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Research Article

"Development And Evaluation Of Once Daily Sustained Release Matrix Tablet Of Propranolol Using Natural Polymers"

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ARTICLE INFO

ABSTRACT

The main objective of the present study was to "Development and Evaluation of Once Daily Sustained Release Matrix Tablet of Propranolol Using Natural Polymers" and to study the effect of particle size & concentration of polymer on the drug release by comparing *in-vitro* dissolution profile of a sustained release tablet. Sustained release Matrix tablet was prepared by direct compression technique by using Olibanum Gum, Olibanum Gum Resin, HPMC K4M as polymer. As the concentration of polymers increases, the release of the drug from the tablet also gets decreased but the difference was found to be insignificant. Comparison of *in-vitro* dissolution profile of batch F3 and F6 showed that there was significant difference in drug release as compared to relative formulation F7, F10 and F13 respectively. All Formulations was having good flow properties. It was concluded that, the release of the drug from SR tablet was independent on Olibanum Gum, Olibanum Gum Resin, HPMC K4M .

Keyword: - Sustained Release Matrix Tablet of Propranolol Using Natural Polymers such as Olibanum Gum, Olibanum Gum Resin, HPMC K4M. Prepared by Direct compression technique.

Introduction

Sustained Release Drug Delivery Systems

Sustained release drug delivery systems are designed to maintain therapeutic drug levels in the body over an extended period, reducing the need for frequent dosing. These systems are commonly developed for oral administration, where the goal is to optimize drug absorption and maintain steady plasma concentrations. Matrix tablets, which use hydrophilic polymers, are a key innovation, allowing controlled release without complex manufacturing processes. [1, 2, 3].

Conventional drug delivery often results in fluctuations in plasma levels, which can cause suboptimal therapeutic effects and reduced patient compliance due to the need for multiple daily doses. Sustained release systems address these issues by providing a gradual drug release, ensuring stable plasma concentrations with once or twice daily dosing, which is particularly beneficial for chronic conditions like hypertension.

The primary classifications of sustained release systems include diffusional systems, where drug release occurs through a polymer matrix or a reservoir membrane, and dissolution systems, which control drug release by modifying the dissolution rate. Other methods, such as ion exchange and osmotic pressure, also allow for controlled drug release. [5, 6, 7].

Biological factors like drug half-life, absorption, distribution, and metabolism play a significant role in designing sustained release formulations. For instance, drugs with half-lives between 2-8 hours are ideal for these systems, as they reduce dosing frequency and improve patient adherence. Physicochemical properties such as solubility, stability, and partition coefficient also influence the development of these systems. [8, 9, 10, 11, 12].

The goal of sustained release systems is to provide a steady, controlled drug release that mimics continuous intravenous infusion, ideally following zero-order kinetics. These formulations enhance therapeutic effectiveness and patient compliance by reducing the peaks and troughs of drug concentration commonly seen with immediate-release forms. [18,19]

In hypertension, sustained release formulations are critical as consistent blood pressure control is necessary to prevent complications like stroke and cardiovascular disease. Various antihypertensive drugs, including ACE inhibitors, ARBs, β-blockers, and diuretics, benefit from sustained release systems to ensure stable therapeutic effects and improve patient outcomes. [24, 25, 26, 27, 28.]

Materials and Method

Propranolol was received as a gift sample from Balaji Drug, Surat, polymer HPMC K4M was procured from Colorcon, Goa, Olibanum gum from Girijan co-operative society,
Vishakapatanam (AP), Microcrystalline cellulose, Magnesium Stearate, Talc was from S.D Fine Chemicals, Mumbai, All the chemicals were of analytical grade.

3.1 Experimental Data:

3.1.1: Pre-formulation Studies:

It is extensive information to bring out good quality at high standard at which optimal dosage desired.Pre-formulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

3.1.2: Solubility Studies:

Propranolol is soluble in water and in ethanol (95%); slightly soluble in chloroform.It is practically insoluble in ether.

3.1.3: Determination of Melting Point:

Melting point of Propranolol was determined by capillary method. The melting point of the Propranolol was found to be in the range of 162- 165 0 C which is same as that of literature value.

3.1.4 UV Spectra of Propranolol .

The UV spectrum of Propranolol was obtained using Shimadzu UV1800. Accurately weighed 100 mg of the drug was dissolved in sufficient quantity of distilled water and volume made up to 100 ml known as stock solution (1000 µg/ml).1 ml of aliquot was withdrawn and volume was made up to 100 ml using distilled water to obtain the concentration of 10µg/ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded.

3.1.5 Compatibility studies:

i.FTIR spectroscopy:

In the preparation of tablet formulations, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FTIR spectroscopy was employed to ascertain the compatibility between Propranolol and selected polymers. The pure drug, drug- polymers combinations and formulations were subjected to FTIR studies. Potassium bromide, pure drug, and the polymers were heated to 105 0C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and or polymer in 9:1 ratio. Grinding in smooth mortar can effect mixing. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 4000 cm-1 to 1000 cm-1 wave number. FTIR spectrum of Propranolol was compared with polymer. The pure drug and the drug with excipients were scanned separately. Disappearance or shifting of Propranolol peak in any of the spectra was studied.

ii. Differential Scanning Calorimetry

From thermal analysis techniques, particularly differential scanning calorimetry (DSC), when critically examined have been found useful in rapid screening for possible drug-additive and drug-drug interactions. Thermal analysis can be used to investigate and predict any physicochemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients. An interaction on DSC will show as changes in melting point, peak shape , area and appearance of a transition.

3.2 Analytical Methods: [20, 21.]

3.2.1: pH 1.2 Hydrochloric acid buffer:

50 ml of 0.2 M Potassium chloride was taken in the 200 ml volumetric flask; to it 85 mlof 0.2N HCl was added. The volume was made up to mark using distilled water.

3.2.2: Preparation of Phosphate Buffer (pH 7.4):

placed 50ml of 0.2 M Potassium dihydogen ortho phosphate in 200ml volumetric flask, added the specified volume of 0.2 M sodium hydroxide.

3.2.3: Preparation of Standard Stock Solution:

Accurately, about 100 mg of Propranolol hydrochloride was weighed and transferred to a 100 ml volumetric flask. The drug was dissolved in 100 ml of Phoshate buffer solution pH 7.4with shaking and then the volume was made up to the mark with Phosphate buffer solution pH 7.4 to obtain a standard stock solution of a drug concentration, 1000 µg/ml. (stock solution I). From the stock solution I, pipette out 1 mL and placed into 100 mL volumetric flask. The volume was made up to mark with distilled water to give a stock solution containing 10 µg / mL (stock solution II).

3.2.5 Calibration curve for the Propranolol :

100 mg of propranolol drug was accurately weighed and dissolved in 100ml of 7.4 PH in100 ml volumetric flask ,to make (1000 µg/ml) std. stock solution (I).then 5ml stock solution (I) as taken in another 50 ml flask to make (100 µg/ml) std. sock solution (II) ,then again 10ml of stock solution (II) was taken in another 50 ml volumetric flask to make (20µg) finaly 1ml , 2ml,3ml,4ml,5ml ,6ml .was pipette out and adjusted to 10ml then final concentration were prepared 2,4,6,8,10,12, and .then absorbance of std. solution as determined using UV/VIS spectrophotometer at 290nm

3.3: Formulation Study

3.3.1 Preparation of Matrix Tablet of Propranolol:

In the present work, direct compression method was used to prepare matrix tablets of Propranolol and the polymer used were : HPMC K4M.
:Olibanum Gum
:Olibanum Resin
Diluents : Microcrystalline cellulose
Lubricant : Magnesium stearate
Glidant : Talc

3.3.2 : Methodology for isolation of Olibanum Resin from olibanum gum [26, 27].

Powdered Olibanum (10 gm) was extracted repeatedly with 4×50 ml quantities of solvent ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40°C to obtain the resin fraction. The dry mass was powdered and the size was reduced to 200 mesh. The carbohydrate fraction remained after ether extraction of resin was collected, dried at 600C for 4 hrs and the size was reduced to 200 mesh.

3.3.3 : Procedure for Preparation of Matrix Tablets:

Sustained release matrix tablets of Propranolol was prepared by direct compression technique using various concentrations of HPMC K4M, Olibanum Gum and Olibanum Gum Resin
All the ingredients were accurately weighed.afer that respective powders (drug, polymer and additives) were passed through a sieve no. 60#.Then desired quantities of previously weighed drug, polymer and diluent were blended in a polythene bag for 15 min.The mixture was lubricated with magnesium stearate and talc and then compressed into a tablet using a 16 Station Tablet Compression Machine (Cadmach machine, Ahemadabad)By using 8mm flat round punch.Three batches were prepared for each formulation by direct compression method.

Table 3.1: Formulation chart of Propranolol Matrix tablet.

Formulations	Propranolol	Olibanum Gum	Olibanum Resin	HPMC K4M	Microcrystalline cellulose	Magnesium stearate	Talc
F1	20	75	_	_	146.25	3.75	5
F2	20	100	_	_	121.25	3.75	5
F3	20	125	_	_	96.25	3.75	5
F4	20	_	75	_	146.25	3.75	5
F5	20	_	100	_	121.25	3.75	5
F6	20	_	125	_	96.25	3.75	5
F7	20	_	_	75	146.25	3.75	5
F8	20	_	_	100	121.25	3.75	5
F9	20	_	_	125	96.25	3.75	5
F10	20	75	_	75	71.25	3.75	5
F11	20	100	_	75	46.25	3.75	5
F12	20	125	_	75	21.25	3.75	5
F13	20	_	75	75	71.25	3.75	5
F14	20	_	100	75	46.25	3.75	5
F15	20	_	125	75	21.25	3.75	5

All quantities are expressed in mg and formula for 250 mg 1 tablet shown in table

Pre-compression parameters.

a. Bulk and tapped Densiy
b. Carr's index

c. Hausner's ratio.
d. Angle of repose.

Post-compression parameters (Evaluation of compressed tablets)
a. Thickness and appearance.
b. Hardness.
c. Friability.
d. Weight variation.
e. Uniformity of drug content.
f. In-vitro dissolution studies.

