

Development and in vitro evaluation of carboxymethyl chitosan based drug delivery system for the controlled release of propranolol hydrochloride

Hernawan^{1*}, Septi Nur Hayati¹, Khoirun Nisa¹, Anastasia Wheni Indrianingsih¹, Cici Darsih¹, Muhammad Kismurtono¹

¹ Research Unit for Natural Products Technology, Indonesian Institute of Sciences, Yogyakarta, Indonesia

E-mail: hern001@lipi.go.id

Abstract. Propranolol hydrochloride is a nonselective β -adrenergic drug and has been used as angina pectoris, antihypertensive, and that of many other cardiovascular disorders. It has a relatively short plasma half-life and duration of action are considered too short in certain circumstances. Thus, it's fascinating to elongate the action. The tablet formula was based on extended-release by a propranolol hydrochloride based carboxymethyl chitosan matrix. Here we used direct compression technique with internal wet granulation to prepare the tablets. The tablets were evaluated for physical properties (hardness, weight variation test, friability) and in vitro release studies. There was no interaction observed between propranolol hydrochloride and excipients. Dissolution profiles of each formulation were followed zero order model. In conclusion, these results strongly suggest that in appropriate proportions carboxymethyl chitosan with internal granulation is suitable for formulating propranolol hydrochloride controlled release.

1. Introduction

Controlling kinetics of drug release from pharmaceutical formulations is important to achieve the therapeutic effects [1]. The optimum therapeutic response of many medications can be observed once adequate blood levels are achieved and maintained with minimal fluctuations. Controlled release products became popular for the oral administration of such drugs because they give more consistent blood levels [2]. Controlled release with zero order kinetics maintains a plasma concentration of drugs at a constant level.

Propranolol hydrochloride or 1-isopropyl amino-3-(1-naphthyl oxy)-2-propanol hydrochloride is a nonselective β -adrenergic blocking agent, and has been used as angina pectoris, antihypertensive drug and that of many other cardiovascular disorders treatment [2][3][4]. It has relatively short plasma half-life so that patients are habitually asked to require the drug once every 6 to 8 h in divided daily doses. Frequent drug administration may reduce patient compliance and therapeutic efficacy [5]. Propranolol



hydrochloride controlled release tablet with zero order kinetics is needed, to improve patient compliance and therapeutic efficacy.

Several methods were describing approaches for controlled release formulations of propranolol hydrochloride. Patra et al. [5] developed a bilayer tablet of propranolol hydrochloride using super disintegrant and immiscible water polymers such as ethylcellulose, Eudragit RLPO, and Eudragit RSPO which showed dissolution kinetics followed the Higuchi model via a non-Fickian diffusion. Sanghavi et al. [2] prepared matrix tablets using hydroxypropyl methylcellulose (HPMC) which exhibited first order release kinetics and Pandey et al. [3] and Chaturdevi et al. [6] develop a floating tablet using HPMC. Javadzadeh et al. [7] promote liquid-solid tablets which showed zero order release kinetics. Velasco-De-Paola et al. [8] described dissolution kinetics of controlled release tablets prepared using eudragit. Mohammadi-Samani et al. [9] described controlled-release dosage forms using ethyl cellulose coating, orodispersible tablets made by employing microcrystalline cellulose have been reported Deshpande and Ganesh [10], and Huang et al. [11].

Our previous research, prepared matrix tablets of propranolol hydrochloride by external wet granulation using carboxymethyl chitosan (CMCh) which exhibited Peppas-Korsmeyerkinetics [12]. Here on this study, we describe a preparation of controlled release matrix by internal wet granulation and study of propranolol hydrochloride controlled release from carboxymethyl chitosan-based matrix tablets aiming to find out release mechanism.

2. Methodology

2.1. Materials

Propranolol hydrochloride was provided by Kimia Farma (Jakarta, Indonesia). Carboxymethylchitosan (CMCh), CMC-Na, hydrochloric acid, lactose, magnesium stearate, xanthan gum and buffer phosphate 7.2. Distilled water was used throughout all experiments, and the other materials and chemicals procured for the studies were of analytical grade

2.2. Instrumentation

Tablets were prepared using (Reickermann Korsch, Germany) single punch tablet machine. Infrared spectra were recorded with FTIR Spectrometer Shimadzu Prestige-21. X-ray diffractogram was performed using X-Ray diffractometer (Shimadzu). The drug content was analyzed using Spectrophotometer UV-Vis Dynamica RB 10.

