

## MULTIPLE UNIT EXTENDED RELEASE PELLETS OF PROPRANOLOL HYDROCHLORIDE: PREPARATION AND CHARACTERIZATION

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### ABSTRACT

The purpose of the present study is to develop and investigate the *in vitro* performance of multiple unit extended release pellets of a model drug, Propranolol Hydrochloride (PPNL HCl) with extreme water solubility, short half-life that provides an effective blood pressure control in hypertension and offers superior patient protection for 24 hours. To achieve the goal, 64% w/w drug pellets were prepared within a relatively narrow size range of 500 microns using diluent- microcrystalline cellulose (MCC) by extrusion-spheronization. These drug pellets were coated with different viscosity grades of extended release polymers- a combination of hydrophobic and hydrophilic cellulose derivatives in the ratios 90:10, 80:20 and 75:25 at different % w/w coating levels. Prepared pellets were evaluated for flow properties, drug content (by HPLC) and *in vitro* drug release (by UV Spectroscopy). The dissolution profile of pellets was evaluated in 0.1N HCl (pH 1.2) for first 1.5 hours followed by phosphate buffer (pH 6.8) for remaining hours and estimated by UV at the wavelength of maximum absorbance at about 320 nm. The effect of concentration, viscosity of polymers on the release rate of the drug that offers flexibility and robustness of the overall formulation was ascertained. It was observed that the formulation with the combination of polymers- ethyl cellulose (EC) and hydroxypropyl methyl cellulose (HPMC) in the ratio 75:25 at a coating level of 8% w/w to the drug pellets exhibited a dissolution pattern equivalent to the predicted release and able to extend the drug release for a prolonged period of time. The optimized formulation was analyzed for surface morphology, release kinetics and stability. The mechanism of drug release followed first order kinetics. An accelerated stability study of the finalized extended release pellets was found to be well within the acceptable range for 6 months.

**Keywords:** Extended release pellets, Microcrystalline Cellulose, Extrusion- Spheronization, Cellulose derivatives and Release kinetics.

### INTRODUCTION

Pellets, a multiple unit particulate drug delivery systems have come to the centre of research attention during the past decades for a variety of reasons like homogeneous spreadability in the gastrointestinal tract, better *in vitro* and *in vivo* release of the drug substances with reproducible release characteristics and minimized risk of dose dumping than single unit dosage forms [1]. Studies of Malinowski and Smith [2] indicated pellets as suitable systems for extended release formulations with respect to their spherical/ semi-spherical shape, low surface area-volume ratios that provides ease of coating and reduction in the dosage regimen. Various techniques like extrusion-spheronization, solution/suspension layering, powder layering etc., are employed in the manufacture of drug pellets [3].

Wet extrusion/spheronization, a simple and commonly used established processing technique in the pharmaceutical industry for the continuous production of pellets. This method facilitates high drug loaded and robust pellets. The physical characteristics of the active ingredients and excipients can be modified to improve physical properties and downstream processing [4].

Propranolol Hydrochloride (PPNL HCl), a synthetic non-selective  $\beta$ -adrenergic receptor-blocking agent with shorter biological half life of 3 - 6 hours; daily dose ranges from 40 mg to 160 mg and hence needs multiple dosing in a day. Consequently, there is a need to develop a dosage form which delivers the drug in extended fashion [5]. A key principle involved in oral dosing of the sustained release preparation PPNL HCl; the blood profile is flatter than after conventional PPNL HCl but the half-life increases to between 10 and 20 hours; thereby increases  $\beta_1$  antagonist activity and offers superior patient protection for 24 hours in hypertension.

Formulating extended release pellets using different extended release polymers reduces dosing frequency, increases effectiveness of the drug by localization at the site of action and provides uniform drug delivery for 24 hours [6-7]. Mixtures of polymers, particularly combination of water insoluble-water permeable and water swellable-water soluble cellulose derivatives are useful in regulating the drug release properties of dosage forms. In matrix tablets,

polymer mixtures modify drug release rate by producing gel barriers of varying consistency [8]. This effect is often due to interactions between the excipients that modify the matrix viscosity and/or polarity as well as the internal structure of the dosage form through which the drug must diffuse [9]. Matrix systems containing hydrophilic polymers have been widely studied since drug release from these matrices is controlled by a combined effect of polymer i.e., swelling, erosion and diffusion through the hydrated gel [10].