3.4: Pre-compression Study:[35.]

Bulk density and Tap density:

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Bulk density is calculated by using a formula:

$$\text{Bulk density (gm/ml)} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

The final volume was recorded and the tap density was calculated by the following equation:

$$\text{Tapped density (gm/ml)} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

Carr's index and Hausner's Ratio [35.]

Carr's index

A simple test has been developed to evaluate theflowability of a powder by comparing the poured (fluff) densityand tapped density of apowder and the rate at which it packed down. Auseful empirical guide is given by Carr's compressibility index.

$$\text{Compressibility Index} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \text{ X } 100$$

Hausner's Ratio:

Hausner found that the ratio tapped density/ bulk density was related to inter particle friction as such, could be used to predict powder flow properties.

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose [22, 24.]

Angle of repose was determined by substituting the values of the base radius 'r' and height of the pile 'h' in the given equation given below,

$\tan \theta = h/r$

Where,

θ = Angle of repose,
h = Height of pile,
r = Radius of base.

3.5: Post-compression Study:

All the prepared matrix tablets were evaluated for following official and unofficial parameters.

Appearance: [38.]

The tablets were identified visually by checking the difference in colour.

Thickness: [38.]

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauze on 3 randomly selected samples.

Hardness: [38.]

Hardness of the all tablet formulations was determined by Monsanto hardness tester. For each formulation the hardness of 5 tablets was determined, the average was calculated and presented with standard deviation. It is expressed in kg/cm2.

Friability: [38.]

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined:

$$\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation: [38].

Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation. The following percentage deviation in weight variation according to USP was allowed.

In all formulations, the tablet weight was 250 mg, hence a maximum deviation of ± 10 % from the average tablet weight was allowed.

Drug content: [40].

Ten tablets were finely powdered and an amount equivalent to 20mg of propranolol was accurately weighed and transferred to a 100 ml volumetric flask and extracted with phosphate buffer (pH 7.4). The mixture was then filtered to remove the un-dissolve particle and 1 ml of the filtrate was suitably diluted and analyzed for propranolol hydrochloride content at 290 nm [12] using double beam UV/Visible spectrophotometer (UV-2450-Shimadzu Japan).

3.6*: In vitro* drug release studies of Propranolol Matrix Tablet [40]

The in vitro release of formulated tablets was carried out in tablet dissolution tester USP- type II apparatus using 900 ml of dissolution medium maintained at 37.0 ± 0.5° C at a stirring rate of 50 rpm. One tablet from each formulation were tested individually in phosphate buffer (pH 7.4) for 12 hr. Samples measuring 5 ml were withdrawn at different time intervals such as 1 hr, 2 hr, 3 hr,6 hr, 9hr, and 12 hr. During sampling samples were filtered through 10 µm filter. The fresh dissolution medium (37° C) was replaced every time with the same quantity of the sample. Collected samples were analyzed at 290 nm using 7.4 pH phosphate buffer as blank. Dissolution was continued till 12 hr.

In vitro drug release studies details:

The apparatus used for dissolution study was- USP Type-2 Model), Electrolab. The Dissolution medium used was phosphate buffer (pH 1.2 & 7.4) .The volume Taken for Dissolution medium was 900 ml .The temerature of medium was maintained at 37.50c.The Speed of paddle rotation was 50 rpm and Sampling intervals was 1 hr .5 ml samplewas withdrawl per hour and The absorbance was measured at 290nm.

3.7 :Release Kinetics of drug: [39, 40].

All the formulations were subjected to study the release kinetics. The drug release profile of all the batches were fitted to

1. Zero order kinetics
2. First order kinetics
3. Higuchi model
4. Korsmeyer-Peppas model

To ascertain the kinetic modeling of drug release and the model with the higher correlation coefficient was considered to be the best fit model.

1. Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation

ft=Kt

Where, ft = The fraction of drug dissolved in time‘t’

K = Rate Constant

t = Time

This model represents an ideal release profile in order to achieve the prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, and osmotic systems.

2. First Order Kinetic

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in theoretical basis.

Log Qt= log Qo + Kt/2.303

Where Qt = Amount of drug released in time't'.
Qo = Initial amount of drug in the solution.
K = Rate Constant.

3. Higuchi Model:

This model is applicable to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrices.

ft = Kt1/2

Where, ft = Amount of drug released in time't'

4. Korsmeyer-Peppas Model:

This model is relating exponentially the drug release to the elapsed time (t):

ft = atn

Where, a = constant incorporating structural and geometric characteristics of the drug dosage form.
n = Release exponent
This model is widely used; when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

3.8 Stability Studies:

To determine any change in physical appearance, drug content on storage, short term stability study (3 months) was performed. Sufficient number of tablets (20) were packed in amber colored screw capped bottles and kept in Stability chamber. Stability study was carried out at 400C ± 20C temperature, 75% ± 5% relative humidity (RH) and 250C ± 20C temperature, 60% ± 5% relative humidity. After every 10 days upto 3 months, samples were analyzed for physical appearance, drug content study.Results of stability studies of formulation F4 are reported in table number.

Result

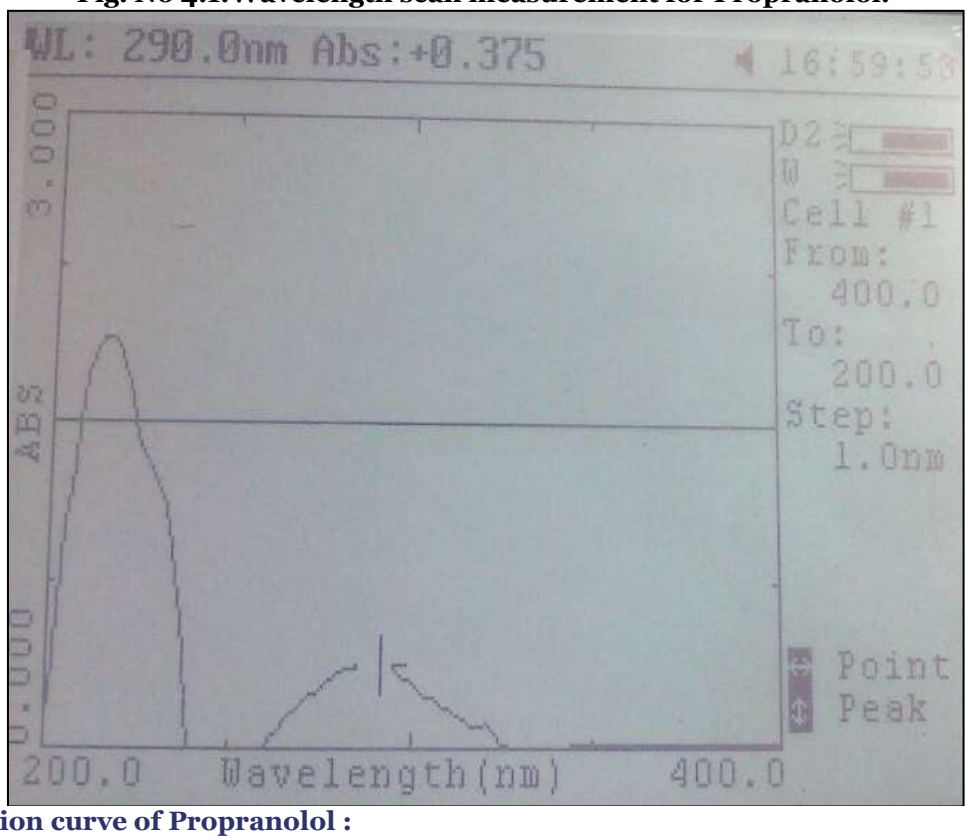
4.1 Preformulation Studies:

4.1.1 Determination of melting point: The melting point of Propranolol was found to be in the range of 163°C to 165 0C.

4.1.2 Solubility Propranolol : Propranolol is soluble in water and in ethanol (95%); slightly soluble in chloroform.It is practically insoluble in ether.

4.1.3: λ_{max} determination of Pure Drug(propranolol)

Fig. No 4.1:Wavelength scan measurement for Propranolol.



4.2 Calibration curve of Propranolol :

Table No 4.1: Standard Graph of Propranolol in pH 7.4 (Phosphate buffer)

Sr. No.	Concentration (µg/ml)	Absorbance at 290nm
1	0	0.000
2	2	0.0152
3	4	0.0261
4	6	0.0382
5	8	0.0486
6	10	0.0587