2.3. Preparation of Matrix Tablets

The controlled-release tablets were prepared by direct compression method Controlled release matrix-embedded tablets were made separately by internal wet granulation process using different proportions of CMCh (2%, 4%, and 6%) and denoted respectively as Fi1, Fi2, and Fi3. The formulations are given in Table 1. Propranolol hydrochloride, CMC-Na, xanthan gum, and lactose were mixed and homogenized in a cube mixer 90 rpm for 10 minutes. After completion, 50 ml CMCh solution was added to the mixture to form granules. The mixture granules were passed through 14 mesh, further dried at 40-60°C for 48 hours and mixed 1.33% of magnesium stearate. Tablets were compressed at 300 mg weight on a single punch tablet machine fitted with 5-mm round-shaped punches with compression pressure 10 kN and dwell time 2 s.

Table 1. Composition of Various Tablet Formulations

Formulation Code	Drug (mg)	CMCh (mg)	CMC-Na (mg)	Xanthan Gum (mg)	Lactose (mg)	Mg-Stearate (mg)	Total Weight (mg)
F _{i1}	120	6	24	100	46	4	300
F _{i2}	120	12	24	100	40	4	300
F _{i3}	120	18	24	100	34	4	300

2.4. Compatibility Studies

The interaction between the propranolol hydrochloride and polymer was investigated by using FTIR spectroscopy and X-ray powder diffraction.

2.4.1. Fourier-Transform Infrared Spectroscopy

Compatibility studies of drug, polymers, and the physical mixture were carried out using FTIR spectrophotometer in the scanning range of 300–4,000 cm⁻¹ by KBr disc method. The samples were previously ground and mixed thoroughly with potassium bromide, at 1:5 (sample: KBr) ratio, respectively. An infrared transparent KBr matrix was prepared by compressing the powders at a pressure of 5 tons in a hydraulic press for 5 min.

2.4.2. X-ray powder diffraction

X-ray diffractogram of drug, excipient and matrix tablets were performed using X-Ray diffractometer (Shimadzu). The samples were exposed to x-ray radiation (Cu K α) at a wavelength of 1.5406 Å. The rate of the scanning was 0.60/min at a range of 5–50° 2 θ . Samples were measured on a flat background quartz plate in an aluminum holder

2.5. Evaluation of Tablets

2.5.1. Physical Properties of Tablets

Tablets were characterized for weight variation, hardness, and friability. The drug content of the manufactured tablets was determined. From each batch, ten tablets were taken, weighed, and finely ground. An adequate amount of this powder equivalent to 10 mg of drug was accurately weighed, dissolved and diluted with distilled water and analyzed using UV-Vis spectrophotometer at 290 nm. Hardness was determined by using a tablet hardness tester (Stokes Monsanto, Germany). Friability test was conducted using Erweka abrasive friability tester (Erweka TA 20, Germany).

2.5.2. In vitro Drug Release

The in vitro drug release was performed by dissolution test on the USP dissolution apparatus (Erweka DPT6R, Germany) which was operated at 50 rpm. The dissolution medium used was 900 mL of simulated gastric fluid (SGF) for the first 2 hours and followed by simulated intestinal fluid (SIF) for the remaining hours. The temperature was maintained at 37±0.5 °C. Five milliliters of the sample was taken using a syringe filter periodically and replaced with an equal volume of prewarmed (37±0.5 °C) fresh dissolution medium. The drug content in each sample was analyzed after dilution using UV-Vis spectrophotometer at 290 nm (Dynamica RB 10).

2.5.3. Drug Release Data Modeling

To identify the release mechanisms of propranolol hydrochloride, we tested concerning the release data. The release data were fitted to five kinetic models (zero order (Eq. 1), first order (Eq. 2), Higuchi models (Eq. 3), Peppas-Korsmeyer (Eq. 4) and Hixson-Crowell (Eq. 5)) [12][13][14][15]

$$R = k_1 t \quad (\text{Eq. 1})$$

$$\text{Log UR} = (k_2 t)/2.303 \quad (\text{Eq. 2})$$

$$R = k_3 \sqrt{t} \quad (\text{Eq. 3})$$

$$\text{Log R} = \text{Log } k_4 + n \text{Log } t \quad (\text{Eq. 4})$$

$$\sqrt[3]{\text{UR}} = k_5 t \quad (\text{Eq. 5})$$

Where R and UR are respectively the released and unreleased percentages, t is time; k₁, k₂, k₃, k₄, and k₅ are constants rate of zero-order, first-order, Higuchi models, Peppas-Korsmeyer, and Hixon-Crowell model, respectively

