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DEVELOPMENT AND CHARACTERIZATION OF CONTROLLED RELEASE TABLET BEARING ANTI HYPERTENSIVE DRUG

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ABSTRACT

Propranolol hydrochloride is used to treat high blood pressure, thyrotoxicosis, capillary hemangiomas, performance anxiety, and essential tremors and used to prevent migraine headaches. In this investigation-controlled release tablet of Propranolol Hcl was prepared using different polymers such as xanthan gum, tragacanth, sodium carboxy-methylcellulose, HPMC K4M, Eudragit S100, ethyl cellulose by direct compression method. All the pre-compression and post compression parameters of designed formulations of F1-F8 were evaluated and found to be within permissible limits. The optimized formulation (F7) showed a maximum percentage of drug release (100%) within 6hrs when compared to other formulations. From the FT-IR study it was concluded that there were no possible drug and polymer interactions. The short-term stability studies were carried out at 40±2°C and 75±5% RH and confirmed no changes in the weight, hardness and friability. Based on study results it may be concluded that tablets prepared will emerge as eminent candidates in treatment of hypertension.

Keywords- Hypertension, Propranolol hydrochloride, FT-IR, friability, Polymer.

INTRODUCTION-Hypertension is a condition in which the force of blood against the artery walls is above the permissible limit. Broadly, Hypertension can be defined as blood pressure (BP) above 140/90 mmHg and 180/120 mmHg considered as a severe blood pressure (hypertension).[1] Hypertension is most common disorder in this modern era. Most of the people are suffering from the hypertension. High blood pressure increases risk of heart diseases and stroke. Hypertension risk factors include obesity, drinking too much alcohol, smoking, family history. Out of many drugs beta-blockers are generally used to control the hypertension. Anyone can have high blood pressure for years without any symptoms. Even though, without having symptoms it damages the blood vessels and your heart continues and can be detected the heart attack and stroke may risk factor of serious health problems. Generally, there are 2 types of high blood pressure primary (essential) hypertension and secondary hypertension.[2,3]

The risk factors behind this are age, history, overweight, not being physically active, mental illness and other co-morbidities. anti-hypertensives are a class of drugs that are used to treat and control the hypertension. It prevents the complication of high blood pressure such as stroke and myocardial infraction[4].

Symptoms of hypertension[5]

So many people have high blood pressure with no signs or symptoms as discussed earlier, even if blood pressure values reach dangerously high levels.

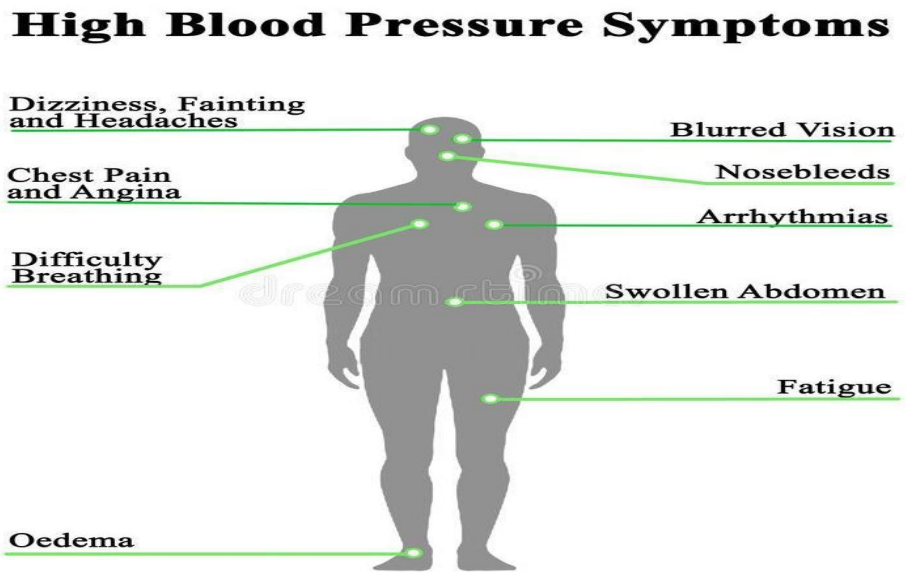

Figure-1 Symptoms of Hypertension

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.[6]

- Delayed release
- Sustained release
- Site-specific targeting
- Receptor targeting

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.[7]

Advantages of Controlled Drug DeliverySystem

- Avoid patient complianceproblems.
- Minimization of dosingfrequency.
- Minimize or eliminate local/systemic sideeffects.
- Minimize drug accumulation with chronicdosing.
- To obtain better therapeutic efficacy and diminishedtoxicity.
- Increased safety margin of high potency drugs due to control of plasmalevels.
- Maximum utilization of drug enabling reduction in total amount of doseadministered.

