FORMULATION, EVALUATION AND SPECTROSCOPIC VALIDATION OF LABETALOL HYDROCLORIDE SR TABLETS USING VARIOUS VISCOSITY GRADES OF HPMC

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ABSTRACT

The primary objective of sustained release drug delivery system is to ensure safety and to improve efficacy of drugs as well as patient compliance by controlling the drug release pattern within narrow therapeutic range, leading to minimize the side effect and ensure the safety. The aim of the study is to design, characterize and evaluate Labetalol hydrochloride sustained release tablets using various viscosity grades of HPMC. The principal physiologic action of Labetalol is to competitively block adrenergic stimulation of β-receptors within the myocardium (β1-receptors) and within bronchial and vascular smooth muscle (β2-receptors), and α1-receptors within vascular smooth muscle which causes a decrease in systemic arterial blood pressure and systemic vascular resistance without a substantial reduction in resting heart rate, cardiac output, or stroke volume, apparently because of its combined α- and β-adrenergic blocking activity. The author in the presence study attempts to formulate the sustained release tablets of Labetalol HCl using different viscosity grades of HPMC i.e. HPMC K4m, HPMCK_{15}M, HPMC K_{100}M with different drug polymer ratio to reducing the dosing frequency, minimize the flections of plasma drug concentration, evaluation has been done of the prepared formulation and compared with the standard. The prepared granules were free flowing and characterized for drug content, DSC, X-ray diffraction study and FTIR. The X-ray diffraction study & DSC obtained from various formulations showed no interaction within these formulations. The in-vitro release studies were performed using pH 7.4 phosphate buffer for 12 hours from which the different drug polymer ratios are followed zero order kinetics. The analytical validation by UV spectroscopic method of the formulation for specificity, Linearity, Accuracy, Precision and intermediate precision and stability of the solution over desired period of time is carried out.

Key words: Labetalol Hydrochloride, DSC, FTIR. HPMC, Analytical validation.

INTRODUCTION:

The term 'Sustained Release' is known to have existed in the medical and pharmaceutical literature for many decades. Sustained release has been constantly used to retard the release of therapeutic agent such that its appearance in the circulation is delayed or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed and duration of therapeutic action is sustained. [1]

The major objectives of the novel controlled release drug delivery system are to fulfill the entire therapeutic requirement and increasing patient compliance. [3] Generally a dosage form consists of one or more active ingredient together with a varying number of other substances (excipients). These excipients enomorously influence the physico-chemical characteristic of the final product. It is now recognized that the excipients can potentially influence the rate and extent of absorption of a drug. [6] Therefore a well established formulation depends on the careful selection of excipients. [2] By reviewing the present and past scenario, it is never worthless to mention the use of polymer as a formulation aid in sustained drug delivery systems become is important area of research and development. [5]

MATERIALS AND METHODS:

1. Materials:

Labetalol Hydrochloride was obtained as gift sample from Caplin Point Laboratories Ltd Chennai. HPMC K4M, K15M, K100M were obtained from M/s Ranbaxy Lab, Gurgaon. [14] PVP, IPA, Sodium Hydrogen Pellet Purified were collected from CDH Pvt. Ltd., New Delhi. Magnesium Stearate and Lactose Monohydrate were received from Lobachem, Pvt. Ltd. Mumbai. Potassium Dihydrogen Orthophosphate was collected from S.D. Fine Chemicals, Mumbai. Other chemicals were of analytical reagent grade**.** [11]

2. Apparatus & Equipments:

The UV/ VIS. Spectrophotometer is of Elico, India Ltd., Dissolution Apparatus is of USP 8 basket Digital Test Apparatus Lab India (Disso-2000) Mumbai., Mechanical Sieve Shaker is of Comprit Electrical Company India, Sieve set is of ASTM Standard Sieves, SISSO, India, Tablet Compression Machine (Single Station) is of Cadmach Machinery Co. Pvt. Ltd., India., Roche friabilator is of Rolex Pvt. Ltd., India., Tablet hardness Tester is of Cadmach Machinery Co. Pvt. Ltd., India., Tray Drier is of Rolex Pvt. Ltd., India , Single Pan Balance is of Adair Dutta AD –50 B, Kolkata., DSC is of Mettler Star^{e} SW 8.01, FTIR is of Parkin Elmer (Paragon), Distillation Apparatus and Glass ware, pipette, beakers, volumetric flask is of Borosil type. [17]

3. Preformulation studies:

The drug was characterized for Density Measurement i.e. Bulk density, Tapped density, Flow property i.e. Angle of Repose, Carr's index and Hausner's Ratio. [3] FTIR study was carried out to identify the drug samples in Alkem Laboratories, Daman, using PARKIN – ELMER FTIR by preparing Potassium Bromide pellet of the sample using Potassium Bromide press. [15] The IR spectrum of the sample of pure drug was preliminary identification of the sample by comparing it with reference standard. The sample give exact absorbance peaks with standard hence the sample is in pure form. [16] DSC studies of individual drug and mixture of excipient with drug in 1: 1 ratio was studied to see whether any interaction exists or not. In the present study no significant interaction was found between the drug and excipients.