3. Results and Discussion

The interaction between propranolol hydrochloride and excipients often leads to identifiable changes in the infrared (IR) spectra of the drug excipient mixture in the formulation. The IR spectra of drug excipient mixture were compared with the standard frequency of propranolol hydrochloride. Carboxymethyl chitosan gives the peak in IR spectrum nearby 3441 cm⁻¹ due to the hydroxyl group. Propranolol hydrochloride provides the peaks in IR spectrum nearby at 2962 cm⁻¹ due to the presence of a secondary amine group, 3286 cm⁻¹ due to the hydroxyl group (secondary), the aryl alkyl ether display a stretching band at 1103 cm⁻¹ and the peak at 771 cm⁻¹ due to α -substituted naphthalene [5]. The IR spectra of the mixture showed broadening of the peak at 3325 cm⁻¹ due to the extensive hydrogen bonding. There is no significant interaction between the propranolol hydrochloride and the excipients used in the formulations, indicating by the characteristic peaks for the functional groups in the propranolol hydrochloride structure are retained. The overlay IR spectrum is shown in Fig.1,

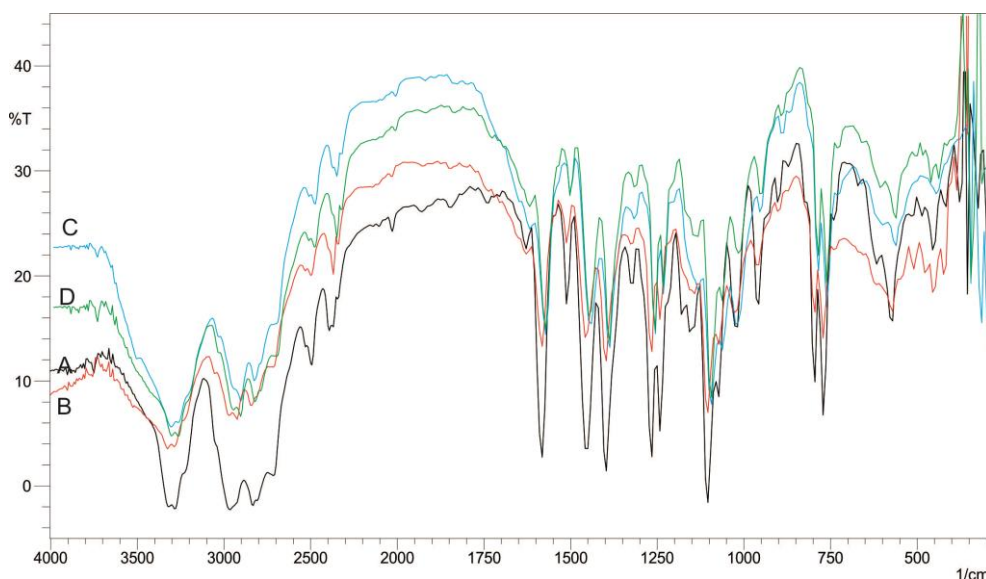


Figure 1. The overlay IR spectra of pure propranolol hydrochloride (A), Fi1 (C), Fi2 (B), and Fi3 (D)

The X-ray powder diffractograms of pure drug and formulations (Fig. 2) were measured for comparison. Pure propranolol hydrochloride showed a typical pattern of a crystalline substance which showed characteristic sharp refraction peaks at 12.54°, 16.76°, 17.23°, 19.92°, 23.68° and 25.12°. This result corresponds to X-ray diffraction patterns of polymorphs two crystalline forms mixture of propranolol hydrochloride as reported by Bartolomei et al. al [4] and Javazadeh et. al [8]. The sharp peaks of the drug were also present in formulations, where it was mixed with excipients. This result indicated there was a physical interaction between propranolol hydrochloride and the excipient, but crystalline nature of propranolol hydrochloride was retained even after formulation [4][5][6].

