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FORMULATION AND EVALUATION OF RANOLAZINE EXTENDED RELEASE TABLETS

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Abstract:

Ranolazine is an anti-anginal drug used to treat chronic stable angina in adults. The main drawback with normal conventional dosage form is that the solubility of Ranolazine is relatively high at the lower pH (4.5 and below) and also having short plasma half- life of 7hrs. The main objective of research work was to develop once daily extended release tablets of Ranolazine by both wet granulation and direct compression techniques and to compare the in-vitro dissolution profiles with the domestic reference product. We evaluated the all physicochemical parameters like drug content bulk density tapped density compressibility angle of repose weight variation hardness friability and dissolution method. All the formulations F1-F12 followed zero order and first order kinetics.F11 is showed the higher cumulative drug percent release compared to other formulations. The in-vitro release of Ranolazine extended release tablets was studied in 900 ml of 0.1N HCl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37±0.5°C for 2hrs, then release studies were conducted in pH 6.8 phosphate buffer for 24 hours. It was found to be stable during accelerated stability studies conducted at 40 °C / 75% RH for three months as per ICH guidelines.

Keywords: *Ranolazine, extended release, HPMC K15M, ethyl cellulose, phosphate buffer.*

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INTRODUCTION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects, when compared to other routes of administration. In general, the oral medication is considered as the first avenue investigated in the discovery and development of new pharmaceutical active ingredients and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost- effective manufacturing process. A dosage form that allows at least a two –fold reduction in dosage frequency as compared to that drug presented as an immediate release (conventional) dosage form are considered as extended-release formulations. Ranolazine is novel drug used in treatment of chronic heart disease such as angina. It has anti-anginal effect that does not depend upon reduction in rate or blood pressure. The exact mechanism of action is unknown, but it was believed to reduce angina/ischemia by selectively inhibiting the late sodium current that results in reduced intracellular sodium and calcium overload during ischemia. The QT prolongation effect of Ranolazine on the surface electrocardiogram is the result of inhibition of IKr, which prolongs the ventricular action potential. Ranolazine and its pharmaceutical salt is having relatively high solubility at the low pH that occurs in the stomach. Ranolazine shows high pH dependent solubility, it is freely soluble in aqueous solutions having pH below 4.5 and then, as the pH increases solubility of the drug decreases dramatically, furthermore Ranolazine has a short half-life 7 hours, the acid solubility property of Ranolazine results in rapid drug absorption and clearance, causing large and undesirable fluctuation in plasma concentration and short duration of action, thus necessitating frequent oral administration for adequate treatment. In order to maintain plasma drug concentration in the body twice daily formulation of Ranolazine is needed for better control of drug release and therapeutic activity up to 24 hrs.

MATERIALS AND METHODS:

MATERIALS

The gift sample obtained by **Ranolazine** (gift sample from Natco Pharma Pvt Ltd, Hyderabad), **Ethyl cellulose** (kemphesol, Mumbai), **Hydroxyl Propyl Methyl Cellulose** (COLORON, INDIA), **Microcrystalline cellulose pH 105** (FMC, IRELAND/U.S.A), **Dicalcium phosphate dehydrate** (Finarchemicals), **Polaxomer 407** (Kemphesol, Mumbai), **Magnesium stearate** (S.d – fine chemicals).

INSTRUMENTS

Electronic weighing balance, Monsanto hardness tester (M/s Campbell Electronics, MODEL EIC-66, India), Roche friabilator (M/s Campbell Electronics, India), Tapped density tester, Mechanical stirrer, pH meter, Mesh #20,40,60, Dissolution test apparatus, Tablet Compression machine, UV-VIS spectrometer(SL-150,ELICO), Stability chambers, vernier calipers.