In the present study, an attempt was made to prepare multiple unit extended release pellets of PPNL HCl. The extrudates were prepared using microcrystalline cellulose, a diluent to process pellets with greater mechanical strength to withstand the successive extended release coating using combination of hydrophobic and hydrophilic cellulose derivatives [11]. Cellulose has three hydroxyl groups (-OH) per unit glucose ring and these hydroxyl groups form regular inter and intra-molecular hydrogen bonds. Due to these hydrogen bonds, cellulose forms a rigid crystalline and stable structure that is insoluble in water or organic solvents. However, cellulose ethers are amorphous in nature; formed by breaking hydrogen bonds and thereby substitutes at least one of the hydroxyl groups in a glucose unit with various substituents by etherification; thus enhances water retention and an excellent film forming ability. Examples of the water-soluble cellulose ethers include methylcellulose (MCC), hydroxypropylmethylcellulose (HPMC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC). Among hydrophilic cellulose ethers; hydroxypropyl methylcellulose (HPMC), a non-ionic cellulose ethers having viscosity grades in the range of 3-100 cps at 20°C; is the first choice of researchers that have been extensively studied regarding both mechanistic and technological factors involved in drug release which facilitates diffusion of drugs due to its gel-matrix network [12-14]. PPNL has high water solubility and hence release retardant, a hydrophobic cellulose ethyl ether was used in the matrix system [15-17] along with a hydrophilic polymer to attain the desired release. Ethyl cellulose (EC), an inert and pH insensitive film former in which some of the hydroxyl groups on the repeating anhydroglucose units are modified into non-ionic ethyl ether groups of cellulose, available in a wide range of viscosities and ethoxy contents, insoluble in water and soluble in organic solvents; was chosen to study the effect of polymer combinations on release kinetics.

## MATERIALS AND METHODS

Propranolol Hydrochloride purchased from Ipca labs (Mumbai) with mean particle size of 24  $\mu\text{m}$ , compressibility index 36.842 % and water solubility 155 mg/mL. Microcrystalline cellulose (MCC) – Avicel PH101 (FMC Biopolymers) was used as diluent for preparation of drug pellets. Different viscosities of extended release polymers used were Ethyl Cellulose-4cps (Colorcorn), Ethyl Cellulose-7cps (Colorcorn), Aqueous Ethylcellulose dispersion (Colorcorn), Hydroxypropyl methyl cellulose-5 cps (The Dow Chemical Company). All other chemicals and solvents were of analytical reagent grade.

### Formulation of Pellets

As a manufacturing method, drug pellets (PPNL HCl) were prepared by extrusion-spheronization and coated in a coating pan to obtain extended release pellets.

### Preparation of drug pellets

The quantities for all pellet components were calculated as percent w/w of the dry formulation, while water contents were given as percent loss on drying, and thus calculated on wet mass as 100%. The drug pellets (64% w/w) were prepared with PPNL HCl and MCC in the ratio 2.84: 1. The dry ingredients were sifted through mesh #20 separately and mixed intimately for 10 minutes in rapid mixer granulator (Gansons pvt.ltd, Thane) with impeller at slow speed and chopper off. Required quantity of water was added slowly during constant mixing to the above dry mix over a period of 2-3 minutes with impeller at slow speed and chopper off to form a discrete wet mass. The process was continued for further 2 minutes with impeller and chopper at slow speed. The wet mass was extruded at room temperature 25+5°C through a cylinder extruder (Umang pharmtech Pvt.ltd, Thane) fitted with a die roller of 0.8 mm diameter. Multiple extrusions were done to minimize process loss. Extrudes were spheronized for 10 minutes at rotating speed of 1800 rpm with air pressure of 2 kg/cm<sup>2</sup> in a spheronizer (Umang pharmtech pvt.ltd, Thane) fitted with a cross-hatched rotor plate of

150 mm diameter and 3 mm thickness. These wet pellets were sifted and collected mesh #16 passed and mesh # 20 retentions. The pellets were dried in a rapid drier (Retsch GmbH & Co., Germany) at temperature 60°C for 30 minutes to get loss on drying in the range 0.5 to 1.5% w/w. After drying, the pellets were sieved through mesh #16 and mesh #30, only #16 passed and #30 retains were used for coating.