MATERIALS AND METHODS:

Propranolol HCl, Xanthum gum,Guar gum,*Sodium bicarbonate*was purchased from Cadila Pharma, Ahmedabad and Lactose,Magnesium sterate,Methanol, HCL was obtained from S.D. Fine chemical Pvt Ltd, Mumbai.

PREFORMULATION STUDIES:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances in order to develop stable, safe and effective dosage forms.

Organoleptic properties

Colour: a small quantity of pure Propranolol hydrochloride powder was taken in a butter paper and viewed in well illuminated place.

Taste and Odour: very less quantity of Propranolol hydrochloride was used to get taste with the help of tongue as well as smelled to get the odour.

Solubility Analysis:

Solubility of Propranolol hydrochloride was determined in methanol, ethanol, dimethyl fluoride, methylchloride, 0.1NHCl.Solubility studies were performed by taking excess amount of Propranolol hydrochloride in different beakers containing the solvent. The mixture was shaken for 10hrs at regular intervals. The solution was filtered by using whatmann filter paper. The filtered solutions were analyzed spectrophotometrically.

Melting point:

The melting point of Propranolol hydrochloride was determined by capillary method, using small quantity of Propranolol hydrochloride was taken and placed in apparatus and determined the melting point and matched with standards.

Loss ondrying:

Determined on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing

bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W1). Put the sample in bottle, replaced the cover, and accurately weighed the bottle with contents (W2). By gently, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator before weighing. Weighed the bottle (W3).The difference between successive weights should not less than0.3%.The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} X\ 100$$

Where, W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sampl

Angle of Repose: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.$\boldsymbol{\Theta = \tan^{-1}(h/r)}$

Where, h = height of heap,
r = radius of heap,
Θ = angle of repose.

Bulk density:

A quantity of 5 gm of powder weighed and transferred to a measuring cylinder . The bulk volume and weight of the powder was determined. Bulk density was calculated using the formula.

Bulk Density = Bulk Mass / Bulk Volume

Tapped density: It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder.Then the tapping was done and the tapped volume was noted. The tapped density was calculated by using the following formula.

$$\textit{Tapped Density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm.

Vf = volume of material after tapping.

COMPATIBILITY STUDY:

Drug excipient compatibility studies:

IR spectra of drug, polymer and drug and polymers, individual excipients, drug and

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Polymers and excipients were obtained by using beaker.Drug and excipients were analyzed by IR spectral studies by using KBr pellet technique. In this method, the drug and KBr were mixed at the ratio of1:100. Then these mixtures were pressed in to a pellet. The FT-IR spectra were recorded using KBr pellet method in the region 400-4000 cm^{-1}. Spectra were recorded for pure drug, pure excipients, and physical mixture of drug and polymer, drug, polymer and excipients.

Standard curve of propranolol hydrochloride drug:

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 240nm. It obeyed Beer's law in the concentration range of 2-10 µg/ml.

Preparation of stock and standard solution:

The stock solution was freshly prepared by dissolving 100mg of Propranolol hydrochloride in few ml of methanol in a 100ml volumetric flask and then made up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N HCl to obtain a solution of strength100 µg/ml (stockII)

Preparation of various concentrations:

0 ml stock solution was taken from stock solution-2 and volume made up to 100 ml by using 0.1 N HCl to get 10 µg/ml concentrations. From this solution with draw2,4,6,8,10ml of solution into the 10ml volumetric flask and volume made up to 10 ml by using 0.1N HC l to get the concentrations 2, 4, 6, 8, 10 µg/ml.

Formulation of Propranolol hydrochloride floating tablets:

Floating controlled release tablets were prepared by direct compression method. Propranolol hydrochloride was mixed with the required quantities of polymers (xanthan gum, guar gum) sodium bicarbonate (12%), and lactose by geometric mixing. The powder blend was then lubricated with magnesium stearate (2%) and mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmedabad, India) using a 6 mm standard flat-facepunches.