METHODS:

Solubility studies

The solubility studies were performed in different media like 0.1N HCl, Distilled water, 5.8 pH phosphate buffer, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer. Excess of Ranolazine was added to 5ml of each fluid in a 25ml stoppered conical flasks and the mixtures were shaken for 24 hours at room temperature (25±1^{o} C) on a rotary flask shaker. After 24 hours of shaking 1 ml aliquots were withdrawn and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for drug by measuring absorbance at 271nm. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

Preparation of a stock solution

Accurately weigh the 10mg of drug transfer into clean and dried 10ml volumetric flask and add a methanol upto 10ml. From this stock solution was subsequently diluted with 0.1N HCl buffer to get a series of dilutions containing 10, 20, 30, 40 and 50 µg/ml of solution measured at 271nm and against same as blank.

Calibration curve

For the estimation of Ranolazine, the stock solution was subsequently diluted with 0.1N HCl to get a series of dilutions containing 10,20,30,40 and 50µg/ml of solution and measured the absorbance at 271 nm (UV-VIS spectrophotometer, SL-150, ELICO) against same dilution as blank. The above procedure was followed to construct calibration curves in different media.

Pre compression Parameters

Preformulation testing is the first step in the rational development of dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and combined with excipients. The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. The following preformulation studies were performed on Ranolazine API.

DETERMINATION OF DENSITIES

Apparent density (Bulk)

Bulk density is the ratio of given mass of powder to its bulk volume. The bulk density, as a measure used

to describe packing material granules, was determined transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The powder was levelled carefully without compacting and the unsettled apparent volume (Vo) was noted. The bulk density in g/mL was calculated by the formula

Bulk density = M/Vo

Where, M is the weight of the sample taken

Tapped density

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted, and the sample was tapped on horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

Tapped density = weight of sample in grams/ tapped volume

Angle of repose

The angle of repose has been used to characterize the flow properties of solids angle of repose is characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane.

$$\text{Tan } \theta = \frac{h}{r} \qquad \Theta = \text{Tan}^{-1}\frac{h}{r}$$

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

A funnel was fixed at a height of approximately 2-4 cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder.

Flow property	Angle of repose (°)
Excellent	25-30
Good	31-35
Fair	35-45
Poor	45-55
Very poor	56-65
Very, very poor	>65

Carr's index (compressibility)

The compressibility and Hausner's ratio are the measures of the propensity of a powder to be compressed. As such, these are the measures of relative importance of interparticulate interaction. In a free flowing powder, such interactions are less significant and the bulk and tapped densities will be closer in value. For poor flowing materials, the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio.

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\%\text{compressibility} = \frac{\text{tapped density} - \text{bulkdensity}}{\text{Tapped density}} * 100$$

Hausner's ratio The ratio of Tapped density to the bulk density of the powders is called the Hausner's ratio.

$$\text{Hausner's ratio} = \frac{tapped\ density}{bulk\ density}$$

The following table shows the acceptance criteria for flow properties of the compound according to USP. The results were given in table.1.

Table.1. Acceptance criteria for flow properties according to USP

Compressibility index(%)	Flow properties	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very,very poor	>1.60

Table.2. Formulae for the tablets of Ranolazine with different polymers

Formula	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
Ranolazine	500	500	500	500	500	500	500	500	500	500	500	500
Ethyl cellulose	106.5	142	177.5	-	-	-	-	-	-	-	-	-
Polaxomer407	-	-	-	106.5	-	-	-	-	-	-	-	-
HPMC K4M	-	-	-	-	106.5	142	177.5	106.5	-	-	-	-
Chitosan	-	-	-	-	-	-	-	35.5	-	-	-	-
HPMC K15M	-	-	-	-	-	-	-	-	106.5	142	177.5	142
DCP	89.3	54	18.5	89.3	89.3	54	18.5	53.8	89.3	54	18.5	-
MCC 105	-	-	-	-	-	-	-	-	-	-	-	54
Magnesium Stearate	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2
Total weight	710	710	710	710	710	710	710	710	710	710	710	710

POST COMPRESSION PARAMETERS

Evaluation of prepared matrix tablets: The compressed extended release tablets from different formulations were evaluated for different compression parameters like hardness, weight variation, thickness, friability and In-vitro dissolution testing is carried out for drug release.

Hardness: Six tablets from each batch were selected and hardness was measured using Monsanto hardness tester (M/s Campbell Electronics, MODEL EIC-66, India).

