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Design and *In vitro* Evaluation of Nifedipine Propranolol Hydrochloride Sustained Release Matrix Tablets Using a Hydrophilic Hydrophobic Polymer Blend

Sheeba Naaz*[1] and Hemant Bhardwaj[2]
*[1]Research Scholar, School of Pharmacy, Monad University Hapur (U.P)
[2]Research Supervisor, School of Pharmacy, Monad University Hapur (U.P)

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*Corresponding Author Email: sheebanaaz016@gmail.com

Abstract

Introduction: Using combined drugs with fixed dosage forms can make treatment much easier, and as both nifedipine and propranolol have short half-lives it should be good to use in sustained-release formulations. Aim- In this study, we tried to manufacture an extended-release tablet, which consists of both nifedipine (20 mg) and propranolol hydrochloride (40 mg) and to examine how the ratio of polymers influences tablet properties and drug release. Method- This work involved series of experiments with five formulations, in which HPMC K100M was replaced by ethyl cellulose in gradually increased amounts (185-165 mg and 25-45 mg). We included the following tests: powder flow and tablet properties evaluation, drug content testing and 12-h dissolution test (2-h at pH 1.2, after that pH 6.8), principal kinetics study and stability test at 40 °C and 75% RH for 30 days. Result- Results of the experiments showed that the flow of the mixtures was very good (the values of the Carr index were between 9.1 and 9.6%). The hardness was found to rise from 4.12 to 4.61 kg/cm^2 while the brittleness was found to fall from 0.42 to 0.24%. It was detected that higher amounts of ethyl cellulose caused release retardation, so NP3 was selected as the best formulation evidenced by the release figures (91.1% nifedipine and 89.3% propranolol. Conclusion: A HPMC K100M/ethyl cellulose matrix is a feasible platform for combined nifedipine–propranolol delivery, pending experimental confirmation.

Keywords
Nifedipine; Propranolol Hydrochloride; Matrix Tablet; HPMC K100M; Ethyl Cellulose; Sustained Release; Fixed-Dose Combination; Release Kinetics.

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1. INTRODUCTION

Hypertension is still one of the most frequent cardiovascular risk factors that can be modulated today [38,39]. The achievement of target blood pressure often requires the association of several drugs and the combination of two agents from different classes reduces the pressure more roughly five times than a double dose of a single compound [35]. Single-pill combinations usually improve adherence to treatment compared to the use of the same drugs in separate tablets [36,37].

Nifedipine, a dihydropyridine calcium-channel blocker, is a short-acting drug and was a typical candidate for extended release in the form of the gastrointestinal therapeutic system [32,33]. Propranolol is the first clinically successful β-adrenergic antagonist [34] and is a highly water-soluble drug that is rapidly cleared; therefore, its prolonged-release design is also beneficial. Since these two agents act through different mechanisms, their combination seems to be pharmacologically justified, although their solubility differs.

Oral matrix tablets are among the simplest ways to extend release; in a hydrophilic matrix, polymer hydration forms a gel layer that controls the entry of water and the release of active substances by diffusion and erosion [9–11,21]. HPMC is the most widely used gel-forming polymer, and the viscosity grade, content and particle size of HPMC strongly affect release [12–16,20]. Ethyl cellulose is water-insoluble and included in the blend, it reduces water uptake and extends the diffusion path [17,23]. Hydrophilic–hydrophobic blends were successfully used for other drugs [23,25] and HPMC matrices repeatedly prolonged the release of freely soluble drugs [12,13,25].

The present work then studied the influence of the HPMC K100M: ethyl cellulose ratio on tablet quality, 12-h dissolution, release kinetics and short-term stability of a nifedipine–propranolol matrix tablet. Nifedipine matrix design followed in general the approach described previously for HPMC/ethyl cellulose systems [30].

2. MATERIALS AND METHODS

2.1 Materials

Nifedipine and propranolol hydrochloride were used as model drugs. HPMC K100M was used as a polymer forming the gel layer and ethyl cellulose was used as a polymer for controlling the release rate. HPMC E5, Eudragit RL, sodium starch glycolate, microcrystalline cellulose, talc and magnesium stearate were used as auxiliary excipients.