Evaluation of floating tablets of Propranolol hydrochloride

Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

Weight variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Tablet hardness:

Tablet hardness was measured using a Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then

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Forced against a spring by turning a threaded bolt until the tablet fractured. The crushing strength of the 10 tablets with known weight and thicknessof each was recorded in kg/cm^2 and the average hardness and standard deviation was reported.

Friability :

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

Content uniformity:

The formulated Propranolol hydrochloride floating tablets were assayed for drug content. From each batch of prepared tablets, ten tablets were collected randomly and powdered. a quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of methanol was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with methanol. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 240 nm by using UV-Visible spectrophotometer.

Buoyancy / Floating Test:

The *in vitro* buoyancy was determined by floating lag time. the tablets were placed in a 100-ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Swelling Index:

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at 37^o$\pm$ 0.5^{o}c, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU).

$$\%WU = (Wt - Wo) * 100 / Wo$$

Where Wt is the weight of the swollen tablet and
Wo is the initial weight of thetablet.

Dissolution study of tablets:

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 10hr, 12hr, 14hr, 16hr, 20hr, and 24hr. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 6 tablets, &determine the mean value. Then the mean values were plotted against time. Each sample was analyzed at 240nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve.

KINETIC DATAANALYSIS:

The analysis of drug release mechanism from a pharmaceutical dosage from is important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation.

Stability Studies:

The optimized formulation was subjected to stability studies as per I.C.H guidelines. Samples were kept at 40^0c with 75% RH and analyzed for weight variation, hardness, friability, drug content and In vitro dissolutions study for every month for a period of three months.

RESULTS AND DISCUSSION:

TABLE 1: Physical Properties Of Drug Excipients Mixtures:

Formulation Code	AngleofRepose	Bulkdensity(gm/mL)	Tappeddensity(gm/mL)	Carr'sindex(%)	Hausner's Ratio
Fl	17.2	0.41	0.52	21.1	1.26
F2	18.2	0.40	0.46	13.0	1.15
F3	16.6	0.41	0.48	14.5	1.17
F4	18.7	0.40	0.51	21.6	1.2
F5	19.2	0.46	0.63	22.9	1.36
F6	23.2	0.39	0.50	22	1.28
F7	27.4	0.45	0.57	13	1.26
F8	34.2	0.40	0.52	23	1.3

Post compression parameters of mini tablets

Organoleptic properties: All the mini tablets show similar colour, odour, taste and physical appearance. There is no impact of different in their organoleptic properties.

Hardness test: By using the different excipients, the hardness values ranged from 4.5-5.5 kg/cm2 for formulations (F1-F8).

Weight variation test: The entire tablet passes weight variation test, as the average % weight variation was within the Pharmacopeial limit - 7.5%. It was found to be 298.6mg – 305.6 mg. The weight of all the tablets was found to be uniform with less deviation.

Drug content uniformity: The concentration of the drug in all the formulations with different polymers was found to be 97.3 – 100.6%. It was within the IP limits. The results are shown in the **Table 2.**

TABLE 2: Quality Control Parameters for Tablets:

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
Fl	299.8±1.48	5.4±0.44	0.36	4.08±0.	100.6
F2	300.4±0.54	4.5±0.31	0.39	3.70±0.	100.2
F3	298.6±0.41	5.5±0.40	0.43	3.81±0.	99.8
F4	300.8±1.64	5.5±0.55	0.12	4.2±0.2	99.4
F5	305.6±1.14	4.6±0.57	0.54	4.08±0.	98.9
F6	299.2±0.83	5.0±0.30	0.58	3.91±0.	99.4
F7	299.9±0.67	4.5±0.57	0.64	4.1±0.7	99.3
F8	299.0±0.43	5.4±0.60	0.37	4.0±0.8	98.9

In-vitro drug release studies of tablets: **In-***vitro* drug release studies of all formulations (F1-F8) were evaluated. The results are shown in the **Table 3 and Table 4**

TABLE 3: *In-Vitro* Drug Release Studies:

Time in	Fl		F2		F3		F4	
	Lactose	**PRO**	**Lactose**	**PRO**	**Lactose**	**PRO**	**Lactose**	**PR**
30min/hr	13.36	8.60	20.0	11.86	15.78	9.80	25.0	14.8
1hr	25.60	17.91	33.14	28.62	28.89	19.76	48.71	32.4
2hr	33.38	21.71	50.31	40.18	38.90	30.32	56.61	43.31
6.8 pH buffer								
3hr	56.67	68.84	68.76	63.15	67.72	43.40	70.68	64.3
4hr	99.89	98.80	100.04	99.46	82.0	77.49	86.60	87.7
6hr	-	-	-	-	98.3	100.1	98.5	99.8
8hr	-	-	-	-	-	-	-	-

