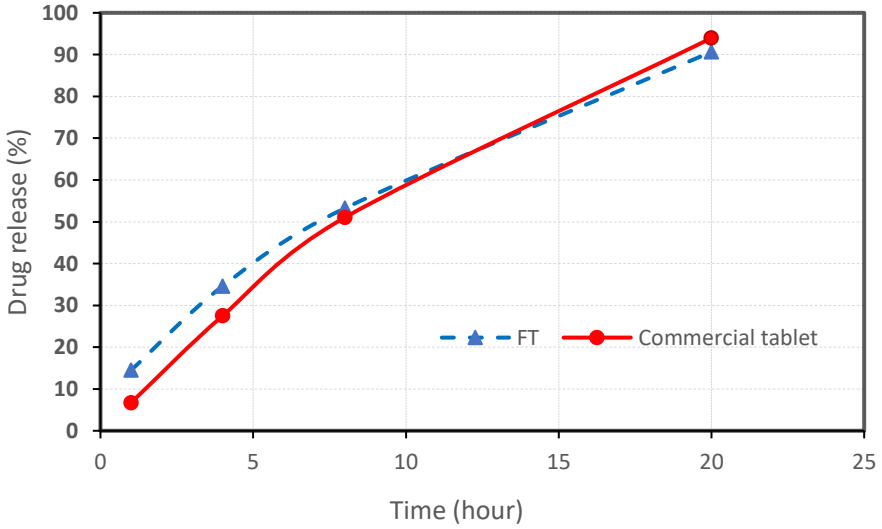


Fig. 2. Plot of F_T drug release versus time

Table 13. Drug release comparison versus commercial tablet

Time (hour)	F_T drug release (%)	Commercial Tablet Drug Release (%)
1	14.48	6.7
4	34.59	27.51
8	53.25	51.03
20	90.63	93.95

Tablet Size in the Solution

When the tablet is inserted in the solution (phosphate buffer), it will absorb water and will expand gradually. To monitor the changes in size over time, pictures were taken from the tablet using an optical microscope. The images were then used to measure [12] the tablet dimensions. The taken pictures are shown in Fig. 3.

