RESEARCH ARTICLE

Formulation and Evaluation of Extended-release Capsule of Propranolol Hydrochloride

Mahendra C. Gunde[1], Amit D. Jambulkar[2], Pravinkumar B. Suruse[3]*

[1]*Department of Pharmacognosy, Datta Meghe College of Pharmacy, DMIMSU (DU), Sawangi (M), Wardha, Maharashtra, India.*
[2]*Department of Pharmaceutics, Kamla Nehru College of Pharmacy, Butibori, Nagpur, Maharashtra, India.*
[3]*Department of Pharmaceutics, SND College of Pharmacy, Bhabhulgaon, Yeola, Nashik, Maharashtra, India.*

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ABSTRACT

The focus of this research was to create novel propranolol hydrochloride (PPH) extended-release capsules for 24 hours release, when compared to the immediate release dosage form for treating hypertension, it reduces the frequency of dose. The formulation has been developed to improve dissolving, which may result in improved oral absorption. The effects of component nature, proportion in the release rate, and dissolution process were explored. Formulation into capsules also reduces the frequency of administration. Even if propranolol tablets are available in market, we can develop pellets since pellets have good intestinal flow qualities and are less expensive to produce.

To accomplish this, we must first formulate and test the capsules. The *in-vitro* dissolution profile is compared to the commercial product's profile, and the formula will be finalized.

Keywords: Extended-release, Propranolol hydrochloride, Capsule

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INTRODUCTION

Delivery systems can be developed to change the rate at which the drug is released over time or after it reaches the desired site. Drug release happens only after a certain amount of time has passed since administration, or for a lengthy duration, or to a particular target inside the body. Improvements in drug release are typically desired to increase drug efficacy, stability and safety or to enhance patient adherence and delivery comfort.[1] Drug delivery systems (DDS) are recommended because direct clinical usage of Active Pharmaceutical Ingredients (APIs) is unusual for a variety of reasons. API handling and precise dose can be hard or impossible for highly strong medications.[2]

Pellets are tiny (0.5–1.5 mm), freely-flowable, rounded particles generated by aggregation of microparticles or granules of pharmacological components and additives using suitable processing equipment. Small rods with an aspect ratio near unity are also called pellets.[3] Capsule is solid dosage form wherein the medicament or a combination of pharmaceuticals is sealed in gelatine capsules, which can be hard or soft. The shells are constructed of gelatine and can be used for oral delivery.[4]

Propranolol is a nonselective -adrenergic receptor agonist without any other sympathetic nervous system effects. Hypertension, migraine, angina, cardiac arrhythmias, and a variety of other cardiovascular problems are all treated with Propranolol Hydrochloride (PPH).[5] It is a highly lipophilic drug with a 15–23% oral bioavailability and a half-life of 3–6 hours.[6] As a result, patients usually take many times during the day. A drug delivery system's objective is to achieve a therapeutic amount of drugs to the right spot in the body and then maintain that concentration.[7] Taking into account all of the delivery challenges associated with PPH, we propose developing a sustained release formulation for an extended-release profile that can reduce the frequency of administration.

MATERIAL AND METHODS

Materials

The PPH main API was provided as a gift sample from Ipca Laboratories Mumbai. Hypromellose E5, pore forming agent and Aqualone-EC-N10 coating polymer obtained from Coloron pvt.ltd. and Ashland pvt.ltd. respectively. All other chemicals and solvents were of analytical grade.

Methods

Drug - Excipients Compatibility Studies

Compatibility studies are conducted to determine whether PPH and other active substances interact. Compatibility tests

**Author for Correspondence: surusepravin@gmail.com*

are conducted with a mixture of drug and excipients in the proportions that would be expected in the innovative product. A portion of the mixture could be stored at varied temperatures, such as 40°C ± 2°C/ 75% RH ± 5%, whereas control samples were held at 2 to 8°C. They are examined in terms of their physical and chemical properties. These samples are taken at regular intervals and FT-IR analysis is performed on them.[7,8]

Preparation of Drug Solution

In a beaker, ethanol and water were mixed thoroughly, and then PPH and hypromellose E5 were added and swirled for 20 minutes. Talc was added and agitated for another 20 minutes to achieve a homogeneous solution.