4. Preparation of Labetalol Hcl SR Tablets using various viscosity grades of HPMC:

All the formulations were formulated by wet granulation method. Different viscosity grades of HPMC such as HPMC K4M, HPMC K15M and HPMC K100M are used in the study. Binders used in granulation were PVPK30 and Isopropyl alcohol (as binder solution). Labetalol HCl, HPMC of suitable grade (both passed through # 60) and lactose were weighed according to the formula given in the table No.13 and mixed properly. [5] PVPK30 was weighed and dissolved in 10 ml of IPA then stirred properly in a mechanical stirrer. Wet granulation was done by adding small amount of PVPK30 solution to the mixture to prepare damp mass followed by passing through # 10 for granulation and Drying for 30 minutes at room temp in open air. Then it was kept in the tray drier for 2 hrs at 40^{0}C.The dried granules again passed through # 16 and lubricated using magnesium stearate followed by compression using single paunch cad mach tablet compression machine with 12 mm punch. [4]

5. Physical characterization of Labetalol Hydrochloride SR Tablets:

The quality control tests for the tablets, such as hardness, friability, weight variation etc. were determined using reported procedure of pharmacopoeia. The tablet crushing strength was tested by commonly used Dial tablet hardness tester. Friability was determined b y Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Weight variation was determined by weighing 20 tablets individually, the average weight Physical characters observed for various batches. [7].

6. In-vitro Dissolution Study:

In-vitro dissolution studies were designed to carry out in such a way that they simulate in vivo conditions. The purpose of in-vitro release study was to provide a fast, easily performed and in-expensive method that correlates with the performance of dosage form in human subjects. The conditions of in-vitro dissolution test were very well defined standardized and enabling comparison between various results. [3] For in-vitro dissolution study it was decided to carry out the dissolution in 0.1 N HCl. The apparatus used is USP XX Apparatus I (Rotary basket) having Sampling interval 0.5th, 2nd, 4th, 8th and 12th hr. Directly 0.9ml sample was pipetted out, filtered and diluted to 25ml with respective dissolution medium and absorbance seen directly against the blank (respective dissolution medium) using UV spectro- photometer at 302nm. [8]

7. Analytical Validation Study:

An UV/Vis spectrophotometrically method based on the measurement of absorbance at 302 nm in 0.05M sulphuric acid for estimation of Labetalol hydrochloride is used. From final formulation of prepared tablets, 10 tablets were collected randomly and powdered. A quantity of powder equivalent to 500 mg of Labetalol hydrochloride was transferred into a 250 ml volumetric flask and shake for 30 minutes. Make up the volume with the same, mix and filter. Pipette out 10 ml of filtrate into a 250 ml volumetric flask and dilute to

volume with 0.05 M sulphuric acid. The drug content as estimated by measuring the absorbance of both standard and sample solutions at 302 nm using UV/Vis spectrophotometer. By using placebo, specificity study was carried out. Precision and intermediate precision, Accuracy, Linearity and solution stability was carried out according to ICH guidelines.

RESULTS AND DISCUSSION:

In this present investigation sustained release tablets of Labetalol Hydrochloride were prepared by wet granulation technique using various viscosity grades of HPMC like HPMC K4M, K15M and K100M.Different formulations (F1 – F6) prepared with drug and individual viscosity grades of HPMC like HPMC K4M +K15M , HPMC K4M +K100M , HPMC K15M +K100M in same ratio. Organoleptic characteristics of pure drug (Ciprofloxacin Hydrochloride) showed that the drug is pure in nature. Spectroscopy study of pure drug showed that maximum wavelength was found to be 302nm. From the pre formulation aspects, compressibility index and angle of repose of all formulations the formulations having excellent flow property comparison to pure drug having poor flow property. The evaluation of tablets study reveals that all formulations carried out for physical parameters like hardness, thickness, friability, weight variation, % of drug content and drug release which shows satisfactory results. Besides other evaluation parameters i.e. Weight variation and Friability of tablets were within IP limits followed by Hardness & thickness. In-vitro dissolution study of pure drug and formulations were carried out with 0.1 N Hcl using basket at 100 rpm which shows that 99.59 % drug release in 60 minutes and 99.48% drug released(F7)at 12 hours. From the dissolution data of all formulations, it is concluded that F7 (HPMC K4M +K15M, 1: 0.25) showed better reproducibility comparison to all the formulations and maintains sustained effects. All the formulations followed Zero order release Kinetics. The FTIR study of pure drug and polymer like different viscosity grades of HPMC showed that there is no interaction between the drug and polymers. The DSC study of pure drug & polymers like different grade of HPMC showed that the endothermic peak leading to melting of pure drug and formulations.

The UV spectroscopic validation of the formulation for specificity, Linearity, Accuracy, Precision and intermediate precision and stability of the solution over desired period of time is highly appreciable and is within the limit. As per specificity interference from Placebo should not be more than 2.0 % where the obtained result is 1.39 %. From stability point of view the absorbance of analyte in test solution should not differ by more than 2.0 % from initial absorbance for the accepted storage time and the result is 0.71 %. From 50 % to 150 % of targeted concentration of the formulation, the linearity correlation coefficient (r^2) should not be less than or equal to 0.995 and the obtained result is 0.999. Accuracy in terms of recovery from 50% to 150% of targeted concentration, the recovery at each level should be between 98.0 % – 102.0 % and the % RSD should not be more than 2.0 and the result is quite inspiring of recovery 98.3% to 100.0% and % RSD is 0.78% to 1.71%. Method precision and intermediate precision reveals that the % assay shall be between 95.0 % and 105.0 % of label claim and % RSD for assay of preparations shall not be more than 2.0 followed by the difference between Average assay of Method precision and Intermediate precision shall not be more than 2.0%. The datas obtained for precision and intermediate precision are assay is 98.3 %, 97.5 % and % RSD are 0.62 %, 1.30 % respectively followed by 0.9 % difference between average assay of method precision and intermediate precision which is quite negligible.

Figure-1: FTIR Study of Labetalol pure drug with HPMC K4M, HPMC K15M & HPMC K100M respectively.

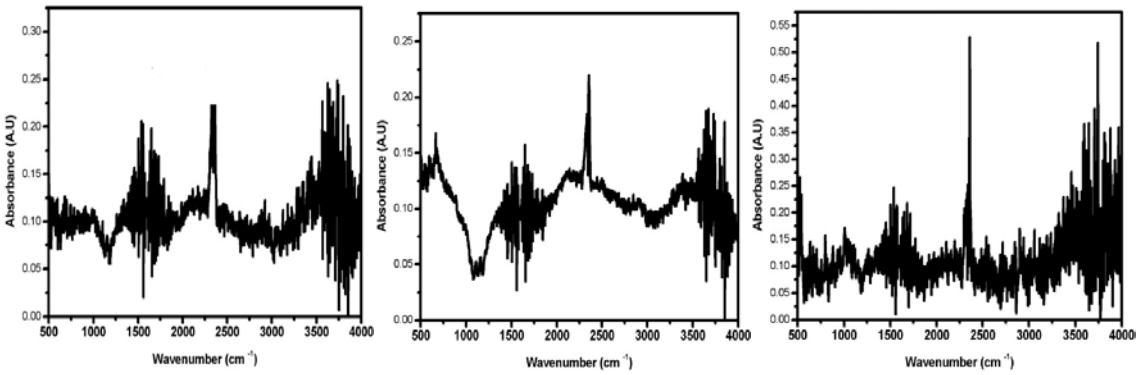


Figure-2: DSC Study graph of pure Labetalol and drug with different grades of HPMC