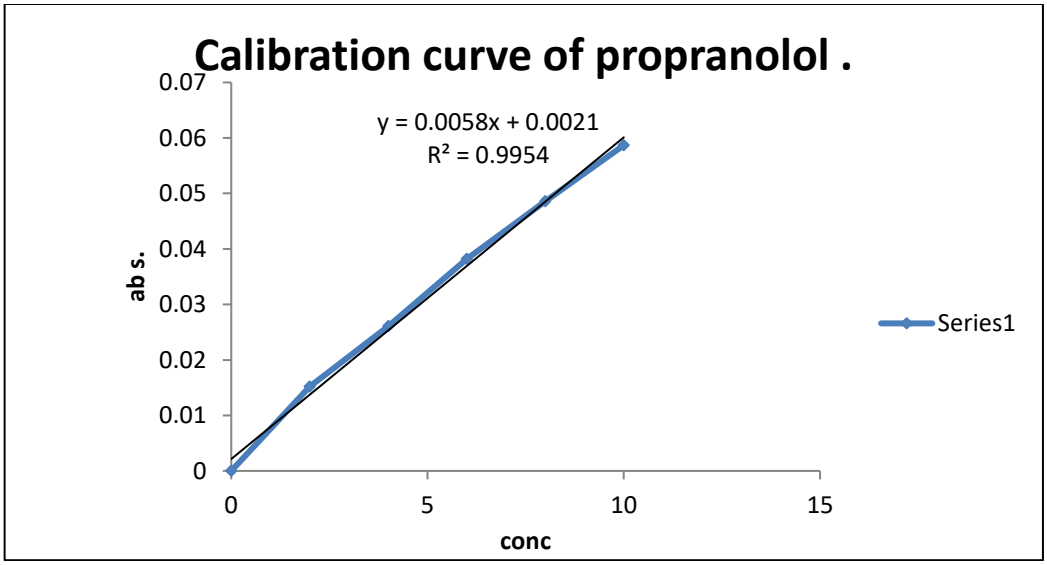
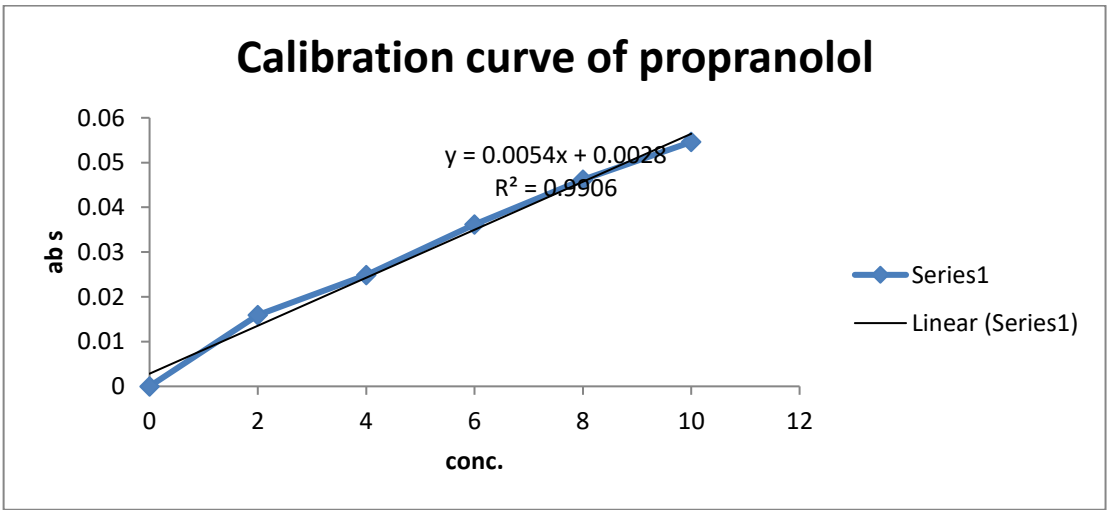


Table No 4.2: Standard Graph of Propranolol in pH 1.2 (Phosphate buffer)

Sr.no.	Concentration (µg/ml)	Absorbance at 290nm
0	0	0.000
2	2	0.0159
3	4	0.0249
4	6	0.0362
5	8	0.0462
6	10	0.0546



4.1.4: FTIR Spectrum of Propranolol .

FTIR spectroscopy is used to study the interaction of electromagnetic radiation with vibrational or rotational resonances within a molecular structure . The principal peaks depicted in Figure 4.2.

Fig .No 4.2: FTIR Spectrum of Pure Drug (Propranolol).

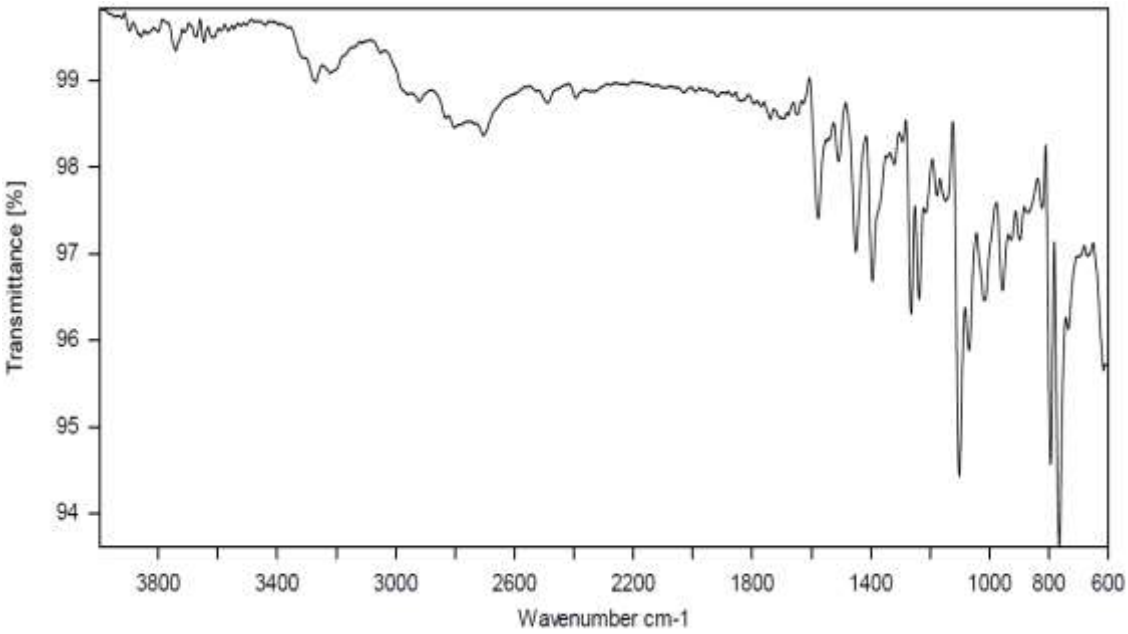


Fig .No 4.3: FTIR Spectrum of Olibanum Gum :

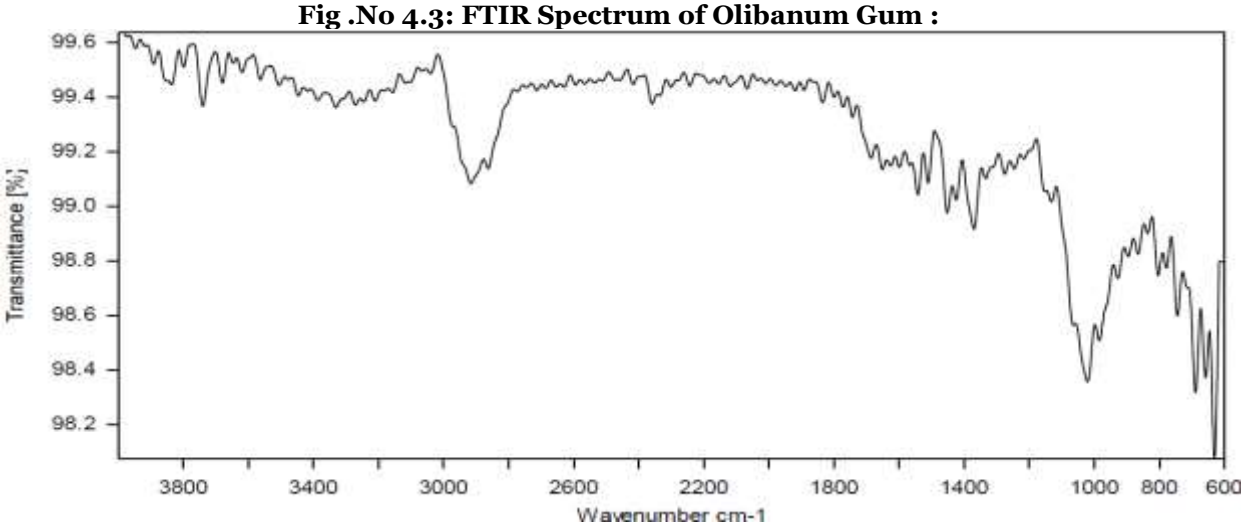


Fig .No 4.4: FTIR Spectrum of Olibanum Gum Resin:

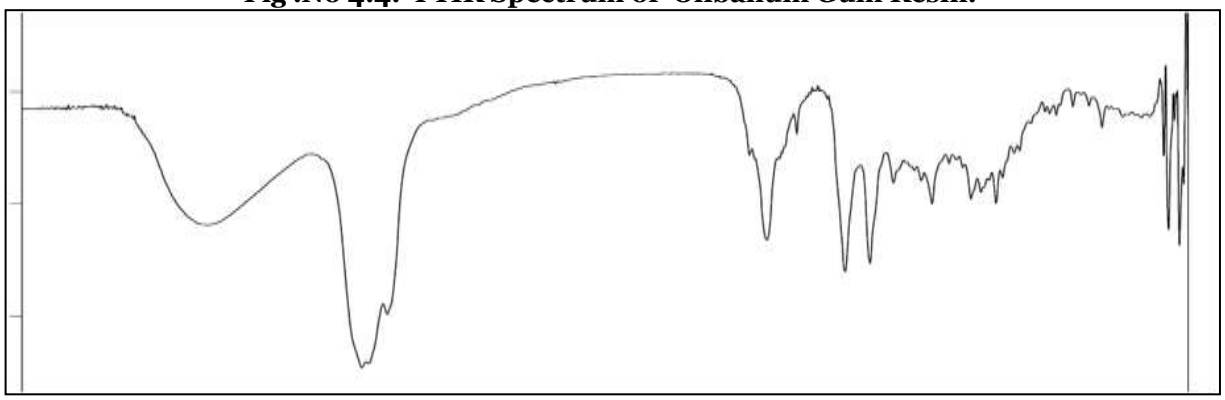


Fig. No 4.5: FTIR Spectrum of HPMC K4M :

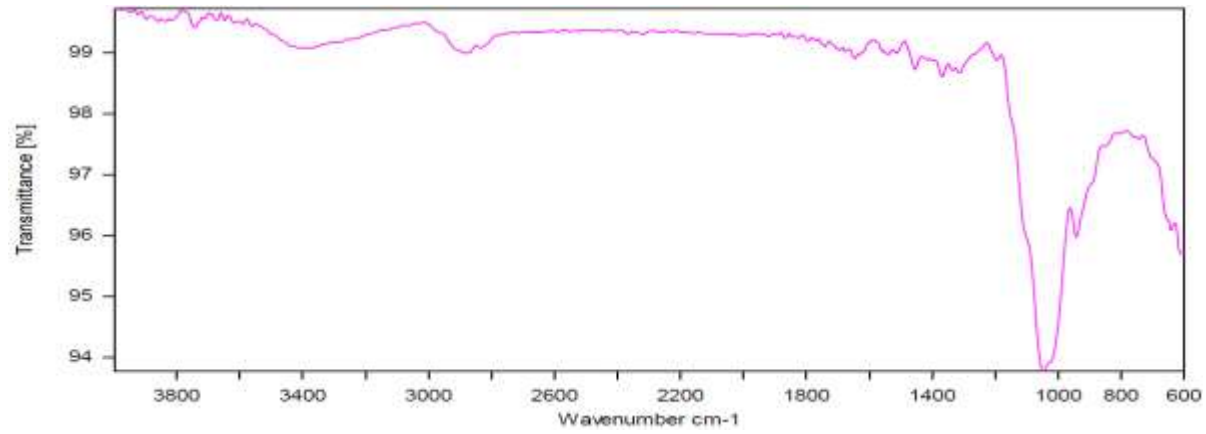


Fig .No 4.6: FTIR Spectrum of Formulation F1 (Propranolol + Olibanum gum).

