Int. J. Pharm. Investigation, 2023; 13(4):763-771.
https://www.jpionline.org

Original Article

Formulation and Evaluation of Propranolol Hydrochloride Sustained Release Matrix Tablets Using Different Grades of HPMC and MCC

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ABSTRACT

Background: To design and develop propranolol hydrochloride sustained-release tablet formulations using different grades of HPMC and MCC and their *in vitro* evaluations. The effect on drug release from tablets and other characteristics by various grades of polymers were studied and compared. **Materials and Methods:** Propranolol hydrochloride, microcrystalline cellulose (PH-101), Microcrystalline Cellulose (PH-102), HPMC (K15 M), HPMC (K100 M), HPMC (K4 M), HPC LF, Isopropyl alcohol, Povidone (K-30), Magnesium Stearate were used in the different formulations. Direct compression, dry granulation and wet granulation methods were used for the preparation of tablets. **Results:** Among different formulations, SR008 having HPMC K100M was showing better sustained release characteristics, 69.1%, 76.6%, 82.3% for 8, 10, 12 hr respectively compared to other formulations with 71% moisture content and 71N hardness. **Conclusion:** The matrix embedding technique using HPMC K100M has successfully extended the release of propranolol hydrochloride. It is particularly suitable for obtaining directly compressed sustained-release matrix tablets with appropriate standards and well-reproducible drug release profiles. In contrast to thrice daily prescriptions of the conventional formulation, the designed formulations can be prescribed once daily dose leading to a reduction in dosing frequency and per-day drug dose. It is concluded that HPMC K100M in appropriate proportions is suitable for formulating sustained-release tablets which exhibit diffusion-controlled Higuchi kinetics for propranolol hydrochloride.

Keywords: Propranolol hydrochloride, HPMC, SR tablet, Direct compression, Optimization, *in vitro* drug release.

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Received: 15-06-2023;
Revised: 01-07-2023;
Accepted: 30-07-2023.

INTRODUCTION

Over the past 35 years, as the expenses and difficulties of introducing new pharmacological entities have increased and the therapeutic advantages of sustained drug administration have come to light, there has been a greater focus on the development of prolonged drug delivery systems.[1,2] Sustained drug delivery is a particular type of modified drug delivery that, for drug candidates with a quick clearance rate because of a short elimination half-life, has the benefit of requiring fewer doses per day than standard dosage forms. In order to maintain a therapeutic level of drug in blood, following administration of a long time, oral sustained release formulations consistently release the drug.[3,4] This improves patient compliance and therapy control. The development of pharmaceutical formulations for oral delivery systems involves the optimization of formulation parameters within the inherent constraints of GI physiology. The molecular weight, pKa, and solubility at various temperatures are important factors that must be considered during the biopharmaceutical evaluation of a drug for prospective application in extended-release drug delivery systems.[5,6] The effectiveness of a medicinal product with sustained release can be affected by a number of variables. The assessment of the adequacy of the dosage form can be complicated by physiological, biochemical, and pharmacological aspects. The extended drug delivery system of the matrix diffusion results in the uniform dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix.[7,8] As the tablet comes into contact with GI fluid, the drug is liberated from hydrophilic matrix dosage forms. In essence, they are a compressed mixture of a hydrophilic polymer and drugs. IUPAC name of Propranolol Hydrochloride is 1-napthalene-1-yloxy-3-(propan-2-ylamino) propan-2-ol hydrochloride ($C_{16}H_{22}NO_2HCl$) [Figure 1]. It acts as Beta-adrenergic receptor antagonists with good solubility property. This study includes tablet form of sustained release of propranolol hydrochloride using different polymers for

DOI: 10.5530/ijpi.13.4.094

once-daily use is designed for migraine prevention and compare with brand product.[9,10]

MATERIALS AND METHODS

Materials

Propranolol hydrochloride, microcrystalline cellulose (PH-101), Microcrystalline Cellulose (PH-102), HPMC (K15 M), HPMC (K100 M), HPMC (K4 M), HPC LF, Isopropyl alcohol, Povidone (K-30), Magnesium Stearate were obtained from Alkem Labs. Ltd., Mumbai, respectively.

Analytical reagents

Hydrochloric acid (AR grade), Sodium Chloride (AR grade), Disodium hydrogen phosphate anhydrous (AR grade), Citric acid monohydrate (AR grade), Sodium hydroxide (AR grade), Potassium dihydrogen phosphate (AR grade), Methanol (HPLC grade), Acetonitrile (HPLC grade), Water HPLC grade (Mili Q) were also obtained from Alkem Labs. Ltd., Mumbai.