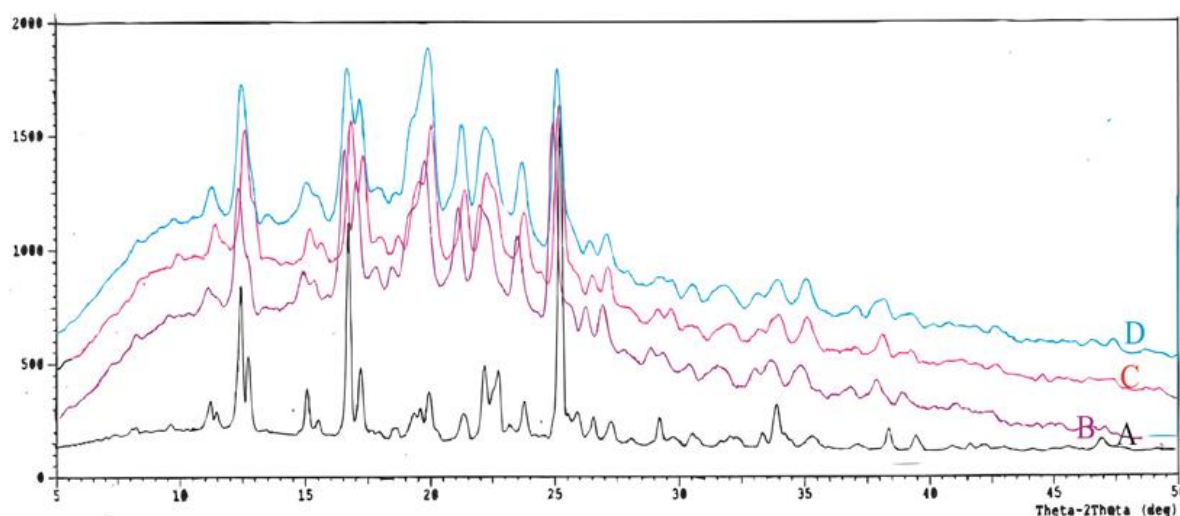


Figure 2. The overlay of X-ray powder diffractograms of pure propranolol hydrochloride (A), Fi1 (B), Fi2 (C) and Fi3 (D)

Polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability [16]. Polymorphism also influences the pharmaceutical implication of the presence of meta stable crystalline forms in the bulk powder and the therapeutic efficacy of the drug. Also, crystal structure might affect tablet porosity, density, disintegration and aggregation mechanism, as well as the plastic and elastic properties of dosage forms [8]. Compatibility studies reveal that the drug is compatible with all excipients used in the formulation.

Physical Properties of Tablets

The physical properties (weight, hardness, drug content, water content and friability) of the tablets for all formulation were noted (Table 2). The average weight variations of all the samples were in the range 300 ± 2.5 mg compliant with the precise requirements of weight uniformity, are not more than 10%. The drug content was found to be close to $99.63 \pm 1.54\%$ of the label claim for propranolol in all formulations which was within acceptable limits. The friability tablets were found to within losing weight or friability less than 0.5%-1% [4,14]. The low friability reveals that the matrix tablets are hard and compact.

Table 2. Physical Properties of Compressed Tablets

Formulation Code	F _i 1 (2% CMCh)	F _i 2 (4% CMCh)	F _i 3 (6% CMCh)
Weight variation	302.00 ± 0.66	302.66 ± 0.93	301.50 ± 0.50
Hardness (kg/cm ²)	6.60 ± 2.50	6.30 ± 2.30	5.70 ± 2.70
Friability (%)	0.16 ± 0.02	0.19 ± 0.02	0.13 ± 0.14
Water content (%)	2.00 ± 0.50	2.00 ± 0.35	2.00 ± 0.68

Release Rate Studies

In-vitro dissolution studies were conducted in triplicate of each of the formulations such as F_i1, F_i2, and F_i3. The results for the fitting of the kinetic model for propranolol hydrochloride release from the tablet are shown in Table 3. The values for the release rate constants (k), the correlation coefficients (R²), and are considered. The correlation coefficient (R²) was used as an indication of the best fit, for each of the models.