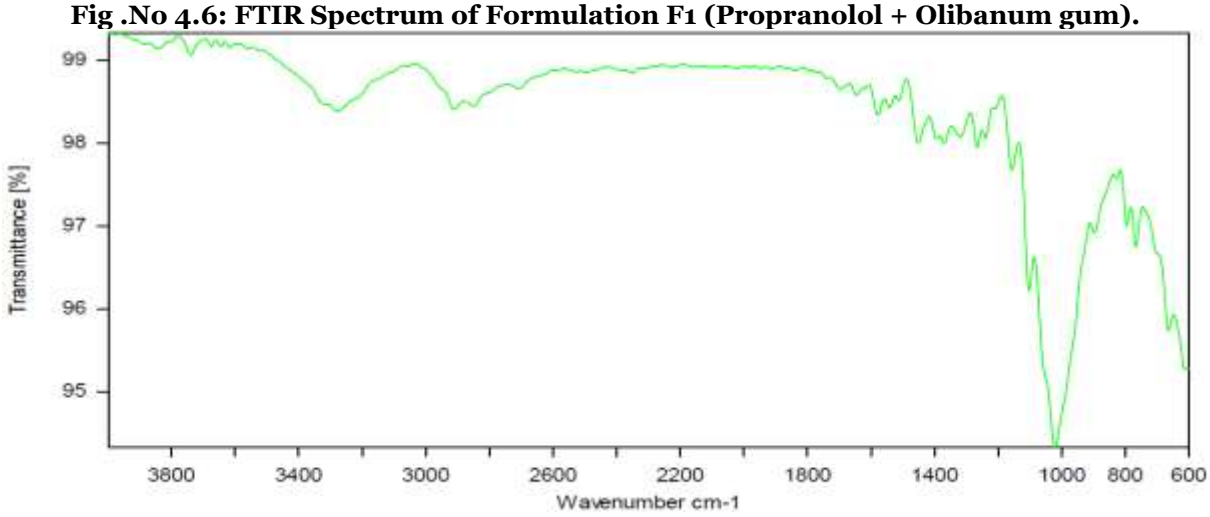


Fig .No 4.7:FTIR Spectrumof Formulation F4 (Propranolol +Olibanum gum Resin)

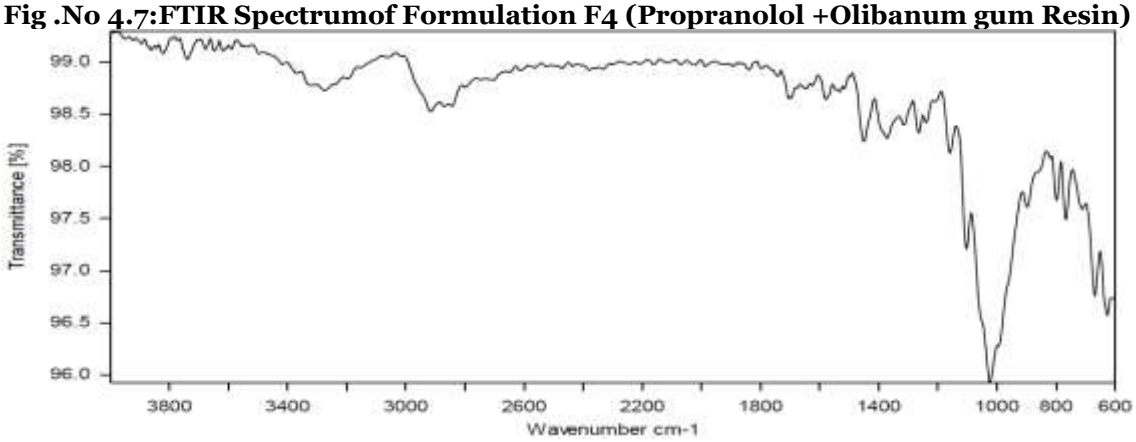


Fig. No 4.8:FTIR Spectrum of Formulation F7 (Propranolol +HPMC K4M)

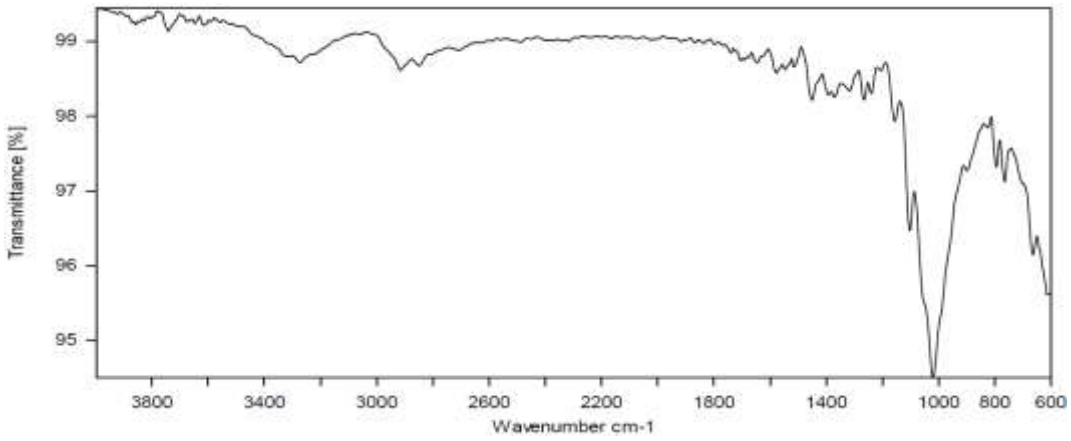


Fig. No 4.9: FTIR Spectrum of Formulation F10 (Propranolol +HPMC K4M +Olibanum gum)

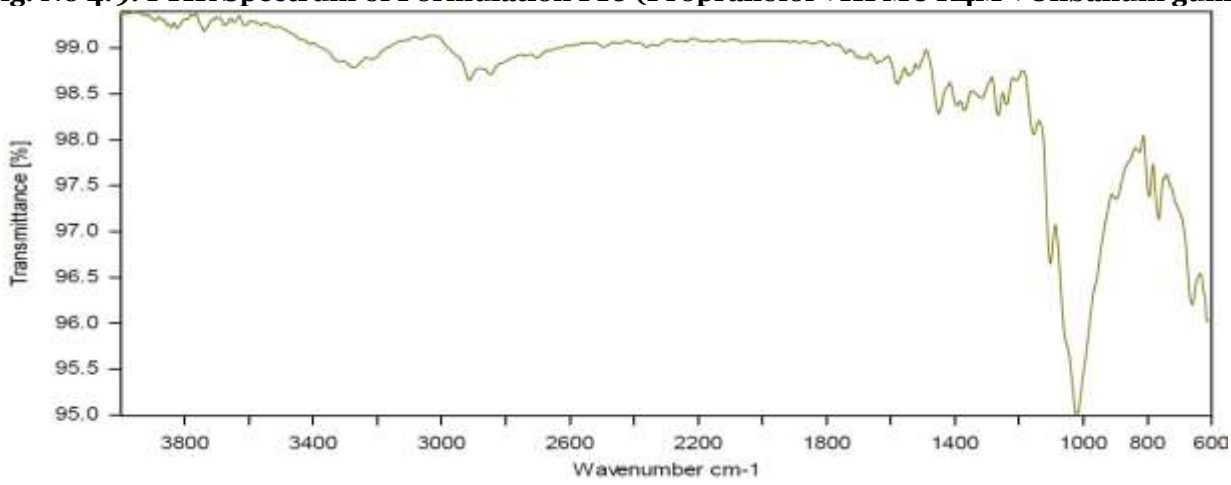
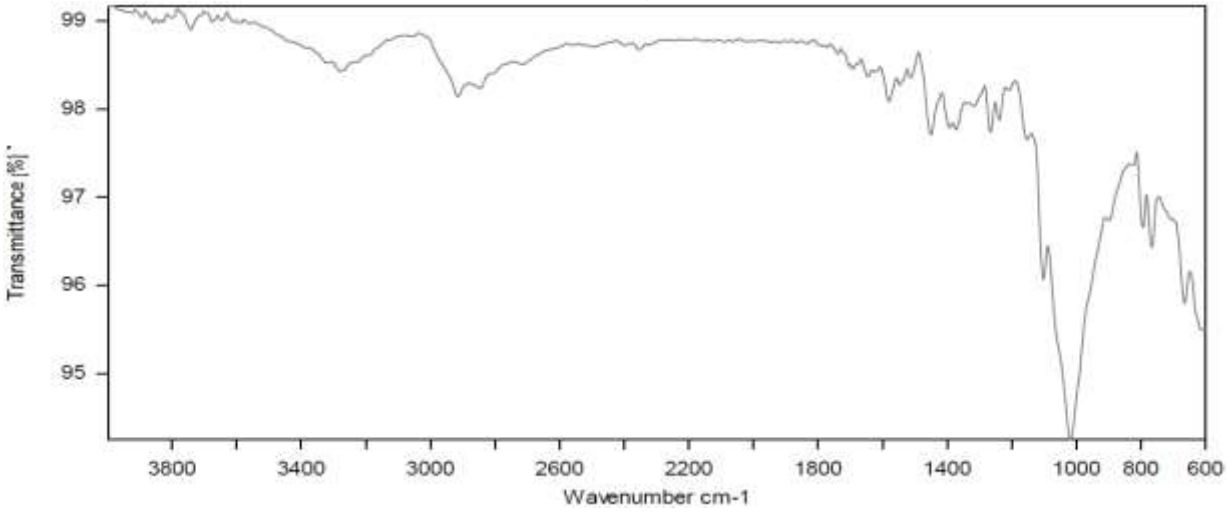


Fig. No 4.10:FTIR Spectrum of Formulation F13 (Propranolol +HPMC K4M +Olibanum gum Resin)



4.1.5:DSC Study of Formulations.

