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Research Article

Formulation and Optimisation of Osmotic pump of Propranolol Hydrochloride using EOP and Microporous concepts

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ABSTRACT

Propranolol Hydrochloride is class I drug and hence completely and rapidly absorbed which shows quick but shorter action which leads to frequent dosing. This fact gives opportunity to develop controlled release formulation. The controlled release tablet of Propranolol hydrochloride was prepared based on osmotic pump technique. Core tablet of Propranolol hydrochloride was prepared using Sodium chloride, Mannitol, PVP K30, MCC, talc & Mg. stearate; and the tablets of selected batch was coated with coating solution containing different proportions of Cellulose acetate, Castor oil and PEG400 and evaluated for in vitro drug release studies. The comparison study of the formulations has shown that all batches showing sustained release profile following zero order and batch F3 showing the maximum correlation with zero order release and hence considered as optimized batch. The observed result revels that osmotic agents have significant effect on drug release up to 12h. in successful development of dual release osmotic pump tablets containing Propranolol Hydrochloride by using Sodium chloride and Mannitol as key excipients.

Keywords: Controlled release tablet; Elementary Osmotic Pump; Mannitol; micro porous osmotic pump; Poly ethylene glycol 400; Propranolol hydrochloride; sodium chloride.

INTRODUCTION

Propranolol Hydrochloride [PHC] is a nonselective β-adrenergic blocking agent widely used for the treatment of hypertension, angina pectoris and migraine. It is BCS class I drug, having high solubility and high permeability, and is almost completely absorbed after oral administration. Apart from other BCS classes which shows solubility or permeability problems leading to poor bioavailability, BCS class I drugs, like Propranolol hydrochloride, have challenge of shorter half life (about 3 hours) which requires frequent dosing which end with poor patient compliance. Thus a controlled release dosage form of Propranolol hydrochloride is desirable. (Cid et al, 1986; Walle et al, 1976)

Studies of the controlled release of drugs for their extended and safe use have recently become an important field of research. By using oral controlled drug delivery system can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit. Also the systems that target the drug delivery to a specific region within the GI tract for either local or systemic action (Salsa et al, 1997).Among controlled-release devices, osmotically driven systems hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero-order rates for prolonged periods (Theeuwes, 1981; Eckenhoff et al, 1981; Eckenhoff et al, 1981; Bindschaedler et al, 1986; Verma et al, 2000; Verma et al, 2002). Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery (Santus et al, 1995; Verma et al, 1999; Ramakrishna et al, 2001).

The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate (Ozdemir et al, 1997; Theeuwes, 1975). To gain the advantages of pH and agitation independent release performance leading to similar *in vitro/in vivo* delivery, osmotically active drug delivery systems have been extensively investigated. Oral controlled release system provides greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule. (Theeuwes, 1975; Mc Clelland et al, 1991; Rose te al, 1995; Zentner et al, 1985)

The drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within

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Table 1: Composition of core tablet

Ingredients	P1	P2	P3	P4	P5	P6
Propranolol HCl	80	80	80	80	80	80
Mannitol	125	150	175	0	0	0
Nacl	0	0	0	80	110	130
PVP K30	20	20	20	20	20	20
MCC	155	130	105	200	170	150
Talc	3	3	3	3	3	3
Mg.stearate	6	6	6	6	6	6
Total Wt.	**389**	**389**	**389**	**389**	**389**	**389**

Table 2: Composition of coating solution

Ingredients	Amount
Ratio of CA:PEG400	75:25
Castor oil (ml)	0.15
Weight gain (%)	3

the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Preparation of an elementary osmotic pump consists of the core containing the active material and a semi permeable membrane that coats the core, having a micro drill produced orifice in order to release the active material. When the system happens to be inside the gastrointestinal tract, the fluid enters the core through the membrane and dissolves the active material. (Zentner et al, 1985; Theeuwes, 1981; Ozdemir et al, 1997)

MATERIALS

Propranolol Hydrochloride (99.9% purity) was obtained as a gift sample from Zydus Cadila Health Care, Ahmedabad, Gujarat, India. Cellulose acetate, microcrystalline cellulose (pH 101), talc and magnesium stearate were purchased from S. D. Fine Chemicals Ltd., Mumbai, Maharastra, India. PEG 400, acetone, NaCl, Mannitol were purchased from Monokem Laboratories, Ahmedabad, Gujarat, India.