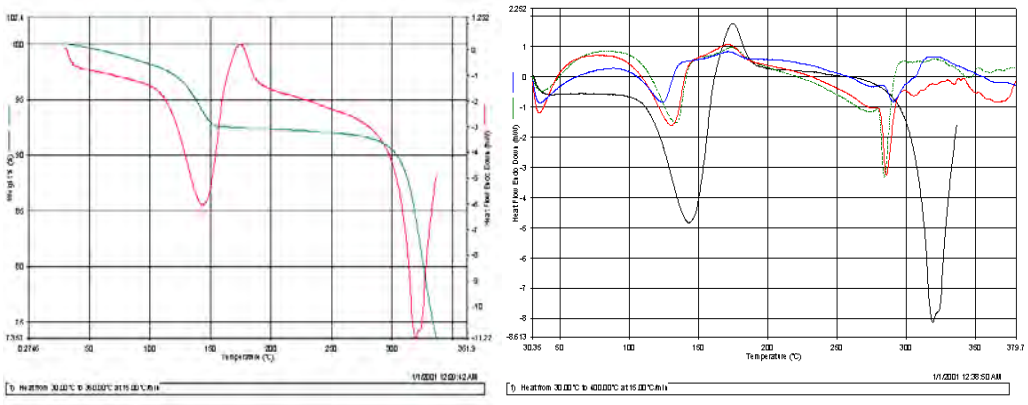


Table No. 1: Formulation of Labetalol SR Tablets using various grades of HPMC.

Ingredients	D:P:: 1:0.25 (F1)	D:P:: 1:1 (F2)	D:P:: 1:0.25 (F3)	D:P:: 1:1 (F4)	D:P:: 1:0.25 (F5)	D:P:: 1:1 (F6)	D:P:: 1:0.25 (F7)	D:P:: 1:1 (F8)	D:P:: 1:0.25 (F9)	D:P:: 1:1 (F10)	D:P:: 1:0.25 (F11)	D:P:: 1:1 (F12)
Labetalol Hydrochloride	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
HPMC	25 mg	100mg	25 mg	100mg	25 mg	100mg	25 mg	100mg	25 mg	100mg	25 mg	100mg
Lactose Monohydrate	237 mg	162mg	237 mg	162mg	237 mg	162mg	237 mg	162mg	237 mg	162mg	237 mg	162mg
PVPK30	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Magnesium Stearate	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
Aerosil	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
IPA	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S
Total Weight	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg

Table No.2: Evaluation Parameters of Labetalol SR Tablets

Formulation	Avg. Wt (mg) n = 20	Hardness(Kg/cm^2) n = 10	Thickness(cm) n = 10	Friability (%) n = 3	Assay (%) n = 3
F1	396.8±4.93	5.84± 0.35	0.345 ±0.049	0.001	99.06±0.065
F2	389.1±4.254	5.77 ±0.41	0.360 ±0.045	0.003	99.160±0.69
F3	395.5±4.778	5.91± 0.42	0.375 ±0.042	0.001	98.26 ±0.23
F4	396 ±5.888	5.64 ±0.38	0.355 ±0.036	0.002	99.31 ±0.31
F5	395± 4.211	5.42 ±0.33	0.345 ±0.036	0.002	99.26± 0.26
F6	388.6± 3.566	5.41 ±0.32	0.355± 0.028	0.001	98.82 ±0.61
F7	396.6 ±5.383	6.10 ±0.37	0.304 ±0.035	0.00	101.61±0.26
F8	394.5 ±5.380	6.11 ±0.29	0.305 ±0.049	0.00	99.96 ±0.31
F9	395 ±4.219	6.55± 0.27	0.325 ±0.042	0.001	99.26± 0.26
F10	394 ±2.41	5.81± 0.31	0.350 ±0.050	0.00	99.38 ±0.29
F11	398.6 ±4.438	5.95± 0.25	0.330 ±0.040	0.001	101.62±0.11
F12	399 ±5.35	5.98± 0.39	0.340 0.049	0.001	99.89 0.62

Table No.3: Percentage cumulative release of Labetalol Hcl formulations (F1 – F12) vs. time.