Fig. No 4.11: DSC of Pure Drug (Propranolol).

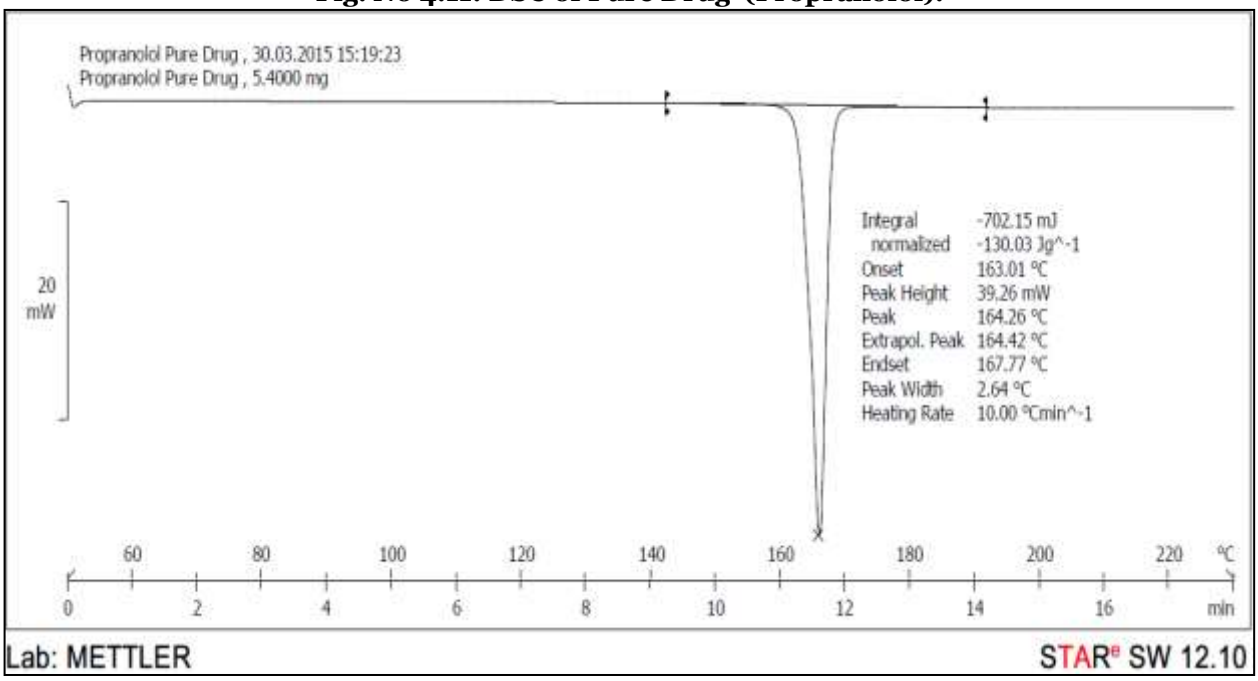


Fig .No 4.12: DSC of Formulation F1 (Propranolol +Olibanum gum).

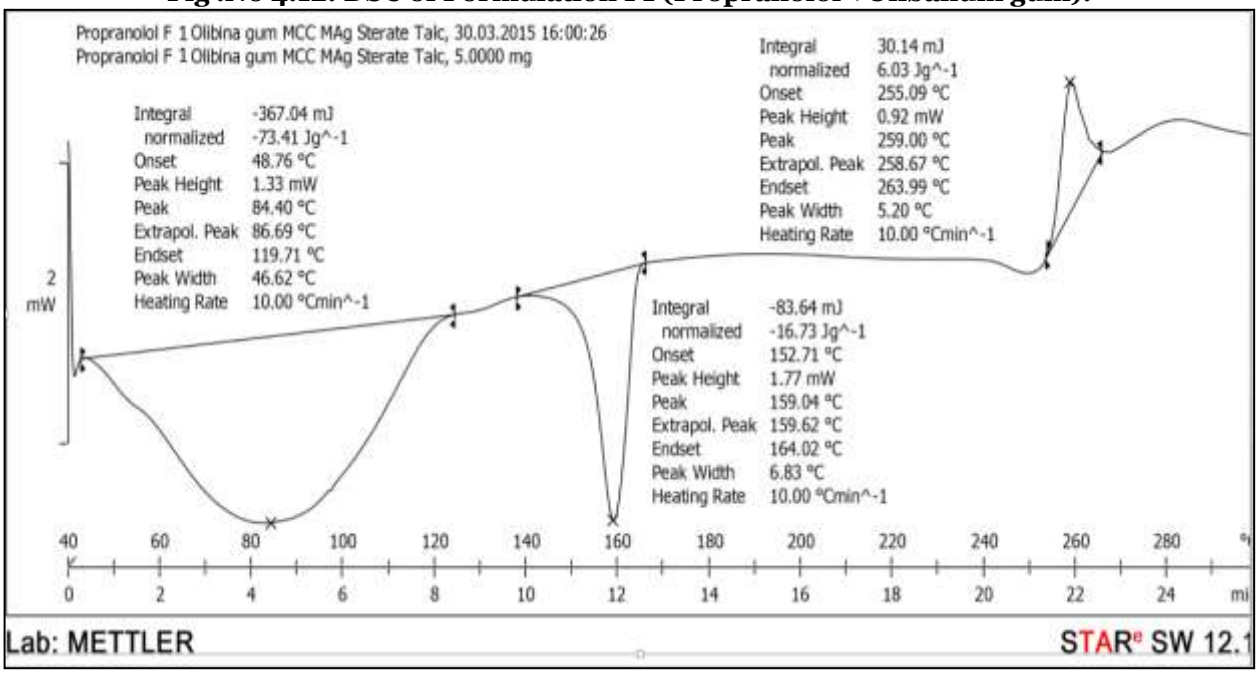


Fig .No 4.13: DSC of Formulation F4 (Propranolol +Olibanum gum Resin).

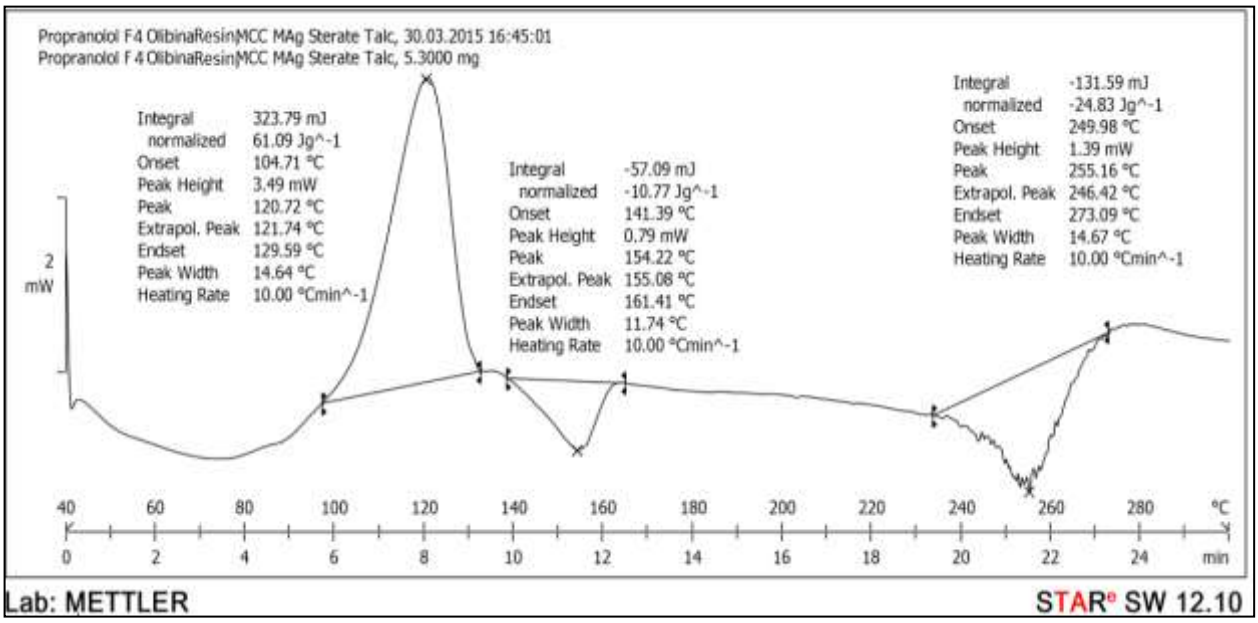


Fig .No 4.14: DSC of Formulation F7 (Propranolol +HPMC K4M)