TABLE 4: *In-Vitro* Drug Release Studies:

Timein /hr	F5		F6		F7		F8	
	Lactos	**PRO**	**Lactose**	**PRO**	**Lactose**	**PRO**	**Lact**	**PR**
30 minutes	13.36	8.60	20.0	11.86	15.78	9.80	25	14.8
1hr	25.60	17.91	33.14	28.62	28.89	19.76	48.71	32.4
2hr	33.38	21.71	50.31	40.18	38.90	30.32	56.	43.3
6.8pHbuffer								
3hr	56.67	38.84	68.76	63.15	67.72	43.40	70.	64.3
4hr	79.89	68.80	80.04	79.46	82.0	77.49	86.	87.7
6hr	99.6	98.7	100.6	99.9	91.5	90.2	10	99.6
8hr	-	-	-	-	100.8	100.1	-	-

In-vitro Dissolution studies:

Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media for 2 hours in 3.2 acetate buffer. This was followed by dissolution in 900ml of 6.8 pH phosphate buffers in USP Apparatus 2. This was rotated at a speed of 50 rpm, and a temperature of 37±0.5°c, for 360 minutes. Based upon the dissolution profile the F7 formulation was optimized as it suits the extended release nature and comparable with the release of other formulations. The dissolution data of and Propranolol Hclresults are shown in the **(Fig 2a.&2b).**