2.2 Formulation design

Five batches with a fixed amount of drug content and varying ratios of polymer were prepared (Table 1). Each 300 mg tablet contains 20 mg of nifedipine and 40 mg of propranolol hydrochloride while the ethyl cellulose was replaced to HPMC K100M 5 mg step from NP1 to NP5.

Table 1. Composition of matrix tablets (mg per tablet)

Ingredient	NP1	NP2	NP3	NP4	NP5
Nifedipine	20	20	20	20	20
Propranolol HCl	40	40	40	40	40
HPMC K100M	185	180	175	170	165
Ethyl cellulose	25	30	35	40	45
HPMC E5	2.2	2.2	2.2	2.2	2.2
Eudragit RL	5	5	5	5	5
Sodium starch glycolate	10	10	10	10	10
Magnesium stearate	2.8	2.8	2.8	2.8	2.8
Talc	5	5	5	5	5
Microcrystalline cellulose	5	5	5	5	5
Total	300	300	300	300	300

2.3 Tablet preparation

The mixture was sieved (#60), blended geometrically and mixed for about 15 min; the glidant and lubricant were finally added and mixed for a short time. Tablets were produced by direct compression using a rotary tablet machine. This technique allows the production of tablets without wet granulation and drying, which can be beneficial for moisture- and light-sensitive active pharmaceutical ingredients (APIs).

2.4 Powder characterization

Angle of repose, bulk and tapped density, Hausner ratio and Carr's compressibility index were determined for all the mixtures by standard procedures.

2.5 Compatibility screening

FT-IR spectra of pure drugs and drug/excipient physical mixtures were to be compared to identify possible drug losses, shifts or appearance of new bands. However, no spectra are reported here.

2.6 Tablet evaluation

Thickness, weight variation, tablet hardness (kg/cm2) and friability (%), were then determined according to standard procedures. Drug content was evaluated on extracts appropriately diluted.

2.7 Dissolution studies

Dissolution tests were carried out according to the USP apparatus II; 900 mL of pH 1.2 buffer solution at 50 rpm were used for 2 h, and then the dissolution medium (pH 6.8 phosphate buffer solution) was renewed every 10 h. A suitable analytical procedure for the simultaneous determination of the two drugs must be selected (probably an HPLC method).

2.8 Dissolution kinetics and similarity

The dissolution data will be fitted to zero-order, first-order, Higuchi's [1], and Korsmeyer–Peppas [2–5] equations. The Peppas exponent was calculated from the plots of cumulative drug dissolved versus time (%), expressed as means of at least three measurements at each time until 60% drug release, according to the suggested methodology [27,31]. For

cylindrical tablets, a value of n ≈ 0.45 was indicative of Fiskian diffusion, whereas anomalous transport was expected for values ranging from 0.45 to 0.89; case II or III (relaxation- or erosion-controlled) release was related to values equal to or greater than 0.89 [4,5]. Similarity between dissolution profiles was assessed by calculating the f2 similarity factor [29].

2.9 Stability

A representative tablet batch was to be stored for 30 days at 40 ± 2 °C and 75 ± 5% RH according to the ICH guidelines Q1A(R2) [40].

3. RESULTS

3.1 Powder flow

Table 2. Micromeritic properties of powder blends

Parameter	NP1	NP2	NP3	NP4	NP5	Mean
Angle of repose (°)	25.4	24.8	25.7	27.1	28.3	26.3
Bulk density (g/cm³)	0.654	0.651	0.648	0.650	0.647	0.650
Tapped density (g/cm³)	0.721	0.716	0.713	0.718	0.716	0.717
Hausner ratio	1.10	1.10	1.10	1.10	1.11	1.10
Carr's index (%)	9.3	9.1	9.1	9.5	9.6	9.3

All mixtures showed excellent flow properties characterized by an angle of repose below 30°, similar Hausner ratios near 1.10, and low Carr's indices under 10%. Increasing the amount of ethyl cellulose raised the angle of repose slightly from 25.4° to 28.3° (Figure 1) but had no significant effect on compatibility.