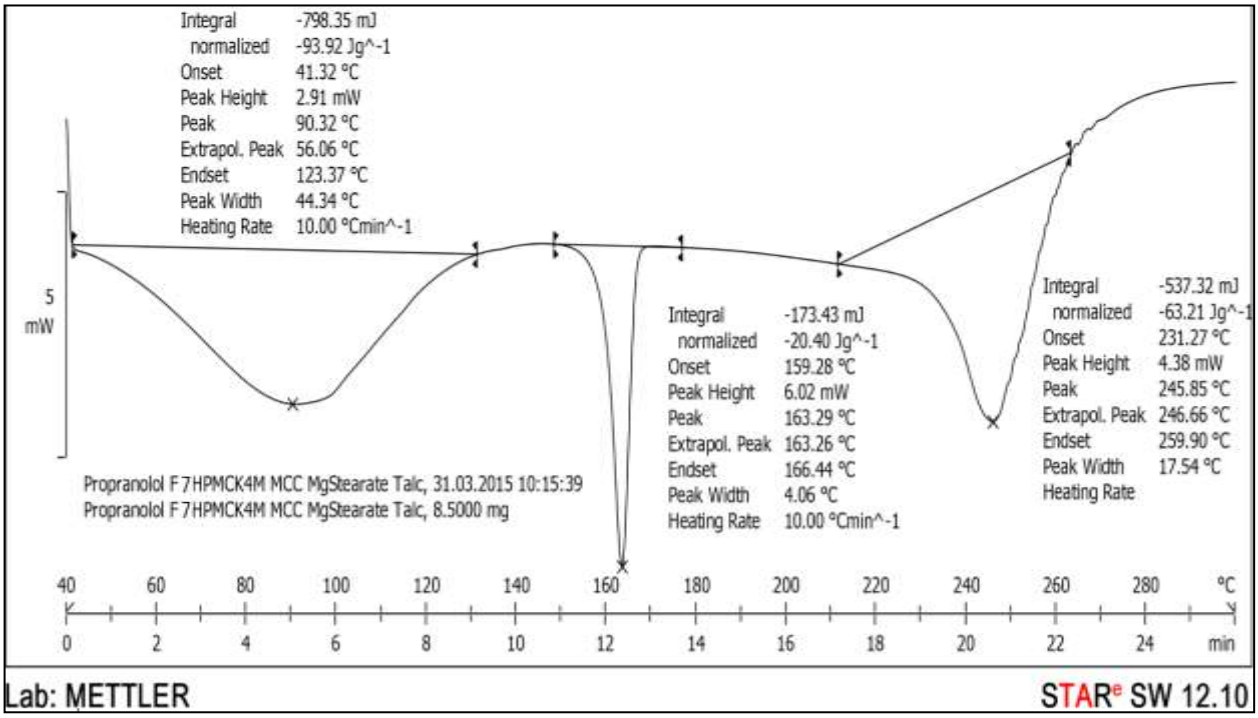


Fig .No 4.15 : DSC of Formulation F10 (Propranolol +HPMC K4M +Olibanum gum)

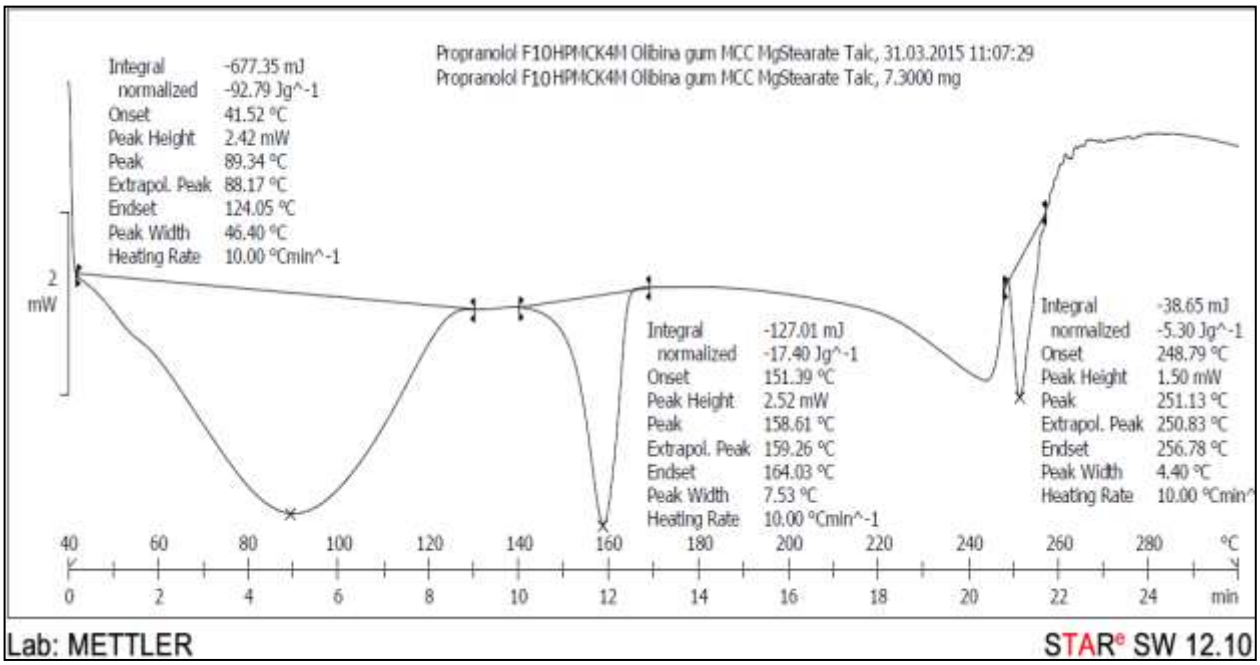
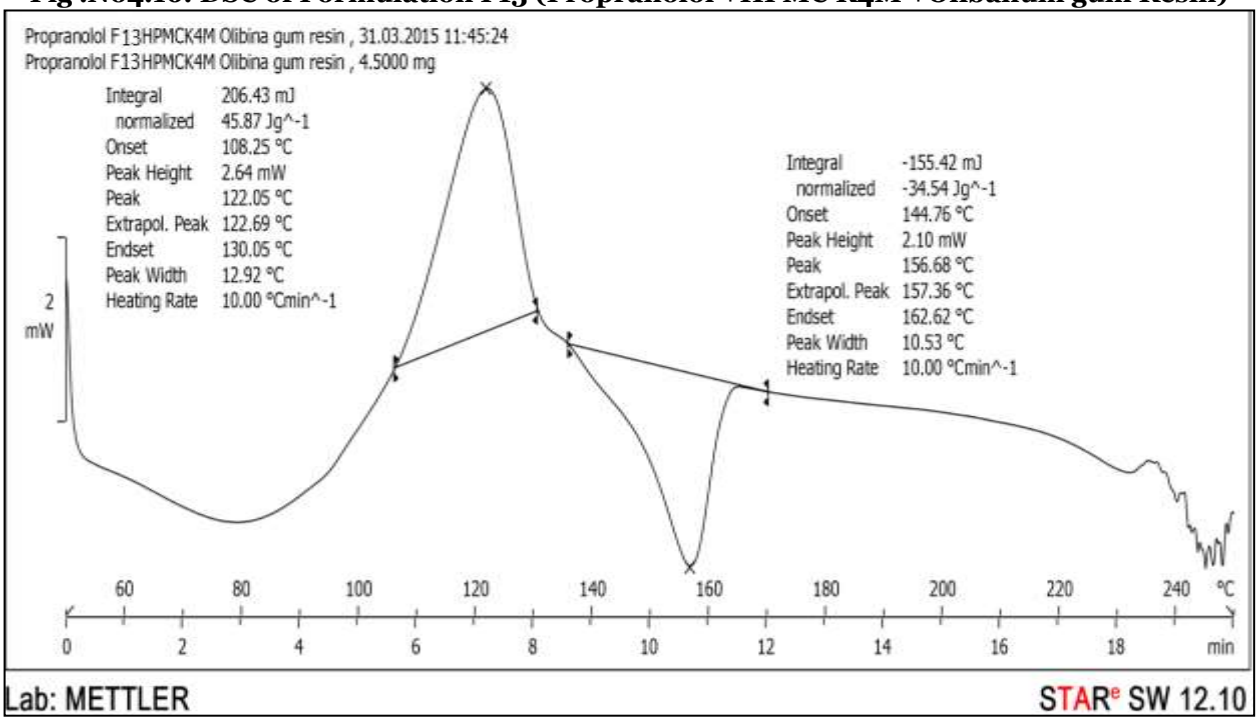


Fig .No4.16: DSC of Formulation F13 (Propranolol +HPMC K4M +Olibanum gum Resin)



4.3: PRE COMPRESSION STUDY:

Table No: 4.3 Results of flow property.

BATCH	ANGLE OF REPOSE (°)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	COMPRESS-BILITY INDEX	HAUSNER'S RATIO
F1	24.6	0.537	0.610	12.23	1.13
F2	23.7	0.524	0.601	12.83	1.14
F3	24.7	0.541	0.626	13.55	1.15
F4	24.8	0.560	0.630	11.55	1.12
F5	23.5	0.580	0.658	11.85	1.13
F6	24.0	0.579	0.670	12.18	1.15
F7	23.5	0.565	0.637	12.80	1.12
F8	22.5	0.540	0.626	11.95	1.15
F9	23.6	0.559	0.631	12.63	1.12
F10	22.4	0.584	0.659	12.45	1.12

F11	25.2	0.545	0.625	11.82	1.14
F12	24.2	0.572	0.664	13.15	1.16
F13	25.25	0.365	0.425	14.07	1.16
F14	25.46	0.361	0.428	15.61	1.19
F15	27.75	0.365	0.434	15.86	1.19

The formulated Powder were characterized with respect to angle of repose, bulk density and tapped density. All formulation show excellent flow properties.

4.4:POST COMPRESSION STUDY.