METHOD

Preparation of Core Tablets

Osmotic tablets were prepared by wet granulation method according to composition given in Table 1. All the ingredients and drug were accurately weighted and mixed in mortar with a pestle for 10 minutes to get the uniform mix. The dry blend was granulated with sufficient quantity of PVP K30 which was dissolved in isopropyl alcohol. The powder mass was dried at 60 ºc in hot air oven for 6 h and pass through sieve no. 20. The dried granules were mixed with magnesium stearate and talc for 3 min. The blended powder was then compressed by single station rotary tablet compression machine. (Karnawati Engineering, Ahmedabad).

Coating of tablets

Coating solutions[4%w/v] were prepared by mixing required quantity of cellulose acetate (semi-permeable membrane forming agent) ,PEG 400 (pore forming agent) and castor oil [20% v/w of total solid CA] (plasticizer) in acetone as specified in the Table 2 and stirred on magnetic stirrer to get homogeneous coating solution. Then the tablets were coated using small size coating pan made up of stainless steel with rotation speed of 25 rpm and 55° C temperature of hot air. Then the tablets were kept in oven at 40° C for about 24 hours and weighed to calculate the percentage weight gain. The tablets were coated repeatedly until the required weight gain was achieved.

EVALUATION

Thickness

The thickness of the core & coated tablets were measured by using weight gain method. Ten tablets from each formulation were randomly selected and used. Thickness is measured in millimetre.

Hardness

The hardness of the core tablet and coated tablets were measured using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm2.

Friability

Friability of the matrix tablets and core tablets of porous osmotic pump tablets were determined 10 tablets are randomly selected, weighed and placed in the Roche friabilator. The apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dedusted and weighed again .The % friability was measured using the formula,

$$\%friability = \frac{Initial\ weight\ of\ the\ tablets - Final\ weight\ of\ the\ tablets}{Initial\ weight\ of\ the\ tablets} \times 100$$

Weight uniformity

The tablets were randomly selected from each batch and individually weighted. The average weight and standard deviation of 20 tablets were calculated.

Table 3: Evaluated parameters of uncoated PHC osmotic pump

Parameters	P1	P2	P3	P4	P5	P6
Weight variation	Pass*	Pass*	Pass*	Pass*	Pass*	Pass*
Hardness	3.5 kg/cm^2	3.2 kg/cm^2	3.4 kg/cm^2	3.5 kg/cm^2	3.6 kg/cm^2	3.6 kg/cm^2

According to USP the % variations of all batches are not exceeding 5% hence all batches passes the tests

Table 4: Evaluated parameters of coated PHC osmotic pump

Parameter	F1	F2	F3	F4	F5	F6
Hardness	4.8 kg/cm^2	4.6 kg/cm^2	4.4 kg/cm^2	4.9 kg/cm^2	4.6 kg/cm^2	4.8 kg/cm^2
Friability (%)	0.376	0.459	0.498	0.469	0.472	0.386
Weight variation	Pass*	Pass*	Pass*	Pass*	Pass*	Pass*
Uniformity of content	97.9	98.3	98.9	97.8	98.4	98.5

According to USP the % variations of all batches are not exceeding 5% hence all batches passes the tests

Table 5: In vitro drug release in percentage study of Propranolol Hydrochloride preliminary batches

Time in Hour	P1	P2	P3	P4	P5	P6
1	24.89	23.28	26.39	18.90	22.23	22.67
2	42.56	48.23	47.18	40.89	45.5	43.26
3	63.78	65.34	70.45	63.67	77.21	66.42
4	80.45	83.39	87.27	85.56	87.95	84.25
5	92.76	93.45	99.78	90.63	95.21	94.37

Tablet dosage forms assay*:* Five tablets were taken and finely powdered; quantities of the powder equivalent to 80mg of Propranolol hydrochloride were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with phosphate buffer (pH 6.8) solution and mixed thoroughly. The solution was made up to volume and filtered. Form this stock solution, 10 ml solution was taken and diluted to 200ml with phosphate buffer and the absorbance of the resulting solution was measured at 289nm using a Shimadzu UV-Visible double beam spectrophotometer.