### Preparation of coating solution

As the present work focus to extend the drug release, the dried drug pellets were coated with dispersion of cellulose ethyl ethers and HPMC (Erweka AR) in a coating pan. The coating dispersion was prepared by dissolving required quantity of HPMC in purified water under constant stirring until uniform solution was obtained. Ethylcellulose was dissolved in isopropyl alcohol, then dispersed into HPMC solution and stirred constantly during coating.

### Coating of pellets

Different compositions of the extended release coatings are mentioned in **Table 1**. The weighed quantity of dried drug pellets were loaded into the coating pan and preheated till the exhaust temperature reaches 35+2°C. The pan was kept rotating and coating dispersion was pumped to the nozzle using a peristaltic pump which was sprayed onto the surface of pellet bed. Batches were coated under the processing conditions at exhaust temperature 50±5°C, a spray rate 5-10 g/min and dried at 60°C after coating for not more than 30 minutes. Inlet temperature was maintained based on exhaust temperature. % w/w coating levels were determined as weight gain i.e., the difference in batch weights before and after coating, taking the polymer contents of coating solution into account. Pellets were always dried for atleast 10-15 minutes after spraying had been completed, before taking any samples or emptying the coating container. Coating efficiency was calculated as the correlation between actual weight gain and theoretical weight gain that would have been expected from the polymer content and the amount of applied coating dispersion/solution.

**Table 1: Compositions of Propranolol Hydrochloride Extended Release Pellets**

Ingredients	mg/unit				
	PF-I	PF-II	PF-III	PF-IV	PF-V
<b>Composition of Drug pellets</b>					
PPNL HCl	160	160	160	160	160
Microcrystalline cellulose (Avicel PH 101)	90	90	90	90	90
Purified water <sup>#</sup>	q.s	q.s	q.s	q.s	q.s
<b>Composition of extended release coating</b>					
Aqueous ethylcellulose dispersion	108	-	-	-	-
Ethyl cellulose (4cps)	-	33.75	-	-	-
Ethyl cellulose (7cps)	-	-	33.75	30.0	28.12
Hydroxy propyl methyl cellulose (5cps)	13	3.74	3.74	7.48	9.38
Isopropyl alcohol	-	320	320	285	318
Purified water	300	103	103	95	104

<sup>#</sup> Quantity taken based on number of cycles of extrusion

### Characterization of pellets

Pellets were characterized for percentage yield, drug content and friability.

### Drug content estimation by HPLC

The amount of drug present in the drug pellets and extended release pellets was assessed by official method in USP 2010 (Revision Bulletin) by HPLC equipped with a chromatographic system containing 220-nm detector and 4-mm × 15-cm column that contains 5- $\mu\text{m}$  packing L1 and software used was empower 2 version 5.03 (Shimadzu). The mobile phase was degassed mixture of phosphate buffer and acetonitrile (650:350). Phosphate buffer was prepared by dissolving 13.6 g of monobasic potassium phosphate in 2 L of water, and mixed. The solution was passed through a filter having a 0.5- $\mu\text{m}$  or finer porosity before use. Diluting solvent was 650 mL of water mixed

with 350 mL of acetonitrile. Standard solution was prepared by dissolving an accurately weighed quantity of PPNL HCl in methanol, diluted quantitatively and stepwise with methanol to obtain a solution having a known concentration of about 200  $\mu\text{g}$  per mL. 5 mL of this solution was transferred to a 50 mL volumetric flask; volume was made with diluting solvent and mixed.

The contents of 10 units were accurately weighed and transferred into a 500 mL volumetric flask. Methanol of 300 mL was added, swirled by mechanical means for 2 hours and allowed to stand for about 16 hours, then sonicated for one-half hour, and swirled for another one-half hour. This was quantitatively diluted with methanol to volume, mixed, and centrifuged a portion of the solution. An accurately measured volume of the clear solution was diluted with diluting solvent to obtain a solution having a concentration of about 20  $\mu\text{g}$  of PPNL HCl per mL.

The filtered mobile phase was pumped at a flow rate of 2 mL/min. The standard preparation was chromatographed and the peak responses were measured. The retention time (RT) of PPNL HCl was about 5 to 9 minutes; the column efficiency determined from the analyte peak was not less than 1000 theoretical plates; the tailing factor for the analyte peak was not more than 3; and the relative standard deviation for replicate injections was not more than 2%.