Table No. 4.4 Evaluation parameters of formulations:

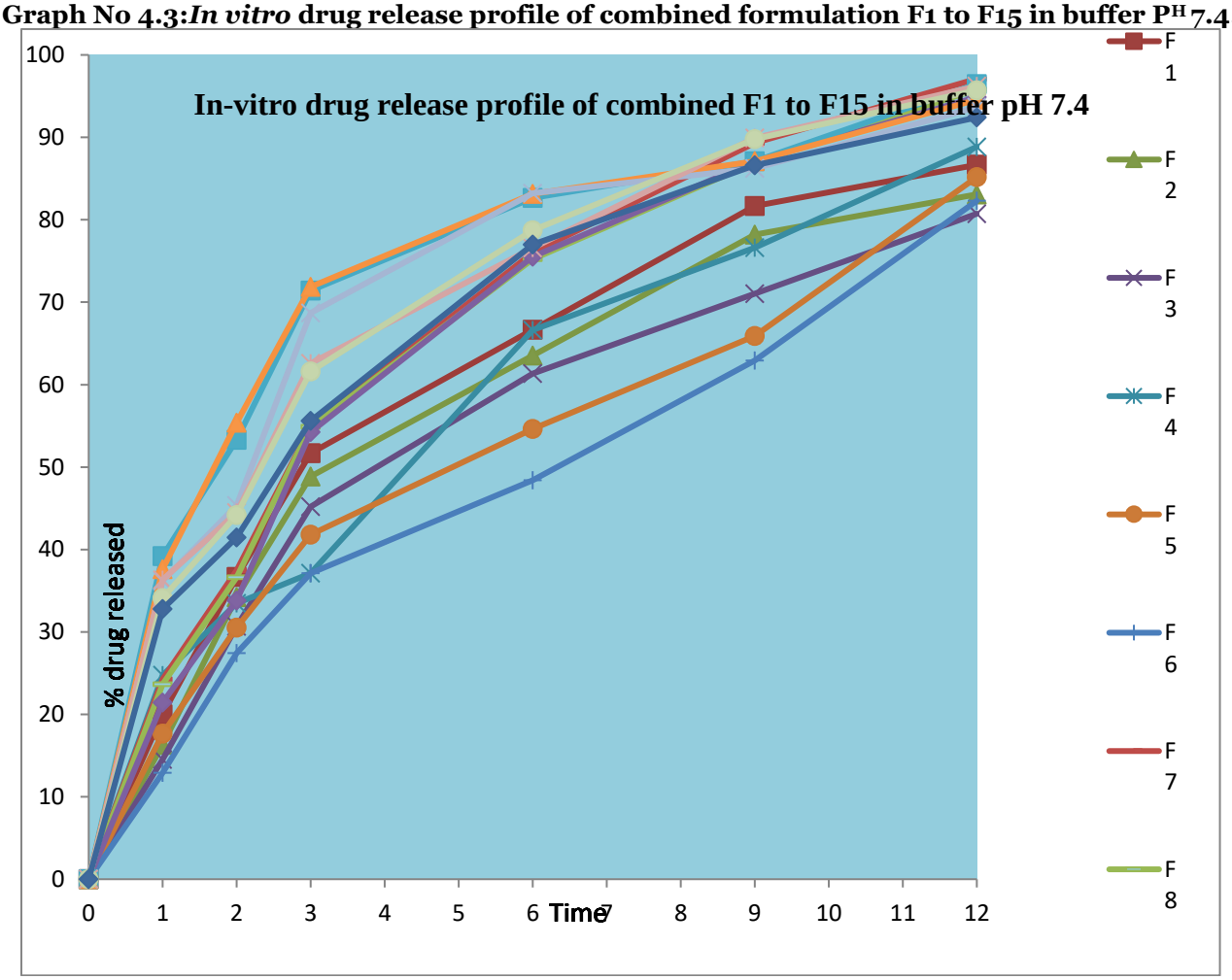
Formulation code	**Evaluation parameter**				
	Thickness ± S.D. (mm) (n = 5)	**Hardness ± S.D. (kg/cm²) (n = 5)**	**Friability (%)**	**Average weight variation (n=20)**	**Drug content (%)**
F1	4.64±0.13	5.86±0.21	0.03	301.6±1.153	93.10
F2	4.55±0.11	5.74±0.41	0.07	306.1±2.111	95.25
F3	4.62±0.23	5.72±0.25	0.11	304.2±2.172	96.12
F4	4.52±0.15	5.82±0.25	0.63	304.6±1.183	97.84
F5	4.53±0.27	5.68±0.13	0.18	303.8±2.211	96.55
F6	4.44±0.19	5.66±0.23	0.21	304.2±1.121	95.68
F7	4.52±0.16	5.96±0.28	0.29	304.8±3.189	98.27
F8	4.53±0.19	5.44±0.23	0.17	305.3±1.198	97.84
F9	4.56±0.22	5.74±0.11	0.29	301.1±1.143	99.13
F10	4.65±0.21	5.62±0.19	0.27	300.9±0.102	98.70
F11	4.53±0.23	5.70±0.15	0.25	300.7±3.172	99.56
F12	4.43±0.21	5.72±0.23.	0.67	304.7±2.173	98.27
F13	5.25±0.50	5.3+_0.425	0.30	300±11	98.70
F14	4.10+_0.80	6.6+_0.50	0.41	298+_10	96.98
F15	5.29±0.84	5.4±0.60	0.39	319±7	96.55

5.5 In-vitro drug release study.

Table No 4.5 :*In vitro* drug release profile of combined formulation F1 to F15 in buffer P^H 7.4

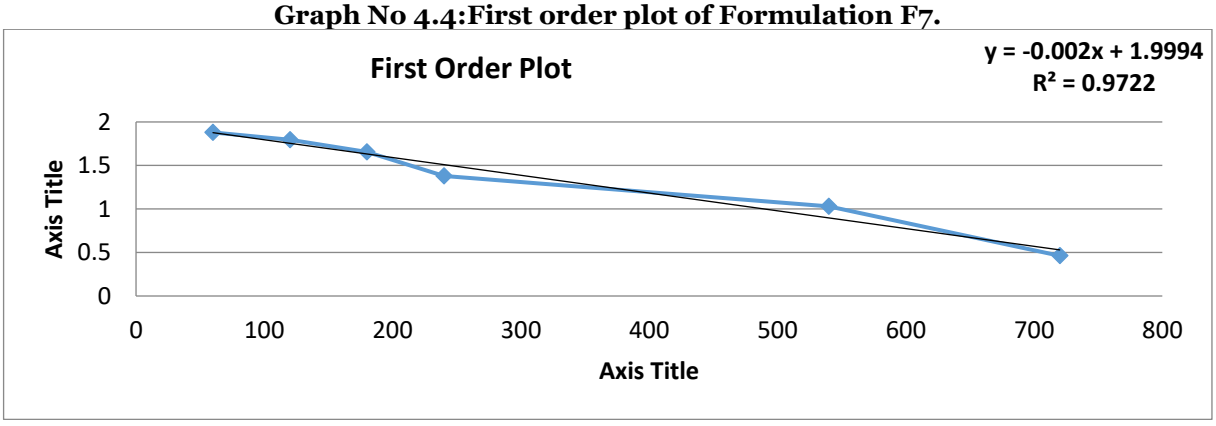
Time in hrs	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F 10**	**F 11**	**F 12**	**F 13**	**F 14**	**F 15**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	20.74	16.29	14.53	24.75	17.67	12.91	24.27	23.64	21.41	39.18	37.60	36.16	36.31	34.09	32.78
2	36.62	34.21	30.67	33.47	30.53	27.43	37.44	36.65	33.79	53.31	55.37	45.32	44.49	44.17	41.46
3	51.67	47.24	45.21	37.12	41.78	37.11	54.89	54.89	54.26	71.39	71.87	68.70	62.57	61.62	55.60
6	66.71	63.53	61.35	66.63	54.64	48.41	75.99	75.20	75.52	82.66	83.13	83.23	76.56	78.74	76.98
9	81.66	78.19	71.04	76.63	65.89	62.94	89.32	86.94	87.10	87.10	87.10	86.23	89.92	89.79	86.62
12	86.58	83.08	80.73	88.85	85.18	82.30	97.10	95.83	94.88	96.46	94.56	93.65	96.21	95.71	92.41

Graph No 4.3:*In vitro* drug release profile of combined formulation F1 to F15 in buffer PH 7.4.

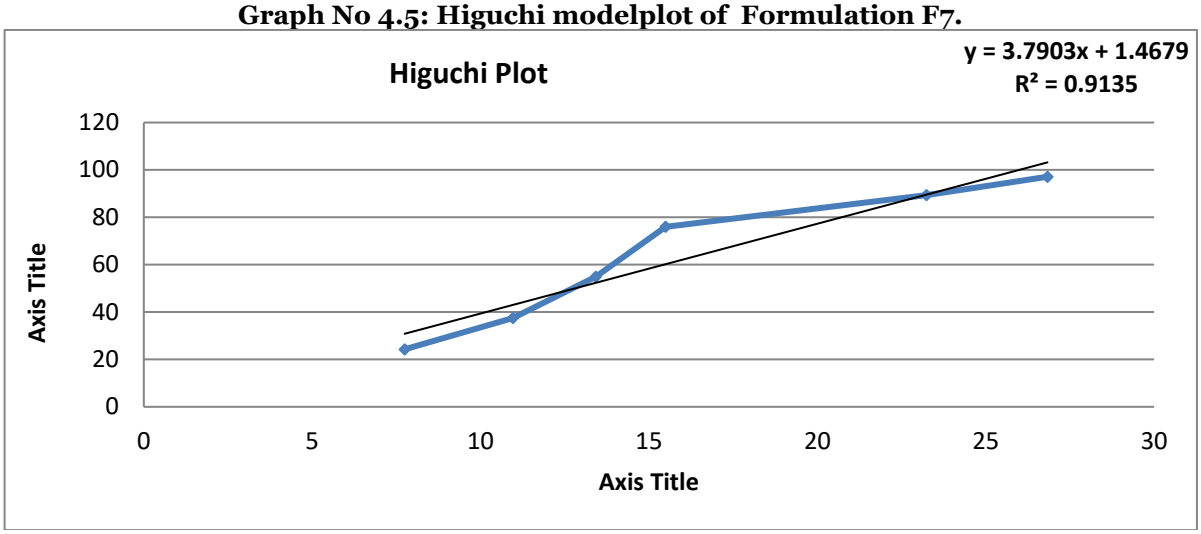


4.6: Drug Release Kinetic study of Formulaion F7.

Graph No 4.4:First order plot of Formulation F7.



Graph No 4.5: Higuchi modelplot of Formulation F7.



Graph No 4.6:Korsmeyer-Peppas plot of Formulation F7.