In vitro drug release studies*:* In vitro release study was performed using USP type II apparatus (Veego VDA-6D USP Standard) in phosphate buffer pH 6.8 medium for 12 hours with the temperature maintained at 37 ± 0.5° C and the stirring speed of paddle was adjusted to 50 rpm. Samples of 5ml were withdrawn at different preset time intervals, filtered and analyzed using spectrophotometer at 289nm.

Curve fitting analysis

For the determination of the of the drug release kinetics from the porous osmotic pump tablets, the invitro release data was analyzed by zero order, first order, Higuchi and Krosmeyer and peppas equations.

1) Zero order release kinetic

To study the zero order release kinetics the release data was fitted into the following equation:

$$DQ/dt=Ka$$

Where "Q" is the amount of drug release 'Ko' is the zero order release rate constant and't' is the release time. The graph is plotted percentage cumulative drug release verses time.

2) First order release kinetic

To study the first order release kinetics the release rate data are fitted into the following equation:

$$DQ/dt=K1Q$$

Where,'Q' is the fraction of drug release,'K1' is te first order release constant and't' is the release time. The graph is plotted log % CDR remaining verses time.

3) Higuchi release model

To study the Higuchi release model the release rate data are fitted into the following equation:

$$Q=KH\ t1/2$$

Where 'Q' is the fraction of drug release 'KH' is the release rate constant and't' is the release time. The graph is plotted %CDR verses square root of time.

4) Krosmeyer peppas release

To study the Krosmeyer & Peppas release kinetics the release rate data are fitted in the following equation:

$$Mt/Minfi=Kkp\ tn$$

Where Mt/Minfi is the fraction of drug release, 'KHP' is the release rate constant and't' is the release time and 'n'is the diffusion exponent related to mechanism of drug release. The graph is plotted log %CDR verses log time.

RESULT AND DISCUSSION

Physicochemical properties

The value of hardness, weight variation of prepared core tablet is recorded in table no.3.1. The hardness,

Table 6: In vitro drug release study of Propranolol Hydrochloride after coating process

Time	F1	F2	F3	F4	F5	F6
1	5.1	6.7	7.01	3.39	4.03	6.53
2	11.46	13.24	15.31	11.84	10.43	14.55
3	15.24	18.76	24.56	16.99	16.76	20.47
4	21.65	23.46	31.91	28.89	22.19	31.32
5	27.65	29.99	42.85	33.59	28.46	36.32
6	32.34	35.39	45.95	42.95	32.95	42.16
7	48.26	52.17	56.92	47.89	43.76	47.95
8	54.78	59.88	65.23	54.12	50.35	64.02
9	60.35	64.95	72.58	64.24	61.38	69.04
10	68.25	73.43	81.9	73.1	69.46	75.51
11	72.59	78.02	90.21	75.63	79.47	87.93
12	78.31	84.51	98.45	77.98	86.39	91.86

Table 7: Summary of drug release kinetic of formulations

Batch	Regression coefficient (R)			
	Zero-order	First-order	Higuchi	Korsmeyer- peppas
F1	0.988	0.909	0.901	0.992
F2	0.987	0.921	0.904	0.989
F3	0.998	0.770	0.878	0.927
F4	0.99	0.813	0.901	0.984
F5	0.989	0.9	0.882	0.997
F6	0.992	0.897	0.889	0.994