Equipment

Tablet compression machine manufactured by Cadmach Machinery Co. Pvt, Rapid mixing granulator manufactured by Kevin Process Technology Pvt Ltd., Planetary mixer manufactured by Kenwood, Dissolution apparatus manufactured by Electrolab (TDT-08L), HPLC manufactured by Water (2695), UV-visible spectrophotometer manufactured by Perkin Elmer (Lambda25), Differential scanning calorimeter manufactured by Mettler Toledo (DSC-822^e), Disintegration apparatus manufactured by Electrolab (ED-2AL), Rapid dryer manufactured by Retsch (TG-100), Karl Fischer titrator manufactured by Mettler Toledo (DL 31), Hardness tester manufactured by Dr. Schleuniger Pharmatron (5Y), Density apparatus manufactured by Electrolab (etd-1020), blender manufactured by Pretime-D, Roche friabilator USP [Electrlab (EF-1W)], Vernier caliper manufactured by Mitutoyo (absolute digimatric), Digital pH meter manufactured by Labindia, Digital weighing balance manufactured by Metter Toledo (AB 204-S), Mechanical Shaker manufactured by Skan were employed for the preparation of SR tablets.

Formulation

Different formulations (SR-001 to SR-008) have been prepared by using drug and excipients which is mentioned in Table 1.

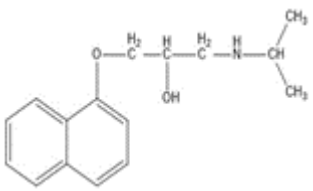


Figure 1: Chemical structure of Propranolol Hydrochloride.

Methods of Preparation

Sustained release tablet formulations of propranolol hydrochloride were prepared by direct compression, dry granulation and wet granulation methods by using Digital weighing balance, Rapid dryer, Rapid mixing granulator, Tablet compression machine. Schematic diagram represents the detail in Figure 2.

Preformulation studies of Propranolol hydrochloride sustained release tablet

Organoleptic characterization

Investigation of the physical, chemical characteristics of API with excipients is known as preformulation testing. The colour, odour, and taste of the drug were recorded.

Solubility study

Propranolol HCl's solubility in different solvents was assessed using Mechanical Shaker and UV-spectrophotometry. The solubility data can be utilized to choose the best solvents to use in the drug formulation.

Compatibility studies of Propranolol Hydrochloride with formulation excipients

Differential Scanning Calorimetry (DSC) thermograms of manufactured tablets and the pure drug propranolol hydrochloride are displayed.

Bulk density and Tapped density

Bulk density and Tapped density determination by Density apparatus by observing the original volume of powder and the sample after tapping (500, 750, or 1250 taps), until no further volume loss was noticed or the percentage of volume difference was less than 2%.

Bulk density= (Weight of sample in g/ Volume occupied by sample in ml)

Tapped density= (Weight of sample in g/ Volume occupied by sample after completion of tapping in ml)

Compressibility index and Hausner ratio

Compressibility index and Hausner ratio measure the material's cohesiveness, moisture content, surface area, size, form, and bulk density. The bulk density and the tapped density of a powder are measured in order to calculate the compressibility index and Hausner ratio.

Compressibility index =100 (Tapped density – Bulk density)/ Tapped density

Table 1: Comparative composition profile of different formulation.

Sl. No.	Ingredients	Batch No.							
		SR-001 (mg/tab)	SR-002 (mg/tab)	SR-003 (mg/tab)	SR-004 (mg/tab)	SR-005 (mg/tab)	SR-006 (mg/tab)	SR-007 (mg/tab)	SR-008 (mg/tab)
1	Propranolol Hydrochloride	40	40	40	40	40	40	40	40
2	HPMC K 4M	12.5	-	-	12.5	25	-	-	-
3	HPMC K 15M	-	25	25	-	-	25	25	25
4	HPMC K 100M	-	12.5	12.5	-	12.5	12.5	15	20
5	HPC LF	-	-	-	25	-	-	-	-
6	Avicel PH 101	-	-	76.95	76.95	76.95	76.95	74.45	69.45
7	Avicel PH 102	221	221	-	-	-	-	-	-
8	Povidone	-	-	4.8	4.8	4.8	4.8	4.8	4.8
9	Magnesium stearate	1.50	1.50	0.75	0.75	-	-	-	-
10	Isopropyl alcohol	qs	qs	qs	qs	qs	qs	qs	qs
	Total weight	300	300	160	160	160	160	160	160

Hausner ratio= (Tapped density/ Bulk density)