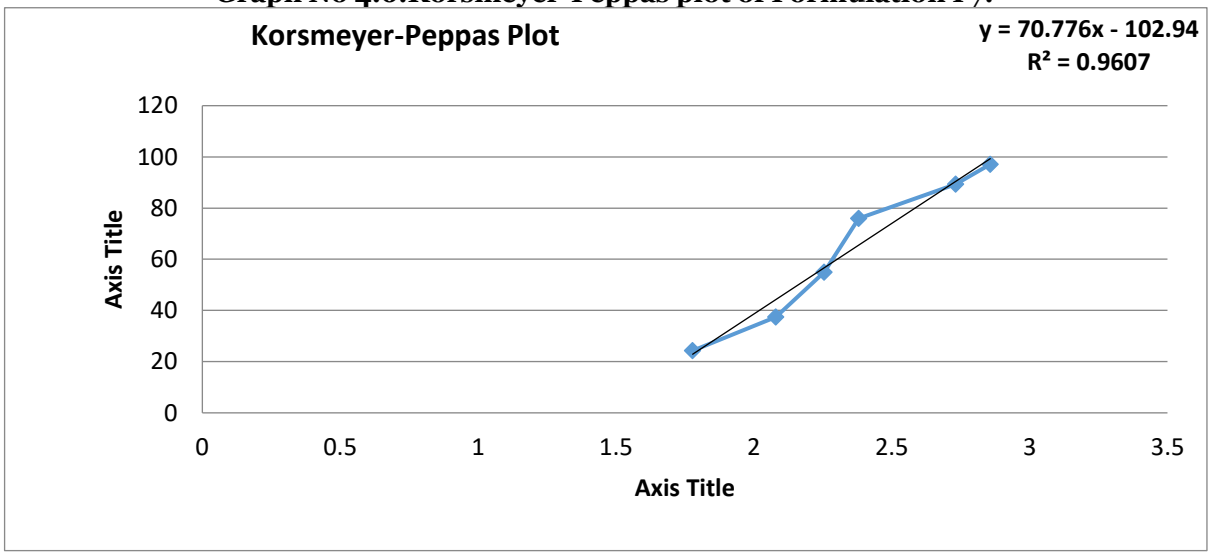


Table No 4.6: Release Kinetic study of Formulation F7.

Sr. No.	Release Kinetic Models	Formulation F 7	
		Slope	Regression
1	First order	0.002	0.9722
2	Higuchi model	3.7903	0.9135
3	Korsmeyer-Peppas model	70.77	0.9607

4.7: Stability studies

Stability of a formulation can be defined as the time period during which the drug product retain its same potency and physical characteristics at the time of manufacturing.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions.

Stability studies for controlled release matrix tablets were carried out by keeping them in aluminium foil and subjected to elevated temperature and humidity conditions of 40° C and 75 % RH. Samples were withdrawn for every 10 days of storage for one months and evaluated for appearance, weight variation, friability, thickness, hardness, drug content and drug release. The optimized batch was subjected to stability studies confirmed that there was no significant change in appearance, Thickness, Friability, Weight variation, Hardness, drug content uniformity and *In vitro* drug release.

Table No.4.7:Data for stability studies (n=3)OF Formulation F4.

Parameter	Initial ± SD	After 10 Days (40°C,75%RH) ± SD	After 20 Days (40° C, 75 %RH)± SD	After 30 Days (40°C,75%RH) ± SD
Description	Whitecolored , round shape	white colored, round shape	white colored, round shape	white colored, round shape
Thickness (mm)	2.61 ± 0.115	2.61 ± 0.112	2.61 ± 0.110	2.61 ± 0.107
Friability (%)	0.531	0.528	0.528	0.528
Weight Variation mg	250±2.40	249± 2.40	249 ± 2.41	249± 2.41
Hardness (kg/cm²)	6.1 ± 0.16	6.1 ± 0.19	6.1 ± 0.23	6.1 ± 0.23
Drug content (%)	97.84 %	97.83 %	97.80 %	97.80 %
Drug Release	88.85 %	88.83 %	88.83 %	88.83 %

Table No. 4.8:Dissolution profile of F4 at 40° C, 75 % RH at various periods.

Time (hr)	Initial ± SD	After 10 days ± SD	After 20 days ± SD	After 30 days ± SD
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	24.75± 0.13	24.73± 0.16	24.73± 0.18	24.72± 0.16
2	33.47± 0.12	33.45± 0.20	33.45± 0.16	33.44± 0.10
3	37.12± 0.17	37.09± 0.18	37.07± 0.18	37.05± 0.20
6	66.63± 0.12	66.62± 0.12	66.60± 0.11	66.58± 0.13
9	76.63± 0.13	76.60± 0.09	76.57± 0.19	76.54± 0.17
12	88.85± 0.14	88.84± 0.18	88.84± 0.18	88.83± 0.18

Discussion

5.1 Preformulation Studies:

a. UV Scanning:

Preformulation studies were conducted prior to the development of sustained release tablets of Propranolol . It was found that the estimation of Propranolol by spectrometric method at 290 nm has good reproducibility.

b. Standard Plot:

The standard calibration curve of Propranolol hydrochloride was obtained by plotting absorbance vs. concentration. Table 4.1 and 4.2 shows the absorbance values of Propranolol . The standard curve is shown in figure 4.1 and 4.2. The standard calibration curve shows the correlation coefficient of 0.9954. The curve was found to be linear in the concentration range of 2 to 12µg/ml (Beer's range) at 290 nm. The calculations of drug content, in vitro drug release and stability studies are based on this calibration curve.

c. Melting point:

The melting point of Propranolol hydrochloride was determined by capillary tube method and it was found to be 163-165°c which is same as that of literature value.

d. Drug-excipients Compatibility Studies:

FTIR Studies:

To study the compatibility of the drug with various polymers, IR spectra of drug and formulation components were carried out. The IR spectra of drug and optimized formulation were shown in figure 4.2-4.10.

5.2 Formulation Design:

Formulation Design study is important for selection of appropriate excipients for preparation of tablets. The three different conc of Olibanum Gum ,Olibanum resin and HPMC K 4M, were used for preparation of tablets. The batches of tablets were prepared by direct compression method using other commonly used excipients. The composition of 15 formulations is given in table 3.1.

5.3 Evaluation of Tablets:

5.3.1 Pre-compression evaluation parameters:

a. Bulk Density and Tapped Density:

The bulk density and tapped density of tablet blends of each batch was determined and was found in the range of 0.36 - 0.53 gm/cm3 and 0.43 - 0.61 gm/cm3 respectively indicate good flow. The results were shown in table no.4.3.

b. Angle of repose (θ):
Table 4.3. shows the results obtained for angle of reposes of all the formulations. The values were found to be in the range of 22.5 to 25.25. All formulations showed the angle of repose within 27°. It indicates that all formulations showed good flow properties.
c. Carr's index (Compressibility index):- Compressibility index of tablet blend of each batch was determined and was found in the range of 11.55-15.86 % indicating the powder blend have the required flow property for compression which is desirable for content uniformity and less weight variation in final tablets.
d. Hausner's ratio:
Hausner's ratio of the powder was determined from the loose bulk density and tapped bulk density. Hausner's ratio of all the formulations lies within the acceptable range. The Hausner's ratio of all the formulations is in the range of 1.12 to 1.19. It is shown in table 4.3.

5.3.2 Post-compression evaluation parameters:
All the formulations were subjected for organoleptic, physical and chemical evaluations. Shape, uniformity of thickness, hardness, friability, weight variation, drug content, in vitro dissolution studies were carried out.
a. Size, shape and color of tablets:
Randomly picked tablets from each formulation batch examined under lense for shape and in presence of light for color. The tablet shows flat, ovate shape and white in color. All ingredients used were white in color. There was no change in color and odour of the tablets in all the formulations. It indicates that all the excipients used were compatible with the drug and did not cause any chemical reaction that affects the properties of formulation.
a. Thickness:
The thickness of the tablets was measured by using Screw Gauge by taking the tablets randomly. The mean values are shown in table 4.4 The values are almost uniform in all formulations. Thickness was found in the range from 4.52±0.15mm to 5.25±0.50mm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.
b. Hardness test:
The result of hardness is given in table 4.4 Hardness test was performed by Monsanto hardness tester or Precision dial type hardness tester. Hardness was maintained to be within 5.3+_0.425kg/cm² to 5.86±0.21 kg/cm². The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness.
c. Friability:
The result is given in table 4.4 was found well within the approved range (<1%) in all the formulation. Friability was in between 0.30% to 0.63%. Results revealed that the tablets possess good mechanical strength.
d. Weight variation test:
All the tablets passed weight variation test as the % variation was within the pharmacopoeia limit of ±7.5 %. The weight of all the tablets was found to be uniform. This is due good flow property and compressibility of all the formulations.

e. Drug content uniformity:
The content uniformity was performed for all 15 formulations and results were shown in table 4.4. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 80.10 to 97.41 % of Propranolol. The results indicated that in all the formulations the drug content was uniform.

5.4 In-vitro dissolution studies:
All the nine formulations were subjected for the in vitro dissolution studies using tablet dissolution tester (USP) Electrolab. The samples were withdrawn at different time intervals, filter, diluted and analyzed at 290 nm. Cumulative drug release (mg) and Cumulative % drug release were calculated on the basis of mean amount of Propranolol present in the respective tablet. The results obtained in the in-vitro drug release for formulations F1 to F15 are given in Table 4.5.
These Formulation (F1-F15) Showed Drug release 86.66%, 83.08%, 80.73%, 88.85%, 85.18%, 82.30%, 97.10%, 95.83%, 94.88%, 96.46%, 94.56%, 93.65%, 96.23%, 95.71% ,92.41% respectively at the end of 12 hrs. This slow drug release of drug might be due to complex nature of polymer which having the net like structure with drug molecule. The drug release was completely achieved within 12 hrs. In all the formulations the drug release within 12 hrs.
In comparative study for the formulations F7 (HPMCK4M) drug releases 97.10%, at the end of 12 hrs and graphical representation was shown in fig. 4.3.
Best Selected batch was F7 because of highest percentage drug release at the end of 12 hrs among all the formulations and best fitted to First order.

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