Equal volumes of standard preparation and assay preparation was injected into the chromatograph. Chromatograms were recorded and responses for the major peaks were measured. The quantity, in mg, of PPNL HCl ( $C_{16}H_{21}NO_2 \cdot HCl$ ) in each unit taken was calculated by the formula:

$$(LC/D)(r_U/r_S),$$

in which L is the labeled quantity, in mg, of PPNL HCl in each unit; C is the concentration, in  $\mu g$  per mL, of PPNL HCl in the Standard preparation; D is the concentration, in  $\mu g$  of PPNL HCl per mL, of the drug content preparation, based on the labeled quantity per unit, the number of units taken, and the extent of dilution; and  $r_U$  and  $r_S$  are the peak responses obtained from the drug content preparation and the standard preparation, respectively. A good linear relationship was observed between concentration and the peak area of PPNL HCl (high correlation coefficient,  $r=0.9999$ ).

### Scanning Electron Microscopy

Photomicrographs of coated and uncoated pellets were taken using a scanning electron microscope (Jeol-6380A, Japan Electron Optical Laboratory) for visualization of pellet surface morphology. Samples were prepared by placing pellets on a double adhesive carbon tape, which stuck to an aluminum stub and were then coated with platinum to a thickness of 300Å using a sputter coater (Auto Fine Coater Jeol, Tokyo, Japan) at the acceleration voltage of 20 mA, chamber pressure of 8 pas for 90 to 120 seconds to assure conductivity.

### Flow Properties

The flow properties of drug pellets and all the batches of extended release pellets were investigated by measuring the Bulk Density, Tapped Density and Hausner's ratio in triplicate.

### Friability

Resistance to abrasion was determined using an Erweka TAB apparatus. A sample of accurately weighed 20 gm uncoated or coated pellets and 10 gm of glass beads (diameter about 2 mm) were placed in friabilator and uniformly tumbled for 30 minutes at 20 rpm. Pellets were then weighed and friability was calculated according to:

$$\text{Friability \%} = (m_b - m_a) / m_b \times 100$$

Where  $m_b$  and  $m_a$  are the masses of pellets before and after testing and the result is the mean of three runs.

### Invitro dissolution studies of Pellets

Drug release profiles, according to the United States Pharmacopoeia (USP- NF 22) was carried out (six replicates) for extended release coated pellets using basket method in simulated gastric fluid (pH 1.2) followed by intestinal fluid (pH 6.8) without enzymes at 100 rpm. The coated pellets were placed in 900 mL of gastric fluid maintained at  $37 \pm 0.5^\circ C$ . After 1.5 hr, the dissolution medium pH was changed from 1.2 to 6.8 by adding 80 mL of conc. phosphate buffer to simulate intestinal fluid and was then run for the time specified. 5 mL of sample was removed at appropriate time intervals, filtered and analyzed using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, by comparison with a Standard solution in water having a known concentration of PPNL HCl. Released amounts of drug were then calculated as percent of total contents, as obtained from the sum of drug released during the test and the drug that had remained inside the pellets in milligram (mg). The mean and %RSD of dissolved drug was calculated.

### Similarity factor

Center for Drug Evaluation and Research (US Food and Drug Administration FDA) and European Medicines Evaluation Agency (EMA) consider some approaches such as difference ( $f_1$ ) and similarity ( $f_2$ ) factors to analyze the dissolution data equivalence. The main advantage of  $f_1$  and  $f_2$  equations is to provide a simple way to describe comparison of data. Difference factor ( $f_1$ ) measures the percent error between two drug release curves over all time points and computed using the following equation:

$$f_1 = \left\{ \frac{\sum_{j=1}^n |R_j - T_j|}{\sum_{j=1}^n R_j} \right\} \times 100$$

where  $R_j$  and  $T_j$  are the cumulative percentage of the drug dissolved at each of the selected 'n' time points of the reference and test product, respectively.

The similarity factor ( $f_2$ ) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test  $T_j$  and references products  $R_j$ , over all time points, n.

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{j=1}^n |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\}$$

Where  $w_j$  is an optional weight factor. This method is more adequate to compare dissolution profile when more than three or four dissolution time points are available and can only be applied if the average difference between  $R_j$  and  $T_j$  is less than 100. If this difference is higher than 100, normalization of the data is required [18].