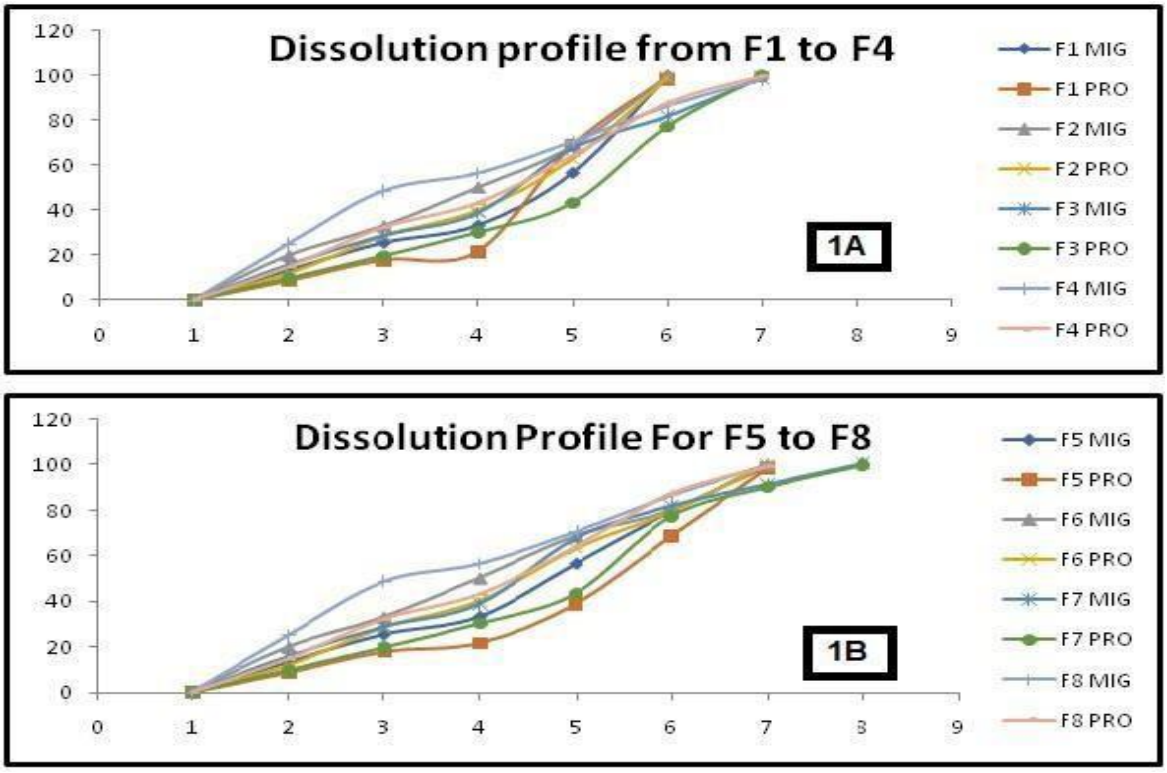


FIG 2A: Dissolution profile for formulation F1 to F4, FIG 2B

Dissolution profile for formulation F5 to F8 FTIR spectral data: The FT-IR represents the peaks of the and propranolol functional groups. These peaks were not affected, they were prominently observed in IR-spectra of and propranolol along with other excipients. There was no difference in the position of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure drugs with the excipients. The results of Drug – Excipient Compatibility Studies by FT-IR were shown below. **(Fig 3, 4)**.