Friability: Six tablets from each batch were randomly selected and weighed. These pre weighed tablets were subjected to friability testing using Roche friabilator (M/s Campbell Electronics, India) for 100 revolutions. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.

%F=1-(loss in weight / initial weight)*100

Weight variation: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method described in USP.

Thickness: Thickness of tablets was determined by using Vernier calipers.

Drug content uniformity: Five tablets were weighed and powdered in a motar. Accurately weighed tablet powder samples equivalent to 20mg of Ranolazine was transferred to a 100ml volumetric flask and the Ranolazine was extracted into 75ml methanol. The solution
was suitably diluted with 0.1N HCl and the absorbance was measured at 271nm. The estimations were carried out in triplicate.

In vitro dissolution studies: The tablet samples were subjected to invitro dissolution studies using type II dissolution apparatus at 37±2°C and 50 rpm speed. As per the official recommendations of USFDA, 900ml was withdrawn at specific time intervals and replaced with fresh buffer. The aliquots were diluted and assayed for anolazine by measuring absorbance at a wavelength of 271nm. The dissolution studies were conducted in triplicate.

Stability studies: Stability studies, carried out according to ICH guidelines by storing the tablets at 40°c/75±5%RH for a period of three months.

RESULTS AND DISCUSSION:

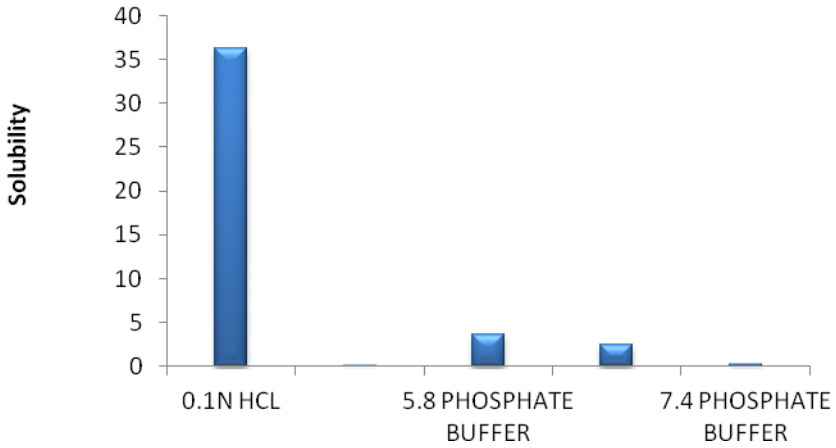

Fig.no.1Solubility studies of Ranolazine in different media

Calibration:

Table.3. calibration curve data for estimation of Ranolazine in 0.1 N HCl

Concentraion (µg/ml)	Asorbance in 0.1N HCl
0	0.000
10	0.054
20	0.105
30	0.160
40	0.210
50	0.271