### Kinetic modeling

In order to get more detailed information on the actual release mechanisms for PPNL HCl extended release pellets, the dissolution profiles were plotted in different plots and regression analysis was performed for each of them. Dissolution rate constants were determined for several release models such as zero order [ $Q_t = Q_0 + K_0 t$ ], first order [ $\ln Q_t = \ln Q_0 + K_1 t$ ] [19], Higuchi [ $Q_0^{1/2} - Q_t^{1/2} = K_2 t$ ] [20] and Korsmeyer-Peppas [ $Q_t/Q_\infty = K_3 t^n$ ] [21], where  $Q_t$  is the amount of drug released at time t;  $k_0$ ,  $k_1$  are the release rate constants;  $k_2$  is the diffusion rate constant and calculated correlation coefficients. Best fits were calculated on basis of the correlation factors as  $r^2$ .

### Accelerated Stability studies

Stability studies of the best fit formulation were conducted under accelerated conditions at  $40 \pm 2^\circ C$  / 75% RH for about 6 months in stability chamber (Thermo lab). Samples were collected at 1, 2, 3 and 6 months and analyzed for drug release.

## RESULTS AND DISCUSSION

### Formulation of extended release pellets

Drug pellets of PPNL HCl (64% w/w) were achieved by extrusion-spheronization using microcrystalline cellulose (Avicel PH101) as diluent. The percentage of microcrystalline cellulose with respect to active ingredient was 56% w/w.

Extended release polymers- different viscosity grades of ethylcellulose (aqueous dispersion, 4cps, 7cps) and HPMC (5cps) were used for coating [22]. Drug pellets of formulation PF-I were coated with aqueous ethylcellulose dispersion and HPMC (5 cps) in the ratio 71.4:28.6 at a coating level of 7.5% and 15% w/w to drug pellets. Whereas the formulation PF-II has combination of EC (4 cps) and HPMC (5 cps) and in PF-III, EC (7 cps) and HPMC (5 cps) were coated in the ratio 90:10 at a level of 7.5% and 15% w/w to drug pellets. A ratio of 80:20 and 75:25 of EC (7 cps) and HPMC (5 cps) at different coating levels of 5%, 6%, 7% and 8% w/w to drug pellets were coated to drug pellets of PF-IV and PF-V respectively [23].

As far as coating efficiency was concerned, all batches showed an excellent reproducibility of the desired coating levels as demonstrated by an actual weight gain of more than 99% of the theoretical weight gain.

**Table 2: Characterization, flow properties and friability of Propranolol Hydrochloride extended release pellets (Mean± SD, n=3)**

Formulation	%w/w ER coating	% Yield	% drug content	Bulk density (gm/mL)	Tap density (gm/mL)	Hauser ratio	%Friability
PF-I	7.5	93.1 ±0.66	98.2 ±0.91	0.75	0.77	1.03	0.15± 0.75
	15	94.8 ±0.23	97.5 ±0.02	0.77	0.78	1.01	0.10± 0.37
PF-II	7.5	95.6 ±0.54	97.8 ±0.24	0.72	0.74	1.03	0.21± 0.21
	15	96.1 ±0.21	97.2 ±0.15	0.74	0.75	1.01	0.19± 0.34
PF-III	7.5	94.3 ±0.11	98.5 ±0.31	0.75	0.77	1.03	0.13± 0.23
	15	96.4 ±0.38	98.1 ±0.67	0.71	0.74	1.04	0.11± 0.52
PF-IV	5	94.5 ±0.97	97.2 ±0.59	0.74	0.77	1.04	0.10± 0.11
	6	93.9 ±0.38	97.6 ±0.44	0.77	0.79	1.03	0.11± 0.54
	7	95.6 ±0.29	98.2 ±0.65	0.79	0.78	0.99	0.13± 0.21
	8	93.5 ±0.59	97.3 ±0.29	0.78	0.78	1.00	0.11± 0.34
PF-V	5	93.3 ±0.97	98.3 ±0.73	0.77	0.78	1.01	0.15± 0.52
	6	95.6 ±0.69	98.7 ±0.55	0.75	0.78	1.04	0.12± 0.47
	7	94.2 ±0.36	97.9 ±0.29	0.76	0.77	1.01	0.11± 0.44
	8	95.2 ±0.39	99.2 ±0.54	0.75	0.77	1.03	0.12± 0.23

### Characterization of pellets

The % yield, drug content and friability of drug pellets was found to be 98%, 98.1% and 0.12% respectively. **Table 2** shows the % yield, drug content, flow properties and friability of extended release pellets of formulations PF-I to PF-V.