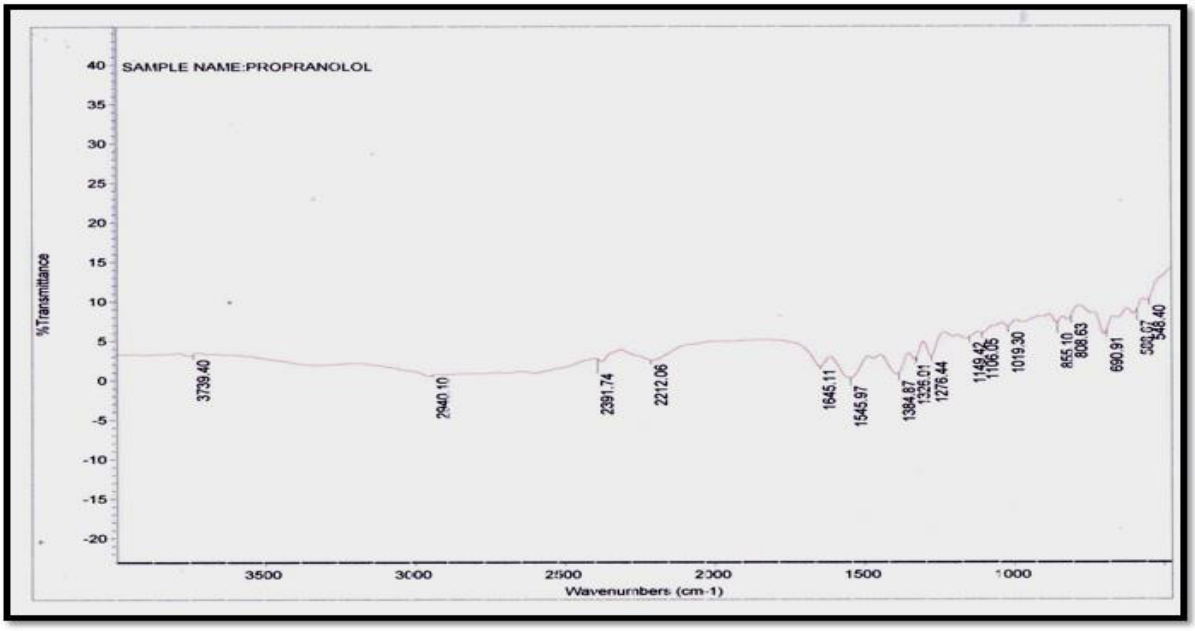


FIG 3: FT-IR spectra of Propranolol HCl

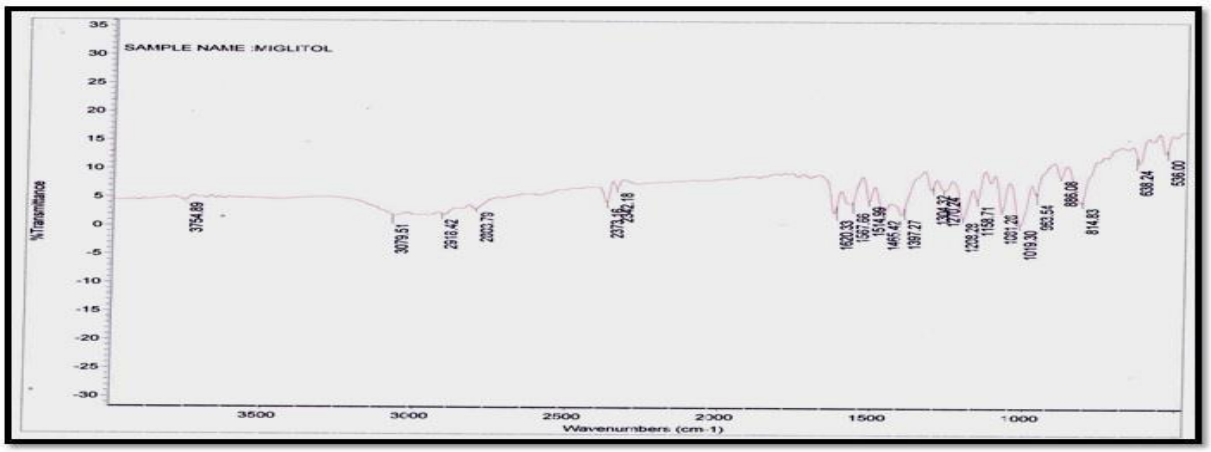


FIG 4: FT-IR spectra of Lactose

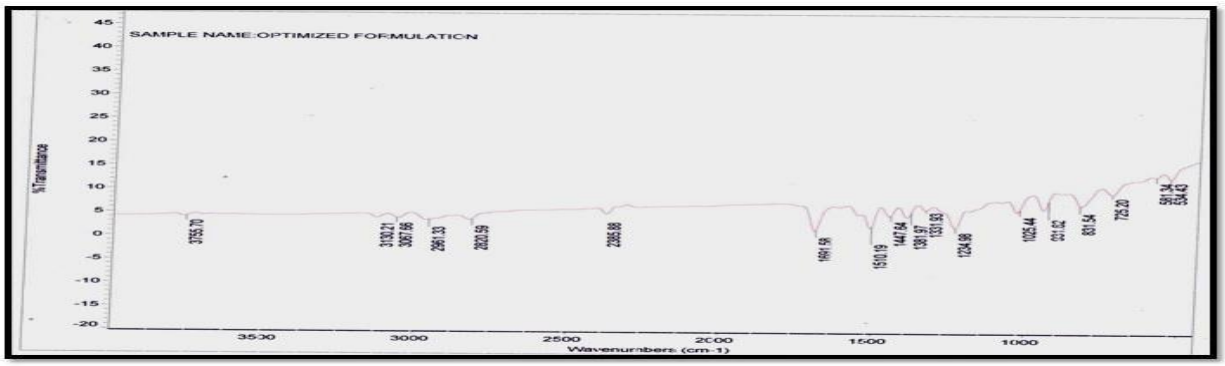


FIG 5: FT-IR spectra of Optimized Formulation

DSC: The DSC represents the melting points of the and propranolol. These peaks were not affected, they were prominently observed in DSC graph of and propranolol along with other excipients. There was no difference in the position of the melting point, hence providing

evidence for the absence of any chemical incompatibility between pure drugs with the excipients. The results of drug by Differential Scanning Calorimetry were shown below in **Fig 6, 7A & 7B**.