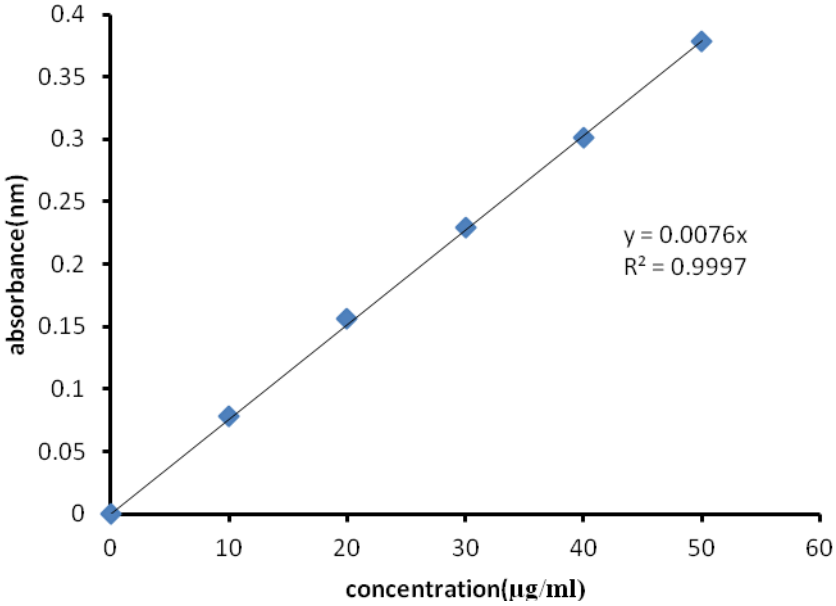

Fig.no.2 Calibration curve of RANOLAZINE

Inference: The solubility states that the drug has its highest solubility in 0.1N HCl (34.238 mg/ml) and its lowest solubility in distilled water (0.02 mg/ml).

Table.4. Precompression parameters

Powder blend	Bulk density(ρ_b)	Tapped density(ρ_t)	Compressibility index(%)	Hausner's ratio	Angle of repose(θ)
Pure drug	0.45	0.63	26.459	1.435	33.24
F1	0.806	0.926	12.90	1.18	18.45
F2	0.820	0.962	14.75	1.12	19.65
F3	0.833	0.962	13.33	1.2	22.35
F4	0.667	0.781	14.67	1.22	25.96
F5	0.658	0.769	14.47	1.25	26.82
F6	0.676	0.781	13.51	1.25	26.96
F7	0.667	0.794	16.00	1.22	25.72
F8	0.676	0.806	16.22	1.19	24.89
F9	0.658	0.794	17.11	1.3	25.78
F10	0.667	0.820	18.67	1.24	26.5
F11	0.676	0.833	18.92	1.25	26.47

Table.5. Post compression parameters

Formulation	Drug content ± SD(mg/tab)	Weight variation ±SD (mg)	Hardness ± SD (kg/cm^2)	Friability (%)
F1	496±1.25	699±1.51	7.0±0.32	0.29
F2	498±1.65	698±1.51	7.0±0.58	0.32
F3	497±1.05	710±0.92	7.0±0.52	0.27
F4	500±0.98	710±1.01	7.0±0.18	0.35
F5	500±0.97	710±1.21	7.0±0.32	0.48
F6	499±0.65	710±0.94	7.0±0.34	0.42
F7	500±0.97	710±1.22	7.0±0.32	0.36
F8	499±0.84	710±0.87	7.0±0.38	0.34
F9	498±0.78	710±1.36	7.0±0.46	0.26
F10	498±0.68	710±1.45	7.0±0.51	0.35
F11	499±0.57	710±0.90	7.0±0.16	0.28