Angle of repose determination

The flow characteristics of solids have been described using the angle of repose. It is an attribute connected to the friction between particles.

$$\theta = \tan^{-1} h/r$$

Moisture content

Moisture content refers to the amount of water present in a substance or material. It is usually expressed as a percentage of the weight of the wet material to the weight of the dry material. Karl Fischer titration is a chemical method that involves adding a reagent to the sample that reacts with water, and then measuring the amount of reagent that is consumed. This method is commonly used for materials with low moisture contents.[11,12]

Analytical method development

Preparation of pH 1.2 Buffer

2.0 g of NaCl were added and dissolved in 1 L of water. The pH of this solution after 7.0 ml of HCl addition was recorded.

Preparation of pH 6.8 Buffer

21.72g of dibasic sodium phosphate were added and dissolved in 1 L of water. 4.94g of citric acid monohydrate was added to this solution to get the pH up to 6.8.

Preparation of pH 7.5 Buffer

6.8g of monobasic potassium phosphate was added and dissolved in 1 L of water to create a pH 7.2 buffer. This solution has 1.6g of NaOH added to it. After that, a 1N NaOH solution was used to adjust pH to 7.5.

Preparation of HPLC Mobile phase

13.6g of monobasic sodium phosphate was added to 2 L of water and dissolved. Acetonitrile was combined with this buffer at a 350:650 ratio. After a 30 min sonication and filter sample is removed.

Preparation of standard solution

A 100 mL volumetric flask was filled with 50 mg of propranolol hydrochloride for the preparation of the standard solution. The Mobile Phase was added in an amount of 80 mL. Next, using the Mobile Phase, the volume was increased to around 100 mL. This mixture served as the standard solution.

Preparation and estimation of sample

Aliquots of 1 mL, 2 mL, 3 mL, 4 mL, 5 mL, and 6 mL of working standard solution were transferred into a series of 50 mL volumetric flasks. Each of these flasks was added approximately 15 mL of specified buffer/mobile phase. After shaking and setting aside for 5 min., the volume was made up to the mark with buffer/ mobile phase the concentrations of each sample's absorbance was assessed using UV-spectrophotometry, with the appropriate buffer serving as the blank. The samples made in the mobile phase of the HPLC were documented.[13,14]