Table 3. Modeling of Dissolution

Kinetic models	F _i 1(2% CMCh)		F _i 2(4% CMCh)		F _i 3(6% CMCh)	
	R ²	k	R ²	k	R ²	k
Zero-order	0.972	2.52 x 10 ⁻³	0.932	2.34 x 10 ⁻³	0.932	3.27 x 10 ⁻³
First-order	0.970	1.97 x 10 ⁻²	0.929	1.98 x 10 ⁻²	0.929	1.94 x 10 ⁻²
Higuchi	0.952	1.84 x 10 ⁻²	0.869	1.70 x 10 ⁻²	0.891	2.22 x 10 ⁻²
Peppas-Korsmeyer	0.961	2.52 x 10 ⁻³	0.875	2.34 x 10 ⁻³	0.880	3.27 x 10 ⁻³
Hixon-Crowell	0.739	2.97 x 10 ⁻²	0.930	3.14 x 10 ⁻²	0.930	3.12 x 10 ⁻²

The results for various models investigated for formulations containing carboxymethyl chitosan ranked in order of Zero order > First order > Peppas-Korsmeyer > Higuchi > Hixon-Crowell. In vitro release data of propranolol hydrochloride from carboxymethyl chitosan based matrix tablet best fitted to zero order model. Carboxymethyl chitosan in appropriate proportions with internal wet granulation is suitable for formulating propranolol hydrochloride controlled release tablets which exhibit zero order kinetics. The ability of the carboxymethyl chitosan to hydrate and form a gel layer around the drug is well-known and is essential to sustaining and controlling the release of a propranolol hydrochloride from the matrix. Zero order release kinetics is the ideal delivery of antihypertensive drugs. Zero order release kinetics refers to the process of constant drug release from a drug delivery device [15].

4. Conclusions

Carboxymethyl chitosan has successfully extended the release of propranolol hydrochloride. No interaction was observed between propranolol hydrochloride and excipients, and crystalline nature of propranolol hydrochloride was not disturbed. Dissolution profiles showed that of each formulation demonstrated that controlled releases of propranolol hydrochloride were following zero order models. It is concluded that in appropriate proportions carboxymethyl chitosan with internal granulation is suitable for formulating propranolol hydrochloride controlled release which exhibits zero order kinetics.

Acknowledgement

The authors would like to acknowledge the Ministry of State for Research and Technology Republic of Indonesia for Improvement the Ability of Researchers and Engineers Incentives Project I.160. 2012

References

- [1] Tamanna T, Bulitta JB and Yu A 2015 *J. Mater. Sci. Mater. Med.* **26**(2) 117
- [2] Sahoo J, Murthy PN, Biswal S, Sahoo SK and Mahapatra K 2008 *AAPS PharmSciTech.* **9**(2) 577–582
- [3] Pandey S, Devmurari V, Paridhi S and Mahalaxmi R 2010 *Der Pharmacia Lettre* **2**(1) 75–86
- [4] Bartolomei M, Bertocchi P, Cotta M, Santucci N and Valvo L 1999 *J. Pharm. Biomed. Anal.* **21** 299–309
- [5] Patra CN, Kumar AB, Pandit HK, Singh SP and Devi MV 2007 *Acta Pharm.* **57**(4) 479–489
- [6] Chaturvedi K, Umadevi S and Vaghani S 2010 *Sci. Pharm.* **78**(4) 927–939
- [7] Javadzadeh Y, Musaalrezaei L, and Nokhodchi A 2008 *Int. J. Pharm.* **362**(1–2) 102–108
- [8] Velasco-De-Paola MV, Santoro MI and Gai MN 1999 *Drug Dev. Ind. Pharm.* **25**(4) 535–541
- [9] Mohammadi-Samani S, Adrangui M, Siahi-Shadbad MR and Nokhodchi A 2000 *Drug Dev. Ind. Pharm.* **26**(1) 91–94
- [10] Deshpande KB and Ganesh NS 2011 *Int. J. Res. Pharm. Biomed. Sci.* **2**(2) 529–534.
- [11] Huang YB, Tsai YH, Yang WC, Chang JS, Wu PC and Takayama K 2004 *Eur. J. Pharm. Biopharm.* **58**(3) 607–614
- [12] Hernawan, Nurhayati S, Nisa K, Indrianingsih AW, Darsih C and Kismurtono M 2013 *Indones.*

J. Chem. **13(3)** 242–247

- [13] Dash S, Murthy PN, Nath L and Chowdhury P 2010 *Acta Pol. Pharm.* **67(3)** 217–223
- [14] Mahapatra AK, Sameeraja NH and Murthy PN 2015 *AAPS PharmSciTech.* **16(3)** 579–88
- [15] Singhvi G and Sing M 2011 *Int. J. Pharm. Stu. Res.* **2(1)** 77-84
- [16] Censi R and Di Martino P 2015 *Molecules* **20** 18759-18776