Preparation of Coating Solution

Aqulone EC-N10, hypromellose E3 dissolved in methylene chloride, and tri-ethylene-citrate dissolved in a specific amount of IPA were mixed and agitated until a clear solution was achieved.[9]

Preparation of PPH Pellets

To make the pellets, a weighed quantity of sugar spheres were put into FBP, and the drug solution was coated onto the sugar spheres. The pellets were then covered with a controlled release coating solution.[10]

Loading of PPH Pellets in Capsules

Before filling pellets into capsules, physical and chemical parameters were used to assess the pellets. For core pellets and coated pellets, characteristics such as Bulk density, tapped density, Hausner's ratio, compressibility, sieve analysis, angle of repose, and assay are performed. Following process control parameters, the weight of pellets equivalent to PPH were put into firm gelatine capsules of size 1 by a capsule filling machine.[11] Different batches of extended-release capsules of PPH were prepared as shown in Table 1. Composition of coating solution shown in Table 2.

Accelerated Stability Studies

The stability of all pharmaceutical formulations must be determined. This will involve storage at extreme and normal temperatures and the necessary extrapolations to ensure that the product will provide medication for absorption at the same rate as when it was first manufactured over its intended shelf life. ICH CS L6AS and IS6B address specification, which contains a list of assessments tests, references to analytical techniques, and suggested acceptance criteria, as well as the concept of multiple acceptable criteria for release and shelf life.[12]

Evaluation of Capsules

Weight Variation Test

20 capsules were weighed individually, and the average weight was computed using the formula below.[13] It should not be more than 5%

Weight variation = (Weight of capsules- Average weight)/ Average weight of capsule X 100

Disintegration Test

The approach and apparatus for the pharmacopoeial disintegration test is same for soft and hard gelatine capsules. The capsules were put into a basket rack assembly that was sunk 30 times minute in a 37°C temperature-regulated fluid and then monitored for the time specified in the monograph. To pass the test, the capsules should completely crumble into a squishy volume with no indisputably solid core and only just a few remnants of the gelatine shell.[14]

Table 1: Composition of different batches of extended-release capsules of PPH

S. no.	*Ingredients*	*Quantity (mg/cap)*						
		F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
1.	Sugar spheres	100	100	66	66	66	66	66
2.	PPH	160	160	160	160	160	160	160
1	Talc	3	3	4	10	14	16	14
2	HPMC E5	17	17	16	20	20	20	20
3	Purified water	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
4	Ethanol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Table 2: Composition of a coating solution

S. no.	*Ingredients*	*Quantity (mg/cap)*						
		F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
1.	Drug loaded pellets	300	280	256	256	260	256	256
2.	Ethyl cellulose	30	31	29	30.80	30.80	25	37.20
3.	Aqualone-EC-N10	11	11	13	5	5	10.8	11.2
4.	Triethylene citrate	4.5	4.08	4.08	2.6	2.6	2.6	2.8
5.	IPA	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
6.	Purified water	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
7.	Ethanol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Dissolution Test

500 mL of dissolution medium was placed in each vessel for capsules and the medium was equilibrated at 37 ± 0.5°C. One capsule was placed in each Paddle and the machine was spinned at 50 rpm for a certain amount of time. 10 mL of solution was drawn from each vessel at regular intervals and substituted with an equivalent amount of solution medium. Finally, the solution was filtered through a 0.45-micron membrane filter. Dissolution was tested in a pH 6.5 buffer for 4, 6, 8, 10, 12, 16, 18, 20, 24 hours.[15,16]

RESULTS AND DISCUSSIONS

FT-IR *Analysis*

The physical mixture of PPH and excipients had a distinctive alcoholic –OH stretch at 3433 cm^{-1}, a –C–O–C stretch at 1260 cm^{-1}, and a –C–O–C stretch at 1060 cm^{-1} in the FT-IR spectrum. The FT-IR spectrum of pure PPH revealed a secondary amine –NH stretch at 3280 cm^{-1}, a C–H stretch at 2964 cm^{-1}, an aryl C=C stretch at 1579 cm^{-1}, an aryl O–CH2 asymmetric stretch at 1240 cm^{-1}, an aryl O–CH2 symmetric stretch at 1030 cm^{-1}, and a peak at 798 cm^{-1} due to alpha-substituted naphathalen. 3280 cm^{-1}, 2963 cm^{-1}, 1577 cm^{-1}, 1241 cm^{-1}, 1031 cm^{-1}, and 797 cm^{-1} were the matching peaks in the mixture.

The results of the FT-IR analysis show that there is no specific interactions between pure PPH and a physical mixture of PPH and excipients (Figure 1).