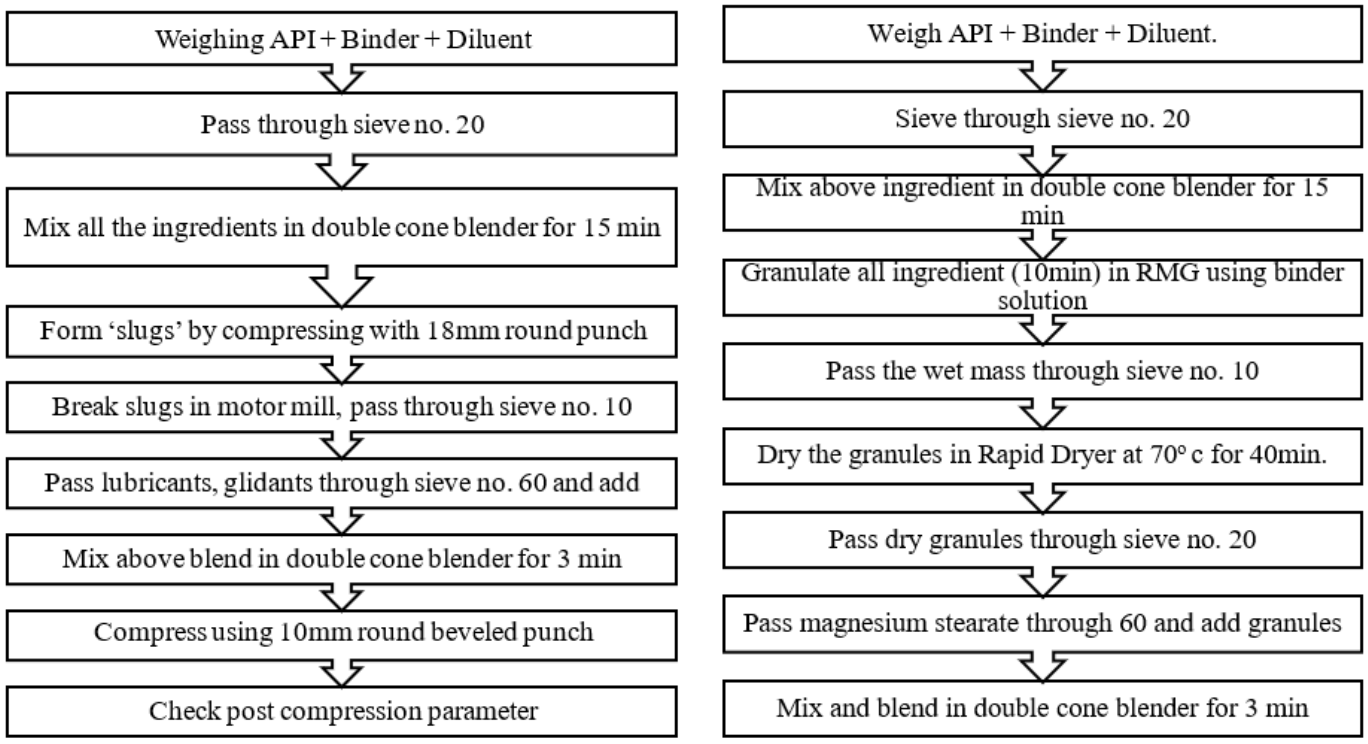


Figure 2: Direct compression, dry granulation (2A) and Wet Granulation process (2B).

Analysis of reference product

Analysis of reference product (Brand-X) was carried out for various physical parameter and *in vitro* dissolution profile.

Evaluation of Post compression parameters of Propranolol hydrochloride sustained release tablets

Thickness

Vernier calipers were used to gauge the thickness of twenty tablets that were randomly selected from the formulae. It was possible to calculate the average and express it in millimetres.

Hardness

A tablet's hardness reveals its capacity to tolerate managing mechanical shocks. Using a Dr. Schleuniger hardness tester, the tablets' hardness was assessed. Newtons were used to express it (N). From each formulation, ten tablets were randomly chosen, and their hardness was assessed.

Friability

The Roche friabilator was used to assess the friability of the tablets. In the friabilator, approximately 6.5 $W_{initial}$ tablets were placed. The friabilator was operated up to 100 revolutions per minute or at 25 rpm for 4 min. Dedusting the tablets and weighing them once more (W_{final}). The percentage of friability as determined by,

$$F= 100(W_{initial}- W_{final})/ W_{final}$$

Weight variation

To check for weight variance, 20 tablets were chosen at random from each formulation and weighed one at a time.[15,16]

In vitro dissolution study

Tablets of each formulation were randomly chosen and weighed. One tablet was transferred into dissolution vessel containing 900 mL of pH 1.2 buffer. After completion of 1 hr, dissolution was halted and samples were collected. then, the dissolution medium was changed to pH 7.5 buffer for the rest of test period, that is up to 12 hr. The amount of drug released was determined by analyzing the aliquots removed at regular intervals by UV-spectrophotometric method.[17]

Mathematical modeling of in vitro Dissolution data

Dissolution test of prepared formulation was done as per the U.S.P monograph of Extended-release capsules of "propranolol hydrochloride". Following are the five categories into which the

data were divided: a. Total drug release percentage shown against time (zero order release kinetics), b. Log cumulative % of the medication kept against time (first order release kinetics), c. Drug release rates cumulatively against time squared (Higuchi model of drug release kinetics), d. Cube root of medication remaining percentage versus time (Hixson-Crowell cube root law), e. Drug release logarithm against log time (Korsmeyer-Peppas drug release kinetics).[11,18]

Study of Dissimilarity (f_1) and similarity (f_2) factors

To determine the dissimilarity, dissimilarity was calculated in a comparison with the reference or the reference product. Always keep the dissimilarity factor (f1) under 15(f1<15). The mean squared difference in percent dissolve between the test and reference products plus the logarithmic reciprocal square root transformation of one was used to establish the similarity factor (f2). To compare the test with reference release profiles, this was determined. The number of sampling points is given by n. Always have the dissimilarity factor (f2) greater than 50 (f2 >50).

$$f1 = \frac{\sum R_t - T_t}{\sum R_t} \times 100, f2\ 50 \times log10 \times \frac{1}{\sqrt{1+\frac{1}{n}\times \sum (R_t - T_t)^2}}$$

Stability studies of formulations

Drug release and drug content study of optimized matrix formulation was performed at three stability storage conditions, as per ICH guidelines (for 30 days).

40 ± 2°C/75 ± 5% RH (minimum study period at least 1 month)

30 ± 2°C/75 ± 5% RH (minimum study period at least 2 month)

25 ± 2°C/60 ± 5% RH (minimum study period at least 2 month)18,19

RESULTS

Preformulation studies of Propranolol hydrochloride sustained release tablet

This study demonstrates the successful transition from SR-004 to SR-008. As can be seen in Table 2, SR-005 and SR-008 exhibit good flow properties.