### In vitro drug release studies

The percent drug release at 1.5, 4, 8, 14 and 24 hours were restricted to 15–30, 35–55, 55–75, 75–90 and 90–110 %, respectively according to the USP specifications. The drug release profiles of different coating levels of extended release pellets in dissolution media are shown in **Figure 1-4**.

The dissolution data clearly depicts the influence of different viscosity grades, coating levels and ratios of extended release polymers on the dissolution rate of PPNL HCl for the formulation PF-I to PF-V. *In vitro* drug release profiles revealed that drug release was faster with combination of aqueous dispersion of EC and HPMC (5cps) whereas considerably slow with increased viscosity grades of EC and HPMC (5cps). A fact of interest was the concentration of EC and HPMC also significantly affect the drug release rate. PF-I formulated with aqueous dispersion of EC and HPMC (5cps) does not show much effect on drug retardation even at different extended release coating levels i.e., 7.5% and 15% w/w to drug pellets (**Figure 1**). The release studies of the formulation PF-II coated with EC (4cps) and HPMC (5cps) in the ratio 90:10 demonstrated that the drug release from extended release pellets was retarded to an extent but 100% release was found within 14 hours in both 7.5% and 15% w/w coating levels to drug pellets. Comparing the release profiles of formulations PF-I to PF-II from **Figure 1**, it was evident that the drug diffusion from drug pellets with the combination of EC (4cps) and HPMC (5cps) was controlled than with aqueous EC and HPMC (5cps). As these formulations did not show any burst release, the reduced possibility of dose dumping was indicated with the combinations of higher viscosity grades of EC and HPMC.

PF-III formulated with EC (7cps) and HPMC (5cps) in the ratio 90:10 showed drug retardation at 8 to 24 hours at coating levels 7.5% and 15% w/w (**Figure 1**) to drug pellets. The literature revealed [7] that the hydrophobic nature of EC restricts the penetration of medium and

retards the release of the drug. In line with this, drug pellets in PF-IV were coated with EC (7 cps) and HPMC (5 cps) in the ratio 80:20 at an average weight build up of 5%, 6%, 7% and 8% w/w to drug pellets to study the affect of amount of coating levels on drug release. It was observed that 100% drug release was not obtained at the end of 24 hours in all the coating levels as shown in **Figure 2**. This might contribute to lower concentration of HPMC, a hydrophilic polymer which can enhance the drug release in combination with a hydrophobic polymer like ethyl cellulose. A known fact that HPMC enhances drug release by swelling, dissolving and forms as opening channels through which dissolution media could enter the core (pore former). Further to enhance the drug release, in formulation PF-V, EC (7 cps) and HPMC (5 cps) were used in the ratio 75:25 and coated at different levels of extended release coating. Drug pellets with a coating level of 5% w/w to drug pellets showed more than 50 at 15 hours; 100% drug release was observed with 6% and 7% w/w coating level to drug pellets at 14 hours; and with 8% w/w coating level to drug pellets the dissolution studies clearly indicate the drug release in extended pattern as observed in **Figure 3**. Therefore, these observations suggest that average weight buildup of 8% w/w to the drug pellets of this formulation was considered to be ideal for formulating extended release pellets of PPNL HCl. The results were in accordance with the USP specifications and also comply with the marketed product (*INDERAL LA*) [20- 21].

### Similarity factor

The difference factor ( $f_1$ ) fits the result between 0 and 15 and similarity factor ( $f_2$ ) 50 and 100 ensure dissolution profile and the sameness or equivalence of the two curves and thus the performance of the two products. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity ( $f_1$ ) increases. The difference factor  $f_1$  and similarity factor  $f_2$  values calculated for optimized formulation PF-V were 6.48 and 61.53 respectively.

### Kinetic models

Release kinetics of formulations PF-I to PF-V and marketed product (*INDERAL LA*) were fitted to different kinetic models and were summarized in **Table 3**. As expected, the formulation PF-V 8% w/w coating level to drug pellets follows first order kinetics and complies with standard limits.