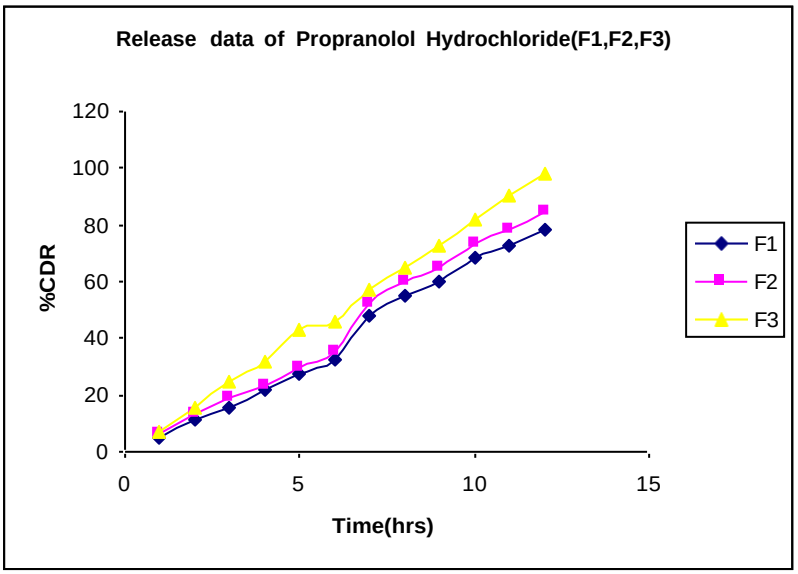

Figure 1: Release data of Propranolol Hydrochloride Tablets (Formulations F1, F2, F3)

friability, weight variation, uniformity of content of prepared coated tablet is recorded in table no.3.2.

Here tablets before coating were coded as P1, P2, P3, P4, P5, and P6. These same tablets were after coating coded as F1, F2, F3, F4, F5, and F6. This different coding is given to differentiate the evaluation tests done in to different steps.

***In vitro* dissolution study**

Table 3.3 shows that without coating none of the batch give controlled release and release of drug limited to 5 hr only which are not meeting the objectives and all the batches shows good and satisfactory release data and selected for the next step for coating them.

In porous osmotic pump tablet the drug release rate is depends on the concentration of osmotic agent and pore former used. The osmotic agent concentration increases then osmotic pressure created inside the tablet also increase; the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug so the release of the drug also will increase. The pore former is added here in coating solution so, it will cause easy leaching out of the drug from the formulation. Here

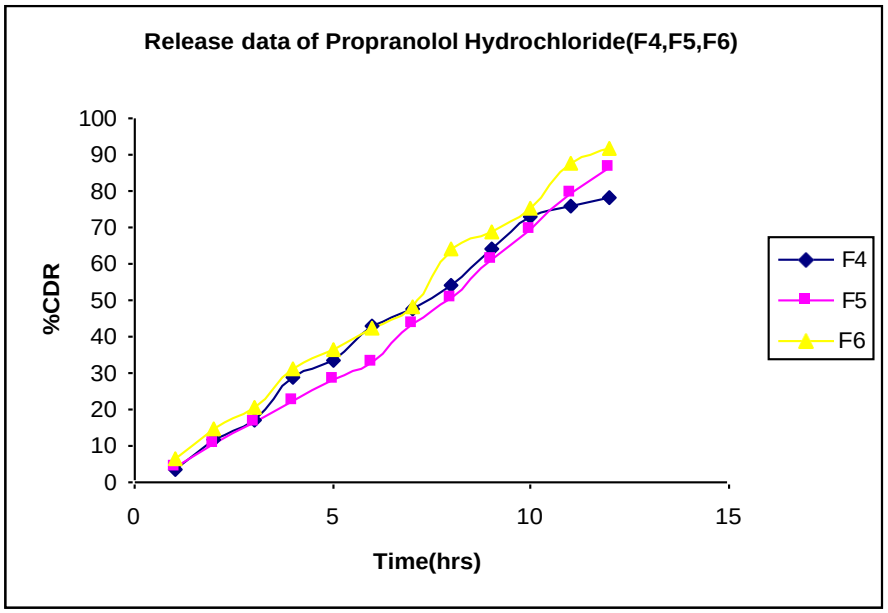

Figure 2: Release data of Propranolol Hydrochloride Tablets (Formulation F4, F5 ,F6)

the mechanical drilling was done for orifice formation after drying of the coating layer. So here the dual concepts of EOP as well as micro porous were used in for release of the drug from tablets. Table 3.4 shows that all 6 batches are showing release up to 12hrs and in that F3 is optimized based on release profile as shown in figure 1.