Compatibility studies of Propranolol Hydrochloride with formulation excipients

According to Figures 3A, 3B, and 3C the DSC thermogram of the drug and excipients demonstrates that there is no interaction between them.

Standard Calibration curves

Figure 4 shows the calibration curve for propranolol hydrochloride in buffers with pH values of 1.2, 6.8, and 7.5 as well as HPLC mobile phase. Table 3 lists the standard absorbance in buffer pH 1.2, 6.8, and 7.5 as well as the standard area in the mobile phase of an HPLC system. Regression coefficients (R^2) of 1.2, 6.8,7.5 buffer solution and HPLC mobile phase are 0.999, 0.996, 0.979 and 0.999 respectively.

Analysis of reference product

Shelf time of reference product (Brand 'X') is 24 months, each sustained release tablet contains propranolol Hydrochloride IP 40mg. The pack size is with 10 tablets each with Alu Alu Blister type packaging. Brand 'X' shows drug release at 1, 3, 6, 8, 10, 12 hr 17.5, 34.4, 51.7, 61.1, 68.6, 75.1 percentage respectively in HPLC. Tables 4 and 5 shows the comparison of evaluation parameters with different formulations. The drug's sustained release profile over an interval of 8, 10 and 12 hr, which determines the value by 64.6%, 72.3%, and 80.9%, respectively.

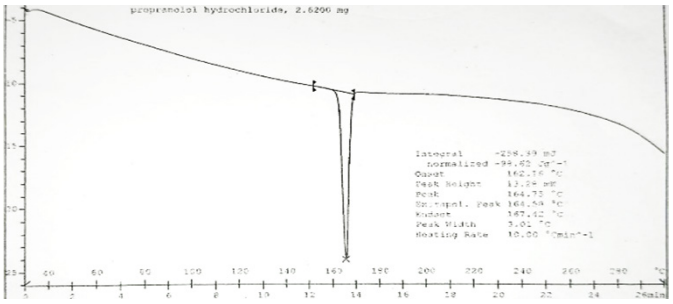


Figure 3A: DSC Thermogram of Propanolol Hydrochloride.

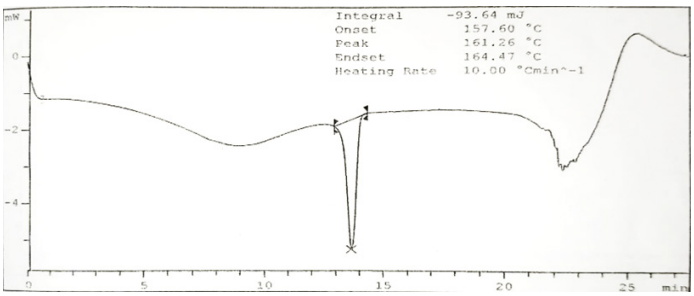


Figure 3B: DSC Thermogram of Propanolol Hydrochloride with HPCLF Propanolol Hydrochloride with HPCLF.

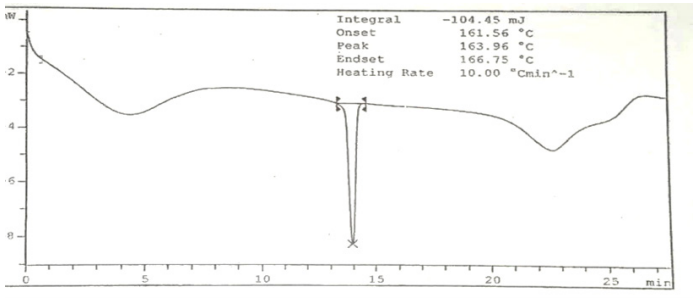


Figure 3C: DSC Thermogram of Propanolol Hydrochloride with HPMCK100 and HPMCK15.

Table 2: Evaluation parameters for Preformulation studies.

Sl. No.	Batch no.	Process of formulation	Moisture content (%)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio	Flow character
1	SR-001	Direct compression	5.19	0.3982	0.5344	29.82	1.42	Poor
2	SR-002	Dry granulation	5.44	0.6172	0.7544	16.31	1.41	Poor
3	SR-003	Aqueous granulation	NA	NA	NA	NA	NA	Poor
4	SR-004	Non-Aqueous granulation	4.9	0.3345	0.4179	19.95	1.24	Fair
5	SR-005	Non-Aqueous granulation	4.67	0.3664	0.4251	13.8	1.16	Good
6	SR-006	Non-Aqueous granulation	5.62	0.348	0.450	19.86	1.24	Fair
7	SR-007	Non-Aqueous granulation	4.45	0.3450	0.4011	14.00	1.162	Fair
8	SR-008	Non-Aqueous granulation	4.31	0.3228	0.3679	12.24	1.139	Good

Table 3: Standard absorbance in buffer pH 1.2, 6.8, 7.5 and Standard area in HPLC mobile phase.