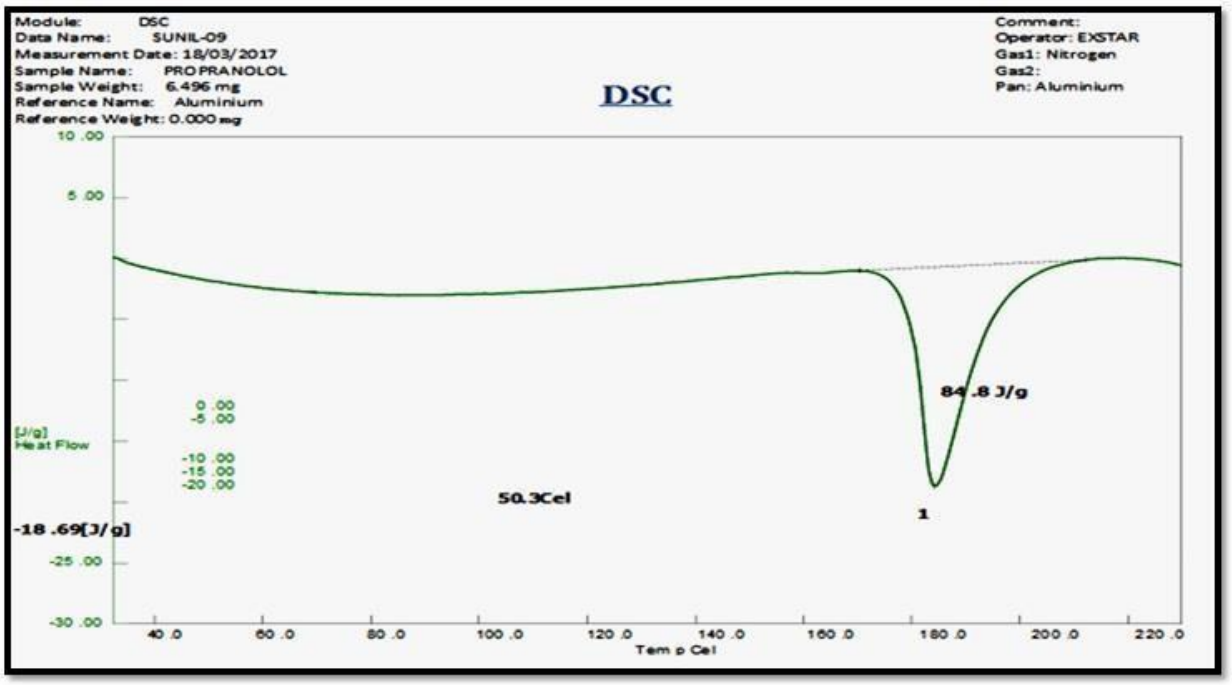
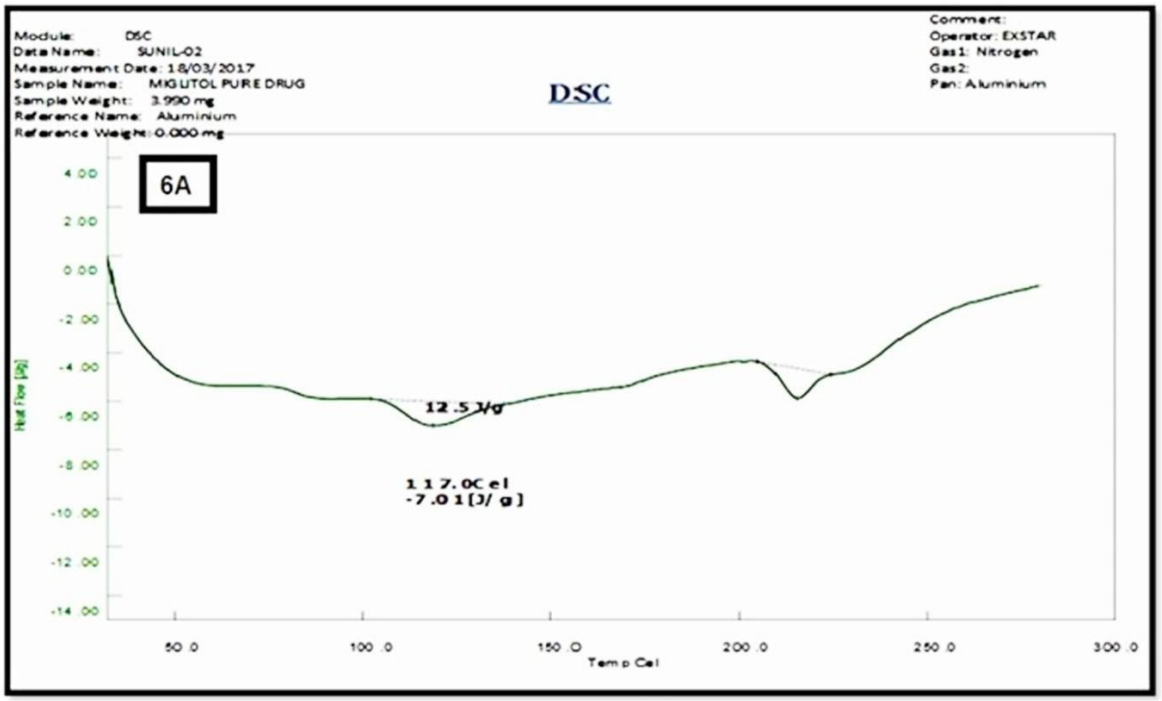