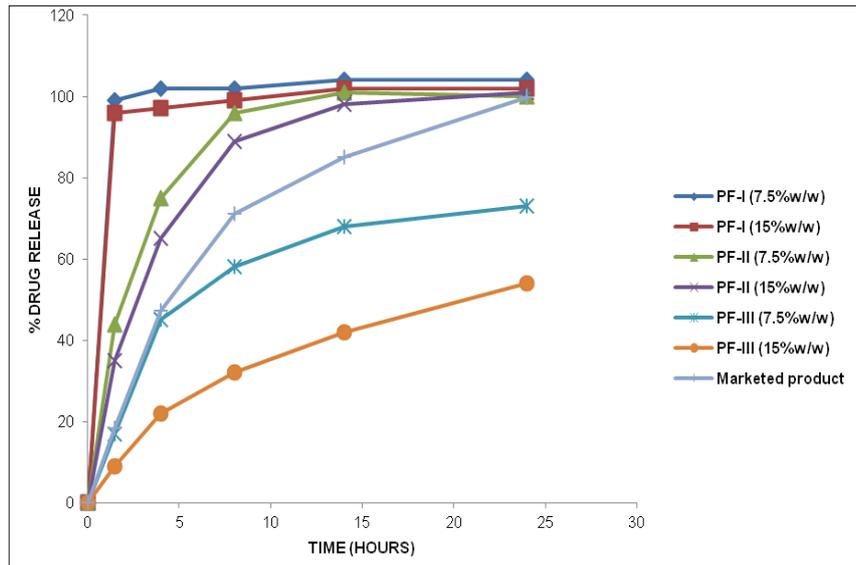


Fig. 1: Dissolution profiles of formulations PF-I, PF-II, PF-III with 7.5% and 15% w/w ER Coating to drug pellets and marketed product

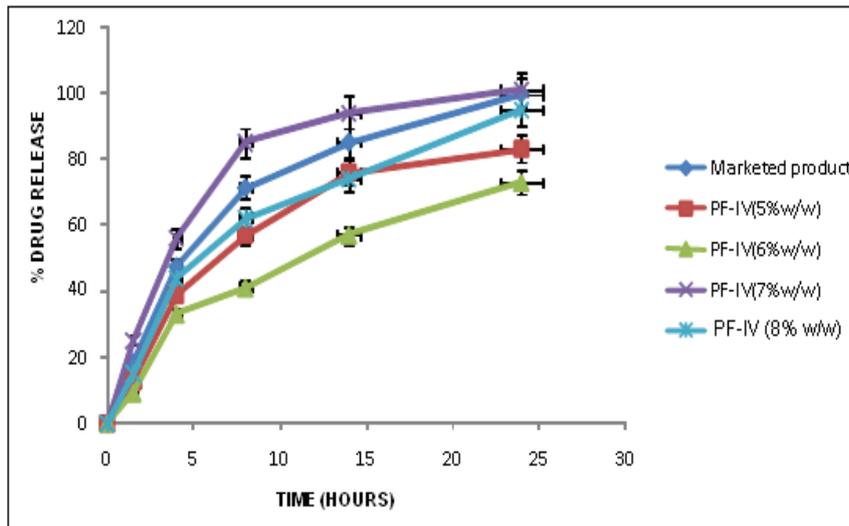


Fig. 2: Dissolution profiles of formulations PF-IV with 5%, 6%, 7% and 8% w/w ER coating to drug pellets and marketed product

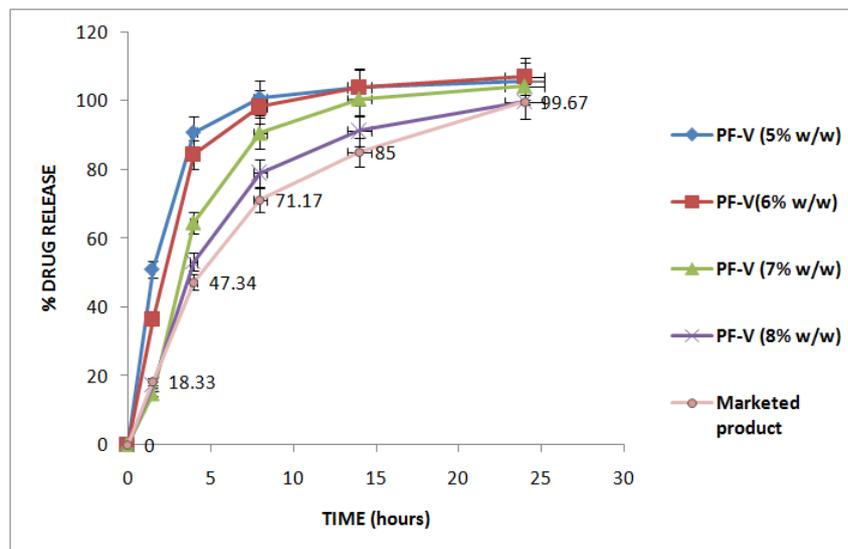


Fig. 3: Dissolution profiles of formulation PF-V 5%, 6%, 7% and 8% w/w ER coating and marketed product