Sl. No.	Concentration (µg/ml)	Absorbance at pH 1.2	Absorbance at pH 6.8	Absorbance at pH 7.5	Standard area (mobile phase)
1	10	0.0590	0.0605	0.0649	2143.411
2	20	0.1183	0.1300	0.1214	4310.44
3	30	0.1727	0.1808	0.1870	6549.428
4	40	0.2343	0.2400	0.2393	8724.016
5	50	0.2862	0.2991	0.2498	10869.418
6	60	0.3419	0.3419	0.03547	12934.860

Table 4: Evaluation of Post-compression parameters of different formulations.

Batch No.	SR-004	SR-005	SR-006	SR-007	SR-008	Test
Thickness (mm)	3.48 ± 0.2	3.47 ± 0.3	3.51 ± 0.3	3.43 ± 0.6	3.46 ± 0.2	3.70 mm
Hardness (N)	70 ± 2	71 ± 2	70 ± 3	69 ± 3	71 ± 2	98 N
Friability (%)	0.022	0.021	0.016	0.018	0.023	0.06%
Weight variation (mg)	160 ± 1.8	160 ± 2.2	160 ± 1.5	160 ± 2.0	160 ± 1.5	157.8± 0.3
Moisture content (%)	4.9	4.67	5.62	4.45	4.31	3.45
Assay (%)	100.6	100.8	99.7	99.5	100.7	99.8

Evaluation parameters of Post compression parameters of Propranolol hydrochloride sustained release tablets

Table 4 shows the evaluation values of Post-compression parameters of different formulations. Table 5 shows better sustain release profile of SR-008. Graphical representation of *in vitro* dissolution profile of different formulations is shown Figure 5.

Study of Dissimilarity (f_1) and similarity (f_2) factors

A statistical compression of dissolution data was carried out using dissimilarity (f_1) and similarity (f_2) in Table 6. The comparison of *in vitro* dissolution profiles of products B. No. SR-007 and SR-008 with reference product (Brand-'X' 40mg) are shown Figure 6. f_1 and f_2 value of SR-007 is 16.52% and 51.45%. f_1 and f_2 value of SR-008 is 7.76% and 68.55%.