FIG 6: DSC of Propranolol



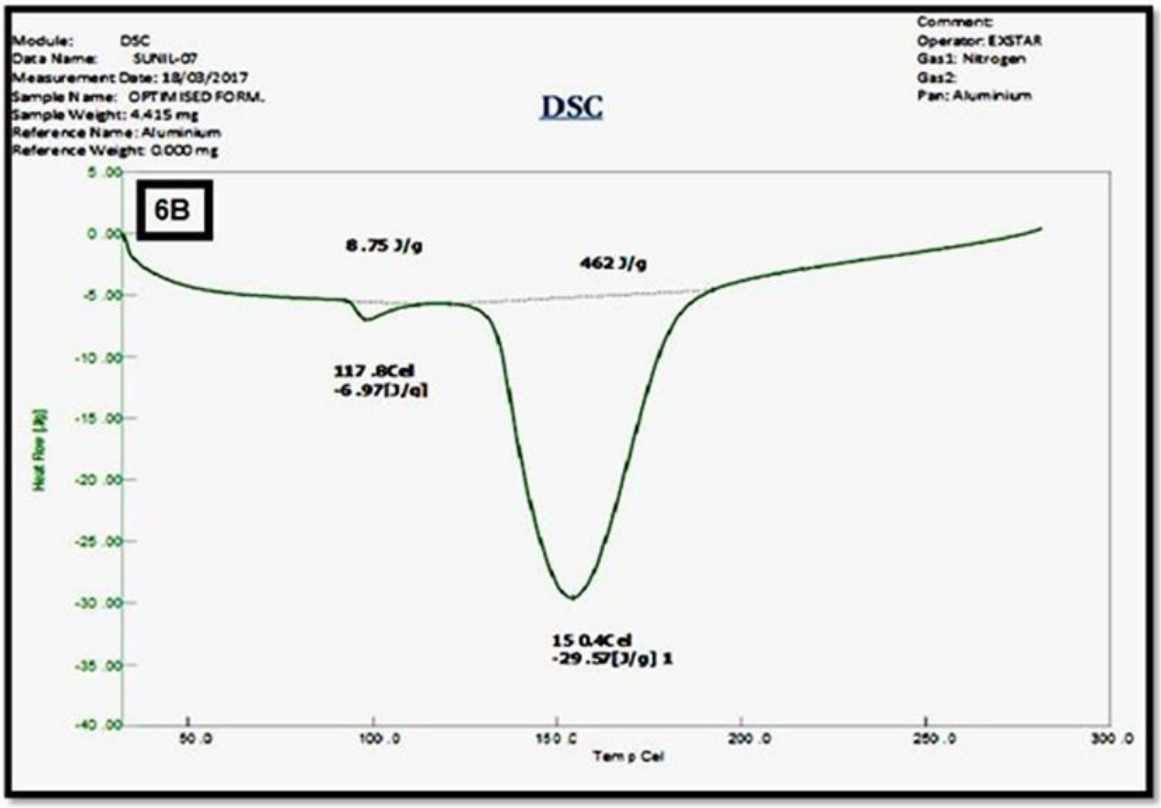


FIG 7A: DSC of, FIG 7B: DSC of Optimized Formulation

Stability studies: From the stability study of promising formulation F7, it was shown that there were no physical appearance changes, but slight decrease in %drug content was seen at 30 days of stability studies. But hardness, friability melting time decrease from 1 day to 30 days but all was within the limits only. The results were shown in **table 5**.

TABLE: 5Stability studies parameters of optimized formulation

Parameters Evaluated	1st Day	30Days
Appearance	White	Nochange
%Drugcontent	99.3	99.0
Hardness(kg/sq.in)	4.5±0.57	4.5±0.57
%Friability	0.64	0.63

CONCLUSION:

The monolithic controlled release tablets containing and propranolol were successfully prepared by direct compression method. Various formulations were prepared and evaluated with an aim of presenting and propranolol as controlled release for improving the patient's compliance. The physiochemical evaluation results for the granules of all trials pass the

official limits in angle of repose, bulk density, tapped density, Hausner ratio and compressibility index. The prepared blend for controlled release tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability and drug content. The optimized formulation F7 from total formulations contains the average thickness of 2.4mm, average hardness of 4.5 kg/cm2, average weight of 299mg, friability of 0.64%. The F7 formulation which releases the and propranolol in controlled manner in 1st hour it releases 15.78 and 9.80 % respectively, but the remaining drug release was sustained up to 8 hours[8]. Hence it may be summarized that the tablets prepared by direct compression method for controlled release tablet might be a perfect and effective formulation in treatment of hypertension and diabetes[9,10].

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DECLARATIONS

Conflict of Interest -The authors declare no potential conflicts of interest.

Ethical Approval -This Article does not contain any studies with human participants or animals performed by the author.

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