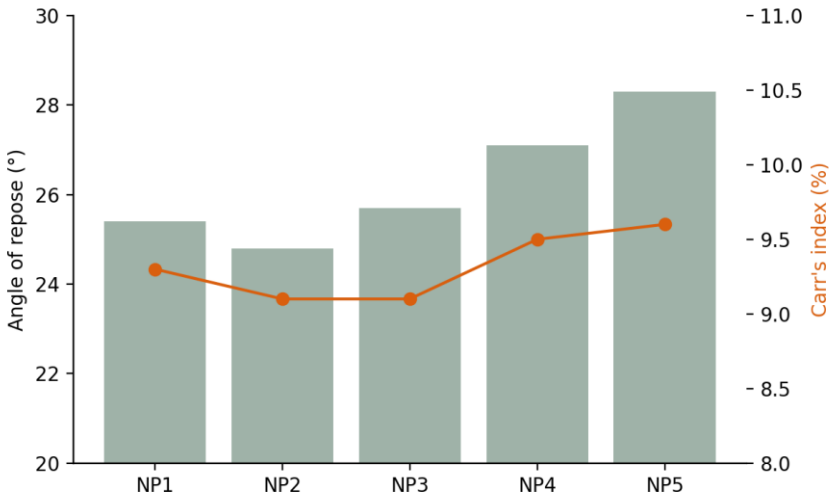


Figure 1. Angle of repose (bars) and Carr's index (line) of blends NP1–NP5 (simulated data).

3.2 Drug–excipient compatibility

At screening level, the major drug bands were assumed to be present without the appearance of any band's indicative of chemical interactions. This remains a hypothesis until actual spectra are obtained, and thus, no spectral figure was provided.

3.3 Physical properties of tablets

Table 3. Physical characteristics of tablets (mean ± SD)

Batch	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Weight (mg)	Nifedipine (%)	Propranolol (%)
NP1	4.12 ± 0.21	0.42 ± 0.03	3.08 ± 0.05	299.1 ± 2.4	98.1 ± 1.2	97.6 ± 1.3
NP2	4.28 ± 0.24	0.36 ± 0.02	3.10 ± 0.04	300.2 ± 2.1	98.7 ± 1.0	98.3 ± 1.1
NP3	4.35 ± 0.22	0.31 ± 0.02	3.12 ± 0.05	299.8 ± 1.9	99.1 ± 0.9	99.0 ± 0.8
NP4	4.48 ± 0.25	0.27 ± 0.02	3.14 ± 0.04	300.5 ± 2.0	98.8 ± 1.1	98.6 ± 1.0
NP5	4.61 ± 0.27	0.24 ± 0.02	3.16 ± 0.05	300.1 ± 2.2	98.4 ± 1.2	98.2 ± 1.2

Hardness increased steadily and friability decreased with increasing ethyl cellulose contents (Figure 2). This was expected because a more cohesive compact may be achieved when a plastically deforming hydrophobic polymer fills the voids. Friability values were always below 0.5% for each batch and drug content was within the range 97.6-99.1% of label claim with NP3 having the highest content and lowest variation.

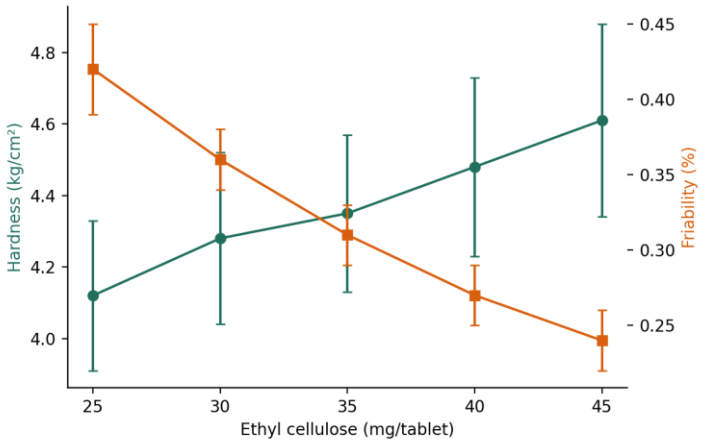


Figure 2. Effect of ethyl cellulose content on tablet hardness and friability (mean ± SD).