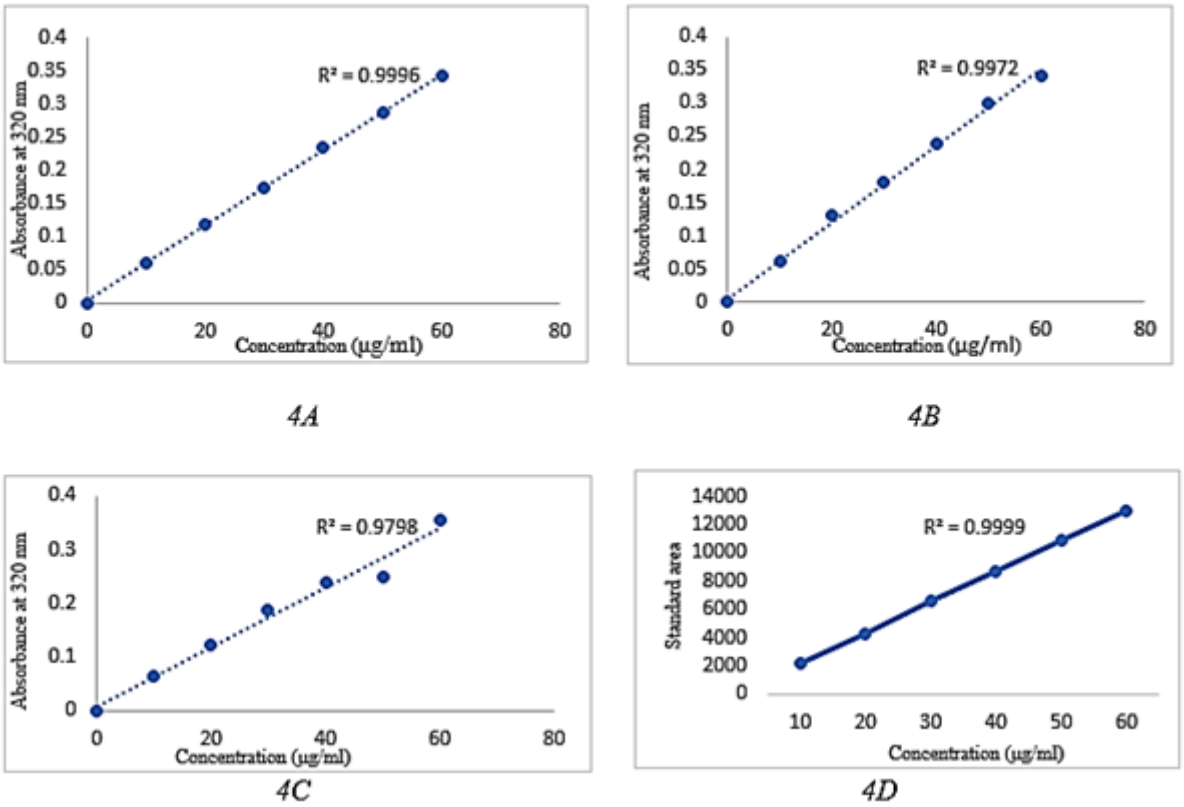


Figure 4: Calibration Curve of API in pH 1.2 buffer (4A), pH 6.8 buffer (4B), pH 7.5 buffer (4C) and HPLC mobile Phase (4D).

Table 5: ***In vitro*** **drug release profile of different formulation.**

Time	% Release					
(hours)	SR-004	SR-005	SR-006	SR-007	SR-008	Test
1	33.72	36.35	32.1	29.8	24.9	21.6
3	66.0	59.12	59.1	46.9	44.2	38.9
6	87.38	78.6	75.8	67.8	60.6	55.8
8	99.9	90.4	84.9	73.9	69.1	64.6
10	107.21	101.43	93.2	80.6	76.6	72.3
12	107.54	102.00	99.1	90.3	82.3	80.9

Mathematical modeling of in vitro Dissolution data

R^2 values of different mathematical models are shown in Table 7 for SR-007 and SR-008.

Stability studies of formulations

Table 8 shows stability study of SR-008 considered as optimum formulation.

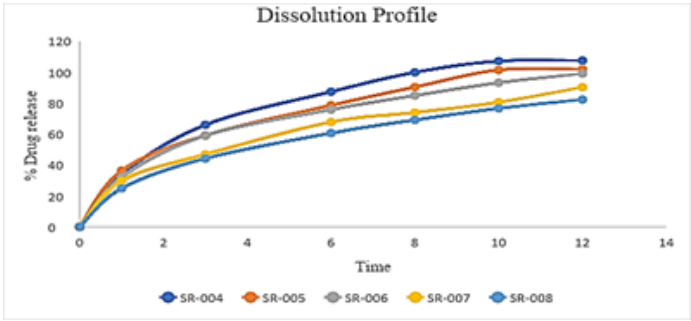


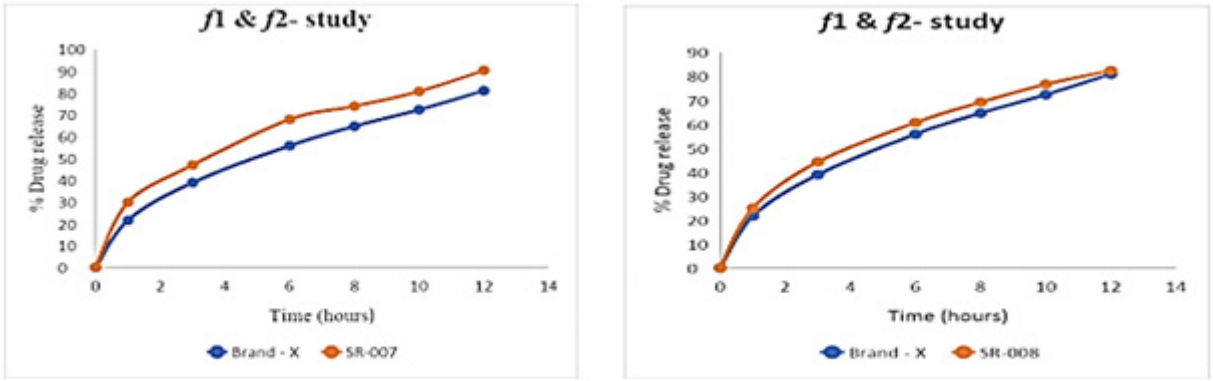
Figure 5: Graphical representation of *in vitro* dissolution profile of different formulations.