Curve fitting analysis

The *in vitro* release data was fitted to various kinetic models like Zero order, First order, Higuchi and korsmeyer Peppas, which is given in the Table no 3.5. When data were plotted according to first-order equation, the formulation F3 showed comparatively poor linearity with regression value of 0.770; whereas the regression value for zero-order equation was 0.998, which indicated that drug release from optimised formulation (F3) was independent of drug concentration.

CONCLUSION

The observed independent variables were found to be very close to predicted values of optimised formulation which demonstrates the feasibility of the optimization procedure in successful development of dual concept osmotic pump tablets containing Propranolol HCL (80mg) by using Nacl and mannitol as osmotic agents and PEG 400 as pore former.

REFERENCES

Bindschaedler, C., Gurny, R. and Doelker, E. 'Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate', J. Contr. Rel, vol. 4, 1986 pp. 203–212.

Cid, E., Mella, F., Lucchini, L., Carcamo, M., Monasterio, J. 'Plasma concentrations and bioavailability of Propranolol by oral, rectal and intravenous administration in man', Biopharm Drug Dispos, vol. 7, 1986 pp. 559-566.

Eckenhoff, B. and. Yum, S. I. 'The osmotic pump; novel research tool for optimizing drug regimens', Biomaterials, vol. 2, 1981 pp. 89–97.

Eckenhoff, B., Theeuwes, F. and Urquhart, J. 'Osmotically activated dosage forms for rate controlled drug delivery', Pharm. Technol, vol. 5, 1981 pp. 35–44.

Mc Clelland, G.A., Sutton, S.C., Engle, K. and Zentner, G.M. 'The solubility- modulated osmotic pump: *in vitro/in vivo* release of diltiazem hydrochloride', Pharm. Res, vol. 8, 1991 pp. 88–92.

Ozdemir, N. and Sahin, J. 'Design of a controlled release osmotic pump system of ibuprofen', Int.J. Pharm, vol. 158, 1997 pp. 91–97.

Ramakrishna, N. and Mishra, B. 'Design and evaluation of osmotic pump tablets of naproxen sodium', Pharmazie, vol. 56, 2001 pp. 958–962.

Rose, S. and Nelson, J.F. 'A continuous long-term injector', Austral. J. Exp. Biol, vol. 33, 1995 pp. 415–420.

Salsa, T., Veiga, F. and Pina, M.E. 'Oral controlled release dosage forms I. Cellulose ether polymer in hydrophilic matrices', Drug Dev. Ind. Pharm., Vol. 23, 1997 pp. 929–938.

Santus, G. and Baker, R.W. 'Osmotic drug delivery; a review of patent literature', J. Contr. Rel, vol. 35, 1995 pp. 1–21.

Theeuwes, F. 'Drug delivery systems', Pharm. Ther., vol. 13, 1981 pp. 149–191.

Theeuwes, F. 'Elementary osmotic pump', J. Pharm. Sci, vol. 64, 1975 pp. 1987–1991.

Verma, R.K. and Mishra, B. 'Studies on formulation and evaluation of oral osmotic pumps of Nimesulide', Pharmazie, vol. 54, 1999 pp. 74–75.

Verma, R.K., Krishna, D.M. and Garg, S. 'Formulation aspects in the developments of osmotically controlled oral drug delivery system', J. Contr. Rel, vol. 79, 2002 pp. 7–27.

Verma, R.K., Mishra, B. and Garg, S. 'Osmotically controlled oral drug delivery', Drug Dev. Ind.Phar, vol. 26, 2000 pp. 695–708.

Walle, T., Conradi, E.C., Walle, U.K., Fagan, T.C., Gaff ney, T.E. 'The predictable relationship between plasma levels and dose during chronic Propranolol therapy' Clin Pharmacol Ther, vol. 24, 1978 pp. 668-677.

Zentner, G., Rork, G. and Himmelstein, K. 'The controlled porosity osmotic pump', J. Contr. Rel, vol. 1, 1985 pp. 269–282.