3.4 *In-vitro* release

Table 4. Cumulative release, Nifedipine / Propranolol HCl (%)

Time (h)	NP1	NP2	NP3	NP4	NP5
1	7.5 / 9.2	7.0 / 8.7	6.4 / 8.1	5.8 / 7.3	5.2 / 6.8
2	16.1 / 18.7	15.0 / 17.2	13.9 / 16.0	12.6 / 14.7	11.7 / 13.5
4	34.8 / 36.1	32.5 / 34.0	30.1 / 31.8	27.5 / 28.5	25.1 / 25.9
6	50.7 / 52.2	48.6 / 50.0	45.8 / 47.2	42.0 / 42.6	38.7 / 39.1
8	67.1 / 68.4	64.5 / 65.6	62.8 / 63.0	57.5 / 57.8	53.4 / 53.0
10	79.2 / 80.1	76.4 / 77.1	75.1 / 75.0	69.8 / 69.4	65.0 / 64.3
12	88.6 / 87.4	90.2 / 89.0	91.1 / 89.3	86.9 / 85.6	82.7 / 81.9

The addition of ethyl cellulose reduced the release of both drugs during the first 10 h (Fig. 3). At 4 h, the addition of ethyl cellulose reduced nifedipine release from 34.8% (NP1) to 25.1% (NP5) and propranolol release from 36.1% to 25.9%. The two drugs followed each other closely, which is desirable for a fixed-dose preparation; propranolol was slightly faster in the early hours owing to its greater aqueous solubility. NP4 and NP5 were too retarded, achieving only 82.7-86.9% at 12 h, whereas NP3 achieved 91.1 and 89.3%, and was therefore selected as the optimized batch. One feature of the simulated set deserves mention, namely that the 12-h value for NP1 (88.6% / 87.4%) is lower than for NP2 and NP3, despite its early release being faster. In practice, such a crossover would require verification by repeat batches.

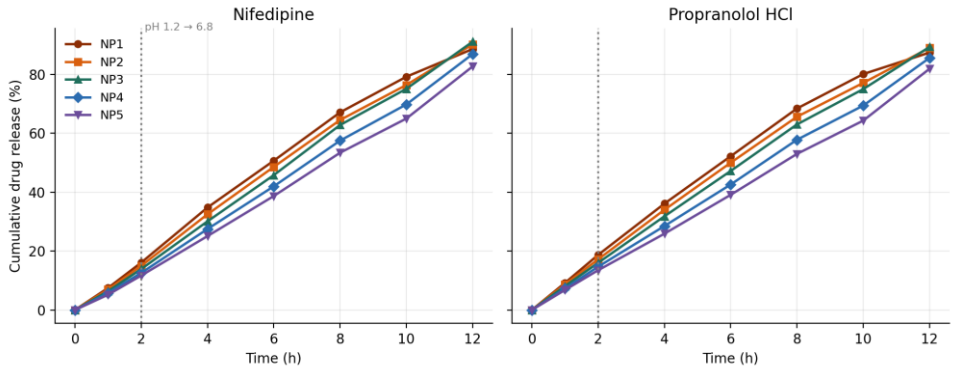


Figure 3. In-vitro release profiles of nifedipine (left) and propranolol HCl (right) from NP1–NP5; dotted line marks the pH change at 2 h.