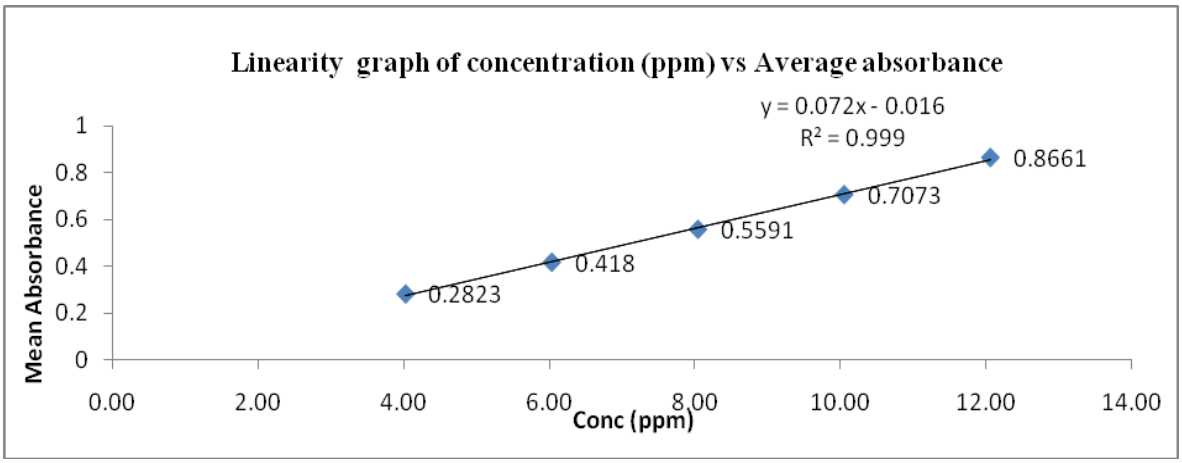
Time in hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	3.723008	2.792256	2.688839	7.342599	6.308431	2.585422	5.687929	2.378588	1.137585	9.30752	0.827335	0.517084
2	18.8	16.44329	15.09887	18.8	17.3	9.6	28	25.44056	19.54579	28.8	28.23281	9.928021
4	32.8	30.1	28	32	31	27.40548	42	45.19318	35.78225	42.4	40	21.61413
8	62.67064	59.3	55.53484	62.5	58.22371	53.2597	76	71.56449	70.84057	76.8	72.5	69.39273
12	86.04286	82.31985	77.149	86.45652	83.35402	82.6301	99.48705	98.5563	96.59138	99.48705	97.00505	96.90163

Table No.4: Analytical Validation of Labetalol SR Tablets

i) % Interference of Drug and Placebo of Labetalol SR Tablets:

Sample No	Sample Abs.	Mean Sample Abs.- Blank	Mean Sample Abs.	% Interference
1	0.0073	0.0070	0.0078	1.39
	0.0089	0.0086		
2	0.5595	0.5592	0.56030	
	0.5617	0.5614		

ii) Linearity & Range of Labetalol Hcl SR Tablets:



iii) Method Precision & Intermediate Precision of Labetalol Hcl SR Tablets:

Set 1(Method precision)		Set 2(Intermediate precision)	
Sample Set No.	% Assay of	Sample Set No.	% Assay
1	98.6	1	96.7
2	97.8	2	95.5
3	99.0	3	99.4
4	97.4	4	97.7
5	98.6	5	97.0
6	98.4	6	97.8
Average	98.3	Average	97.4
SD	0.59	SD	1.30
% RSD	0.60	% RSD	1.34
Difference average assay of method and intermediate precision			0.9

iv) Accuracy Study of Labetalol Hcl SR Tablets:

Level--->	50%	100%	150%
% recovery	99.3	98.0	98.0
% recovery	98.8	99.6	98.5
% recovery	102.0	98.9	98.3
Average	100.0	98.8	98.3
SD	1.713	0.768	0.216
% RSD	1.71	0.78	0.22

v) Stability for solution of Labetalol Hcl SR Tablets:

Stability in hrs.	% Assay	% Difference from initial absorbance
IMS	97.31	---
5.0	97.97	0.67
7.0	98.00	0.71
15.0	97.88	0.58
24.0	97.82	0.53

CONCLUSION:

Sustained release tablets are prepared with 3 viscosity grades of HPMC i.e. HPMC K4M, K15M and K100M by wet granulation method out of which total 12 formulations (F1 – F6) i.e. with individual polymers in different ratio and (F7 – F12) i.e. with mixture of different grades of HPMC were formulated. All these prepared formulations were evaluated for weight variation, hardness, thickness, drug content and drug release pattern which showed satisfactory results according to IP specifications. Among all the formulations F7 (HPMC K4M + K15M, 1:0.25) showed better release maintaining sustaining effect comparison to pure drug followed by Zero order kinetics of all formulations. As the results of the above study shows a promising path for development of once daily oral sustained release Labetalol 250 mg tablets and as the result of the studies are giving positive sign towards successful development of desired products, it automatically shows the path for the further research towards this. So this research gives a broad horizon towards the development of a modified release preparation and comparative evaluation of their release pattern. The analytical validation for drug and placebo interaction by specificity is very less. The precision and intermediate precision carried out by two different analyst results similar assay value in all respect. The formulation is linear over 50 to150 percent and the recovery value is optimum within the same range. The stability study reveals that the absorbance of formulation in test solution is not differ significant from initial absorbance for the accepted storage time.

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