Table 3: Release kinetics

Formulation	%w/w ER coating	Zero order	First order	Higuchi	Korsmeyer-Peppas
PF-I	7.5	0.811	1.00	0.848	0.875
	15	0.922	0.705	0.865	0.793
PF-II	7.5	0.785	0.991	0.891	0.939
	15	0.843	0.997	0.942	0.958
PF-III	7.5	0.722	0.850	0.861	0.920
	15	0.928	0.962	0.990	0.975
PF-IV	5	0.819	0.948	0.933	0.960
	6	0.902	0.978	0.972	0.919
	7	0.722	0.972	0.863	0.953
	8	0.875	0.978	0.961	0.934
PF-V	5	0.498	0.992	0.659	0.785
	6	0.546	0.994	0.760	0.796
	7	0.626	0.985	0.784	0.811
	8	0.741	0.975	0.878	0.887
Marketed product	-	0.835	0.935	0.942	0.936

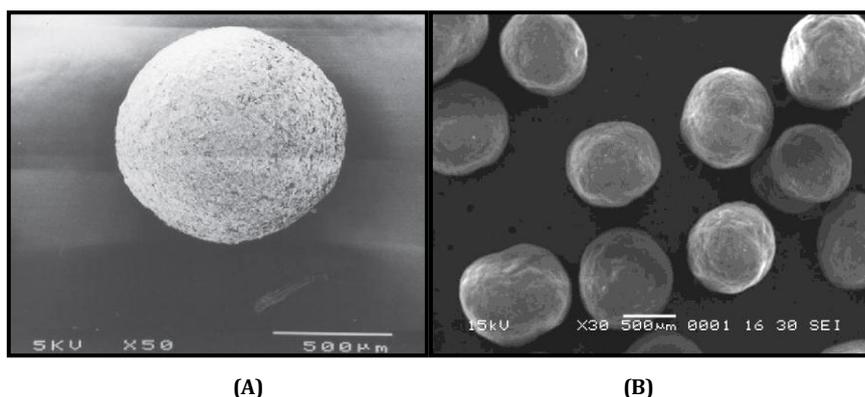


Fig. 4: SEM analysis (A) Drug Pellet (B) PF-V (8% w/w) extended release pellets

### Scanning Electron Microscopy

This is the technique of choice for measuring the shape and surface morphology of the pellets to support visually the other qualitative and quantitative results. Shape and surface morphology of the selected pellet formulations of PF-V 8% w/w (drug pellet and extended release pellets) are mentioned in **Figure 4**. Photographs indicated that drug pellets by extrusion-spheronization were uniform, spherical shape and porosity was less.

### Accelerated Stability studies

The extended release pellets of PF-V 8% w/w coating level to drug pellets showed no significant change in *invitro* release profile and found that the formulation was a stable one at 40°C/75%RH for 6 months.

### CONCLUSION

The observations of the research work were in agreement with those of the earlier reports [6, 7, 8, 9, 11, 12, 13, 16]. The influence of different viscosities and different polymer ratios on drug release was evident in the present work. The most important parameters were the type and the applied level of coating polymer. The dissolution data clearly over-rides the influence of different viscosity grades and % w/w coating levels of extended release polymers on the dissolution rate of PPNL HCl. A fact of interest was that the ratios of EC and HPMC also significantly affect the drug release rate. The current results demonstrated that among the all viscosity grades combination of EC (7cps) and HPMC (5cps) in the ratio 75:25 was qualitatively consistent.

In conclusion, the investigation summarized the findings attributed that the combination of both hydrophobic and hydrophilic polymers successfully employed a stable formulation of multiple unit extended release pellets of an extremely water soluble, short half-life antihypertensive model drug, Propranolol Hydrochloride.

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