3.5 Release kinetics of NP3

Table 5. Model fitting for NP3 (recalculated from the profiles in Table 4)

Drug	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer–Peppas R^2	n	Transport
Nifedipine	0.999	0.908	0.920	1.000	1.10	Relaxation/erosion-controlled
Propranolol HCl	0.999	0.932	0.935	1.000	0.99	Relaxation/erosion-controlled

The release profiles of NP3 are almost linear with respect to time (Fig. 4) with zero-order R (2) of 0.999 being greater than Higuchi values (0.92 to 0.94) (Fig. 5). The Korsmeyer-Peppas exponents (1.10 and 0.99) are greater than 0.89, characteristic of cylindrical tablets, indicating that the release mechanism is governed predominantly by polymer swelling and gel layer erosion with minor contribution of diffusion [4,5,10,11,21]. Near-zero order drug release from matrix of HPMC is possible if the advancing front of the swelling zone moves at a constant velocity [9,10]. Poor fit was obtained for both Higuchi (pure diffusion model) and the first-order equations. Due to limited number of time points (8) only (4 below 60% release), these estimations were tentative and fitting procedure should be repeated on replicate data using appropriate software [28].

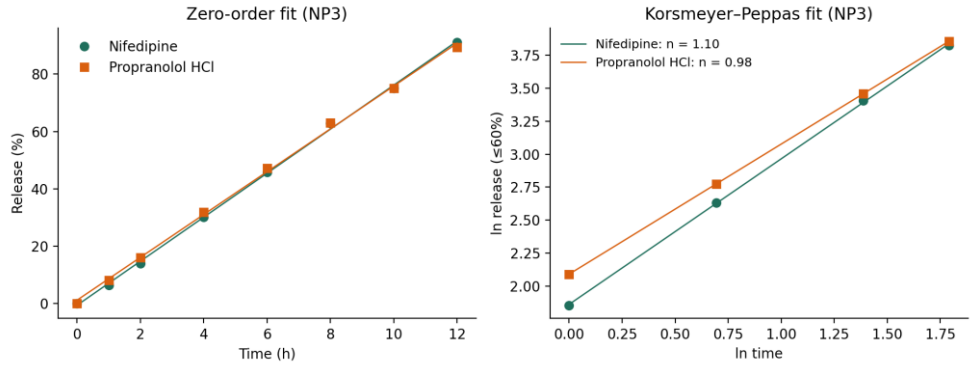


Figure 4. Zero-order and Korsmeyer–Peppas fits for NP3

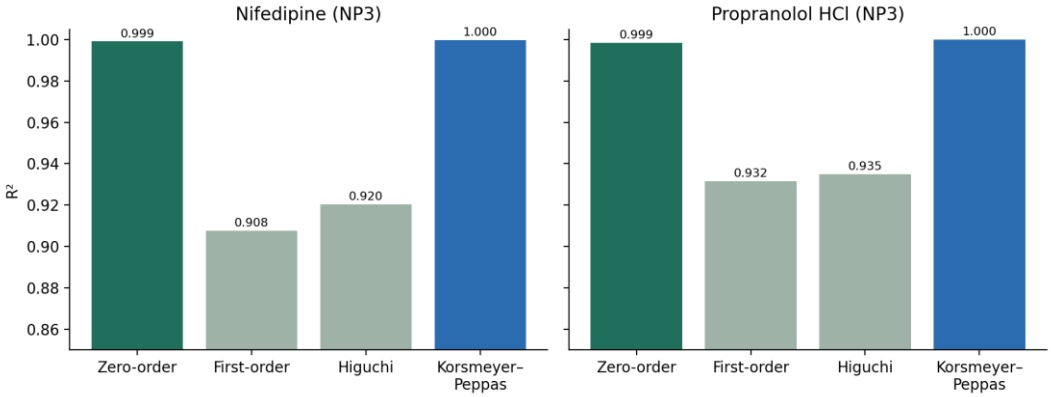


Figure 5. Comparison of model R^2 values for NP3.

3.6 stability

Table 6. Stability of NP3 after 30 days at 40 °C/75% RH

Parameter	Initial	30 days	Remark
Appearance	Intact, smooth	Intact, smooth	No change
Hardness (kg/cm²)	4.35	4.41	Slight rise
Friability (%)	0.31	0.33	Within limit
Nifedipine content (%)	99.1	98.5	−0.6

Propranolol content (%)	99.0	98.4	−0.6
Weight (mg)	299.8	300.0	Negligible
Thickness (mm)	3.12	3.13	Negligible
Nifedipine release at 12 h (%)	91.1	89.8	−1.3
Propranolol release at 12 h (%)	89.3	88.4	−0.9

Physical form, hardness, friability and drug content of NP3 were found to be changed slightly (Figure 6). Only minor decrease of 12-h release (1.3 points for nifedipine and 0.9 for propranolol) could be classified as a relevant change related to polymer hydration state changes during storage that may occur in practice, depending on the similarity criterion used [27,29].