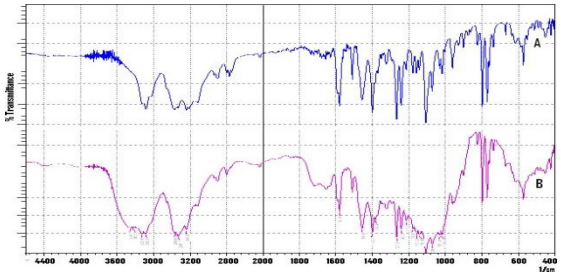

Figure 1: FT-IR spectrum of PPH (A) and physical mixture of PPH with excipients used (B).

In-vitro Drug Release

It was carried in 500 mL, 0.1N HCl acid stage for 2 hours followed by pH 6.8 phosphate buffer by using USP type I (basket) at 100 RPM, results were shown in Table 3, Figure 2

In-vitro Dissolution Profile of Formulations F1-F7

In-vitro dissolution profile of formulation batches F1-F7 was compared with standard PPH, results were shown in Table 4 and Figure 3.

Table 3: *In-vitro* drug release study

Dissolution media	*Time (Hr)*	*500 mL, 0.1N HCl acid stage for 2 hours followed by pH 6.8 phosphate buffer by using USP type I (basket) at 100 rpm*
		% Drug release of DMF (innovator)
0.1N HCl	1.5	16
	4	48
	6	59
	8	66
pH 6.8 phosphate buffer	10	71
	12	74
	14	77
	18	79
	24	81

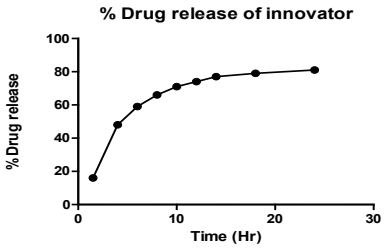

Figure 2: % *In-vitro* drug release

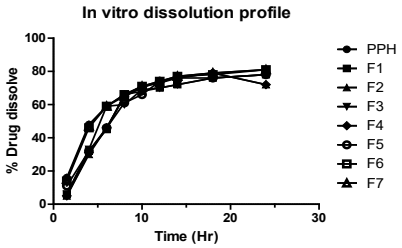

Figure 3: *In-vitro* dissolution profile of F1-F7

Table 4: *In-vitro* dissolution profile of F1-F7

S. no.	*Time (Hr)*	*PPH*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
1	1.5	16	6	5	6	5	11	14	15
2	4	48	32	30	33	31	32	46	47
3	6	59	45	46	59	46	46	59	59
4	8	66	66	65	60	65	61	66	65
5	10	71	68	71	69	70	66	71	71
6	12	74	70	73	70	74	74	74	73
7	14	77	72	76	72	76	76	77	77
8	18	79	76	79	76	79	76	78	79
9	24	81	78	72	78	72	78	81	81
10	Recovery	82	80	80	80	81	80	82	82

Table 5: Evaluation of capsule

S. no.	*Parameter*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
1	Weight variation (mg)	371	372	374	371.9	371.5	374.1	378.1
2	Content uniformity% (160 mg strength)	99.7	100.25	98.4	100.4	99.4	105.2	96.4

Table 6: Moisture content values of all formulations

S. no.	*Parameter*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
1	Moisture content% (uncoated)	0.79	0.68	0.58	0.78	0.80	0.65	1.02
2	Moisture content% (coated)	0.80	0.80	0.61	0.82	0.99	0.72	0.86

Evaluation of Capsules

Weight variation or content uniformity can be used to illustrate the uniformity of dose units. The following results shown in Table 5

Moisture Permeation

To ensure that single unit and unit dose containers are suitable for packing capsules, the USP mandates that their moisture permeation properties should be determined. Results were shown in Table 6

CONCLUSIONS

The active pharmaceutical ingredient PPH was exposed to a preformulation research, which included an accelerated drug excipient compatibility study and the results revealed that selected excipients were compatible with the PPH. Using commercially available sugar pellets, PPH coated pellets were made, and capsules were filled with various excipients using an automatic capsule filling machine. PPH extended release capsules were compared to innovator (Inderal-LA) capsules in terms of dissolution profile. The release was discovered to be comparable to the innovator's. The initial release is controlled by changing the concentration of Ethylcellulose EC-N10 in the F9 formulations and the HPMC. It produced better results, and the formulation procedure will be simple, safe, and effective. Finally, I believe that prolonged release pellets in capsules of formulation F9 have a comparable drug release rate to the innovator, as well as higher stability and bioavailability.

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