DISCUSSION

To choose the best method for creating sustained-release tablets, the trial formulations SR-001, SR-002, and SR-003 were used. The third formulation developed lumps during aqueous wet granulation, while the first two formulations had poor flow characteristics. After analyzing their flow characteristics, non-aqueous wet granulation was chosen as the best method. SR001, SR002, SR-003. Formulations are not compressed due to poor flow properties. In order to achieve a sustained-release

Table 6: Study of f_1 and f_2 factors for Batch No. SR-007.

SR-007					SR-008			
Time (hours)	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$
0	0	0	0	0	0	0	0	0
1	21.6	29.8	8.2	67.24	21.6	24.8	3.3	10.89
3	38.9	46.9	8	64	38.9	44.9	5.8	28.09
6	55.8	67.8	12	144	55.8	60.8	4.8	23.04
8	64.6	73.9	9.3	86.49	64.6	69.9	4.5	20.25
10	72.3	80.6	8.3	68.89	72.3	76.6	4.3	18.49
12	80.9	90.3	9.4	88.36	80.9	82.3	1.4	1.96
Σ	334.1	389.3	55.2	518.98	334.1	357.7	23.2	102.72
Number of Points		7			Number of Points	7		
f_1	16.52				f_1	7.76		
f_2	51.45				f_2	68.55		



6A 6B

Figure 6: f_1 and f_2 study for B. No. SR-007 (6A) and B. No. SR-008 (6B).

Table 7: R^2 values of different mathematical models.

Batch No.	Zero order	First order	Higuchi model	Hixson-crowell	Korsmeyer-peppas	Best fit model
SR-007	0.9841	0.8912	0.9978	0.9799	0.9895	Higuchi
SR-008	0.991	0.9293	0.998	0.971	0.9762	Hixson-Crowell

Table 8: Stability study at 40 ± 2°C/5% RH of Batch No. SR-008.

Time	Condition	Drug Release (%)					
(days)		1 hr.	3 hr.	6 hr.	8 hr.	10 hr.	12 hr.
0	Initial	24.9	44.2	60.6	69.1	76.6	82.3
30	40 ± 2°C/75 ± 5% RH	22.2	42.4	60.3	71.8	78.8	85.3

profile, combinations of HPMC K4M and HPC LF and HPMC K4M and HPMC K100M were not successful, as shown by a comparison of the percentage release rates of formulations SR-004 and SR-005. Instead, a combination of HPMC K100 M and HPMC K15 M, which contains high-viscosity polymers, was used (1,00,000 cps and 15,000 cps for HPMC K 100M and HPMC K15M respectively). Three distinct formulations (SR-006, SR-007, and SR-008) that contained HPMC K 100 M and HPMC K 15 M in variable proportions were examined. Of these, formulation SR-008 had the highest similarity factor and lowest dissimilarity

factor to the reference product in terms of dissolving profile. The melting point of propranolol hydrochloride is within range, according to the thermograms. Therefore, it may be said that the excipients and the drug do not interact. To better understand the drug release behavior, kinetic treatment was applied to the release rates obtained from the optimized formulations B.No. SR-007 and SR-008. Upon the application of different drug release model kinetics, it was found that B.No. SR-007 and B.No. SR-008 follow the Higuchi model which shows continuous drug release for sustained period of time.

CONCLUSION

Propranolol Hydrochloride has been successfully formulated into a stable sustained-release swellable matrix tablet using HPMC K100M and HPMC K15M polymers with *in vitro* drug release characteristics that are identical to the reference product brand 'X'. Also, the produced product is less complicated in terms of formulation ingredients and processing considerations. Propranolol Hydrochloride sustained-release matrix tablet formulation is physiochemically stable. In particular, B.No. SR-008 was determined to be the optimized sustained-release formulation as it is showing better sustained and controlled release 82.3% for 12 hr compared to other formulations. Higher HPMC K100M shows better sustainable profile of drug release.

ACKNOWLEDGEMENT

The facilities required to conduct the research were provided by Brainware University in Barasat and Alkem Laboratories Ltd. in Mumbai, which the authors gratefully acknowledge.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HPMC: Hydroxypropyl methylcellulose; **SR:** Sustained release; **MCC:** Microcrystalline cellulose.

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Cite this article: Khamkat P, Barik V, Barik BB, Chakraborty A, Patra D, Mondal P, *et al*. Formulation and Evaluation of Propranolol Hydrochloride Sustained Release Matrix Tablets Using Different Grades of HPMC and MCC. Int. J. Pharm. Investigation. 2023;13(4):763-71.