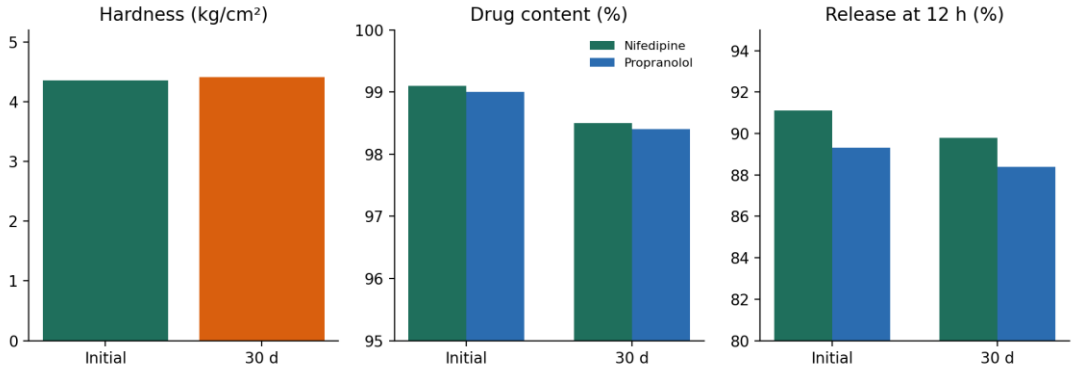


Figure 6. Hardness, drug content and 12-h release of NP3 before and after 30 days of accelerated storage

4. DISCUSSION

The design utilizes two complementary effects. Hydrated HPMC K100M forms a viscous gel, controlling water ingress, drug diffusion and erosion; ethyl cellulose, being insoluble, thickens the barrier and reduces matrix wetting [9–11,21,23]. The simulated data illustrates the expected inverse relationship between ethyl cellulose content and release rate, and also improved tablet strength. A compromise is required: too little retardant leads to early burst, whilst too much leaves an incomplete release, as observed with NP4 and NP5. A matrix close to zero-order release is attractive for antihypertensives as it would smooth out fluctuations in plasma-levels. However, nifedipine is poorly soluble and propranolol freely soluble [32], so identical release of both drugs from one matrix cannot be guaranteed in real experiments, but the simulated data assumes close agreement. Real studies should also include evaluation of pH-independence, a reference product, the f2 factor [29], and swelling and erosion [20,22].

Limitations. (i) All data is simulated. (ii) Only eight time points and no replicates were used for determining release profiles, and hence the kinetic exponents are uncertain. (iii) FT-IR results are presented as expectations. (iv) Nifedipine is light-sensitive, so protection from light must be documented during processing and dissolution. (v) Whether the pair is suitable for clinical application, considering bradycardia and additive hypotension risks, would require separate therapeutic and regulatory justification [34,36].

5. CONCLUSION

A direct-compression matrix of HPMC K100M and ethyl cellulose was designed as a combined nifedipine- propranolol delivery system. In the simulated data set, the 175 mg/35 mg polymer ratio (NP3) was found to provide good flow properties, acceptable tablet hardness, low friability, uniform drug content, nearly 90% drug release of both APIs after 12 h, and adequate 30-day stability. Recalculated release kinetics suggested a near-zero-order mechanism associated with the erosion/swelling-controlled process.

6. FUTURE WORK

The proposed work includes experimental preparation of NP1-NP5 in triplicate; development and validation of a selective HPLC method for both drugs; actual FT-IR/DSC compatibility studies; the determination of swelling and erosion; the optimization using factorial or response-surface design; comparison with reference products using f2; longer stability studies and, if justified, an in-vivo pharmacokinetic evaluation.

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