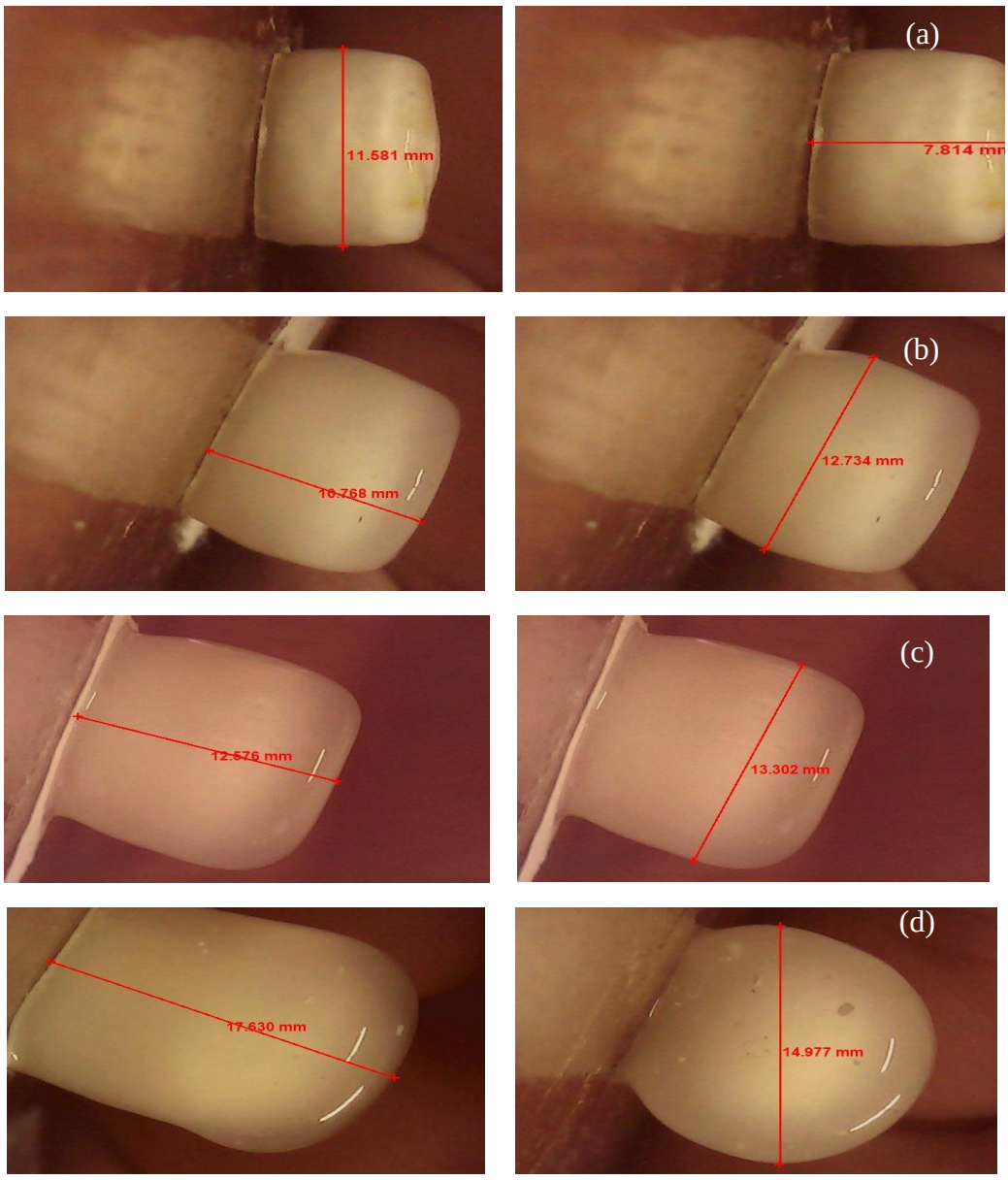


Fig. 3. Tablet size after 1 hour (a), 4 hours (b), 8 hours (c), and 20 hours (d)

Table 14. Tablet dimensions in solution

Time (hour)	D (mm)	Z (mm)
1	11.581	7.814
4	12.734	10.77
8	13.302	12.576
20	14.98	17.63

Mass Transfer Calculations

To estimate the mass transfer coefficient, the Biot number should be first calculated. In the metoprolol solvation test, 500 ml of phosphate buffer was used in a propeller-type mixer. The size of the beaker in which the solution is mixed, the level of the liquid, and the mixer diameter are all the parameters that influence the Reynolds and Sherwood number. Mass transfer coefficient k_C can be derived from the Sherwood number using the following equation:

$$Sh = \frac{k_C d_T}{D} = 0.267 Sc^{0.25} Re^{0.75} {N_p}^{0.25} \left[\frac{{d_T}^4}{V d_i}\right]^{0.25} \quad (1)$$

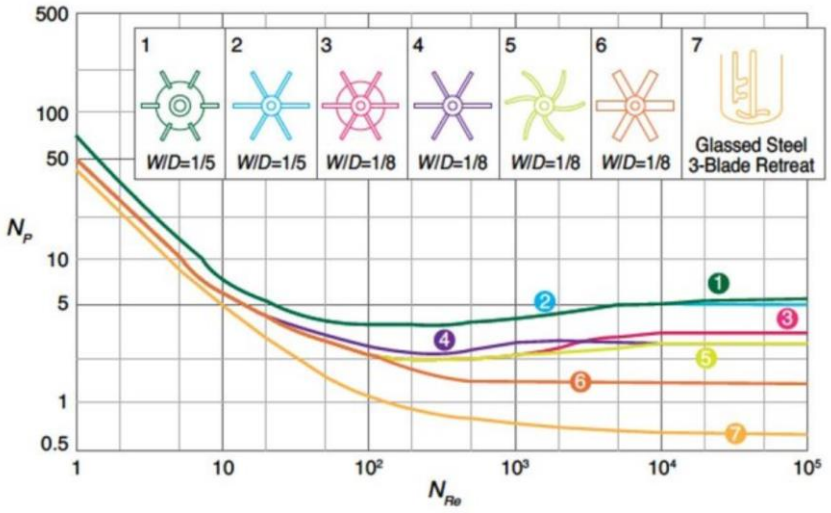


Fig. 4. Relation of N_p with Reynolds number for different impellers [13]

From Fig. 4 and Fig. 5, the N_p for the mixer is equal to 5. N_p is a dimensionless number which is defined as below:

$$N_p = \frac{P}{\rho_l N^3 d_i^5} \quad (2)$$

where P is the rotor/agitator power, ρ_l is the liquid density, N is the agitator speed, and d_i is the impeller diameter. Moreover, For the Schmidt number, we have:

$$Sc = \frac{\mu}{\rho D_{AB}} \quad (3)$$

To estimate the D_{AB} easier, an initial value is assigned to it. The equilibrium solubility factor (α) is calculated below:

$$\alpha = \frac{C_A^S}{C_A^F} = \frac{0.09\ mg}{0.86\ mg} = 0.105 \quad (4)$$

where C_A^F is the concentration of released drug and C_A^S is the concentration of the remaining drug. The concentration of the drug in the solution after 20 hours is 0.86 mg while the tablet contains 95 mg of the drug at the start.

Finally, for Biot number, we have:

$$Bi = \frac{\alpha K_C L}{D_{AB}} \quad (5)$$

where L=0.1033 and Bi=4. Consequently, Bi=∞ should be used for the estimation of the drug diffusion coefficient. The coefficients are calculated using Gurney-Lurie charts [14]. To use Lurie charts, an initial value is assigned to the diffusion coefficient in the solid (which should be lower than that of the liquid), then using Eq. 6, X is calculated.

$$X_D = \frac{tD_{AB}^S}{L^2} \quad (6)$$

Then, a perpendicular line is drawn from X on The Bi curve (Bi=∞) and another one from there on the Y axis to give the value of $1 - M(t)/M_\infty$. The calculated mass transfer coefficients are presented in Table 15.

Table 15. Diffusion coefficient of metoprolol in the polymer

Time (hour)	D_{AB}^S (m^2/s)	α (D_{AB}^S/D_{AB}^l)
1	0.10×10^{-9}	0.258
4	0.13×10^{-9}	0.336
8	0.15×10^{-9}	0.388
20	0.30×10^{-9}	0.780

Conclusions

The amount of drug release is dependent on the kind, concentration, and viscosity of the polymer used in the tablet structure. In this study, the drug release of metoprolol succinate was investigated in tablets made from HPMC (K100M), HPMC (K4M), polyethylene oxide, ethyl cellulose, and Eudragit (RL100). The experiment results showed that between the compounds tested, HPMC (K100M) is the best choice for extended release of metoprolol since the drug concentrations are well in the range of USP32 standards. The concentration of metoprolol was also calculated using theoretical equations and the results were similar to the experimental data. The diffusion factor of metoprolol in HPMC (K100M) polymer was not significantly different from the diffusion factor in water, due to the seeping of water in the polymer structure and contraction. Furthermore, since the drugs were made using the direct compression method, there is no need for driers, fluidized beds, and millers.

Nomenclature

N	Agitator speed
Bi	Biot number
C_A^F	Concentration of the released drug
C_A^S	Concentration of the remaining drug
h	Curved height
D_{AB}	Diffusion coefficient
H	Flat height
N_p	Power number
R	Radius
Re	Reynolds number
Sc	Schmidt number
Sh	Sherwood number
t	Time
μ	Viscosity

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