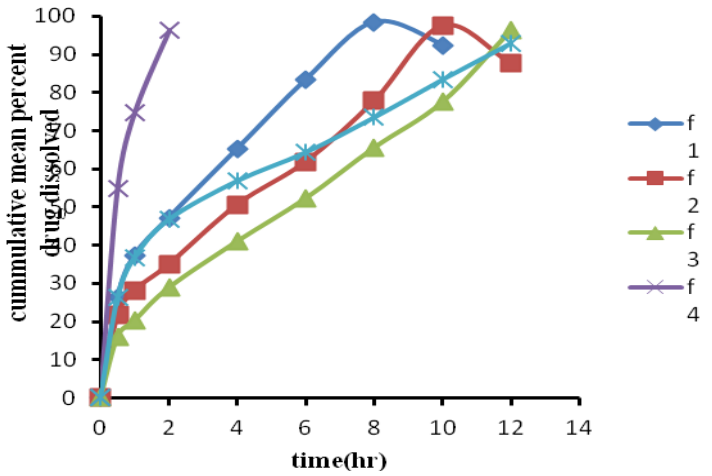

Fig.3.dissolution profile for formulations F1, F2, F3, F4 and F5

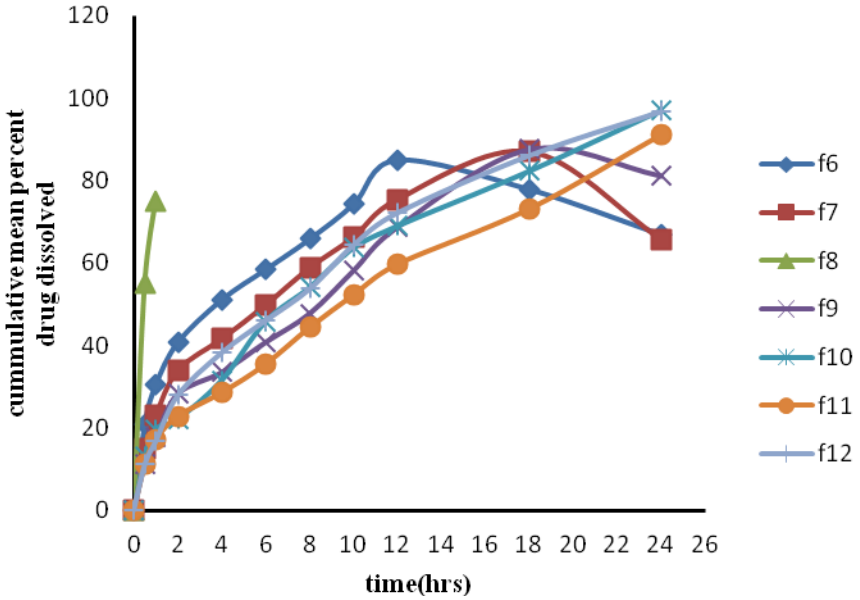

Fig.4.Dissolution profile for F6, F7, F8, F9, F10, F11 and F12

FTIR studies:

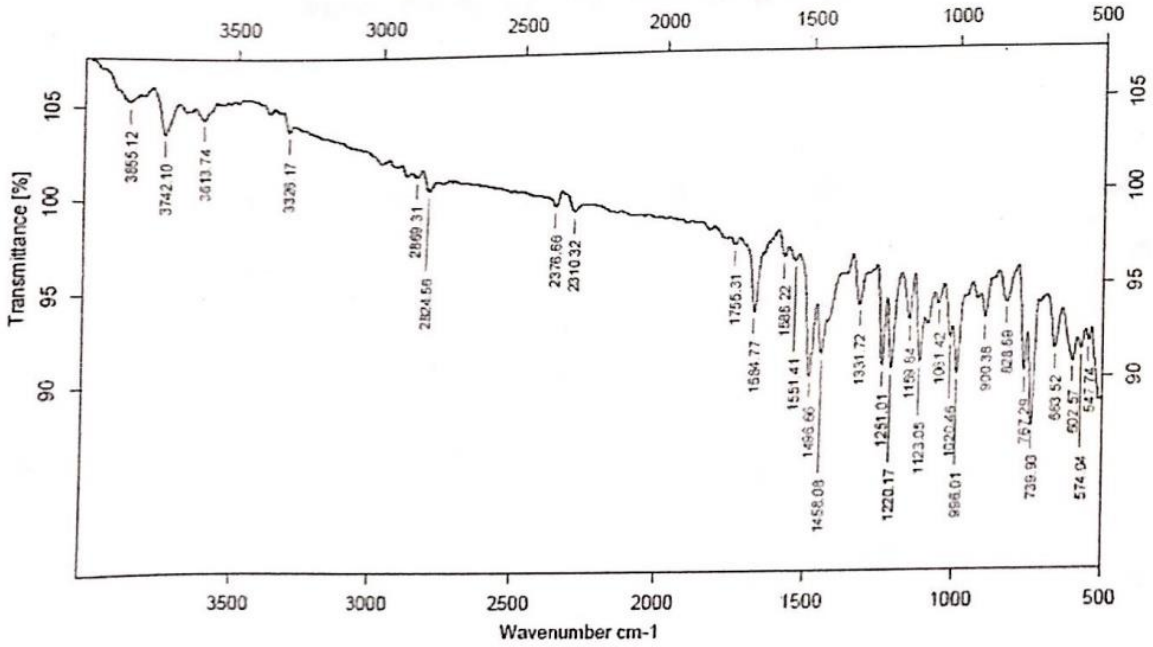

Fig.5. FTIR spectrum for pure drug Ranolazine

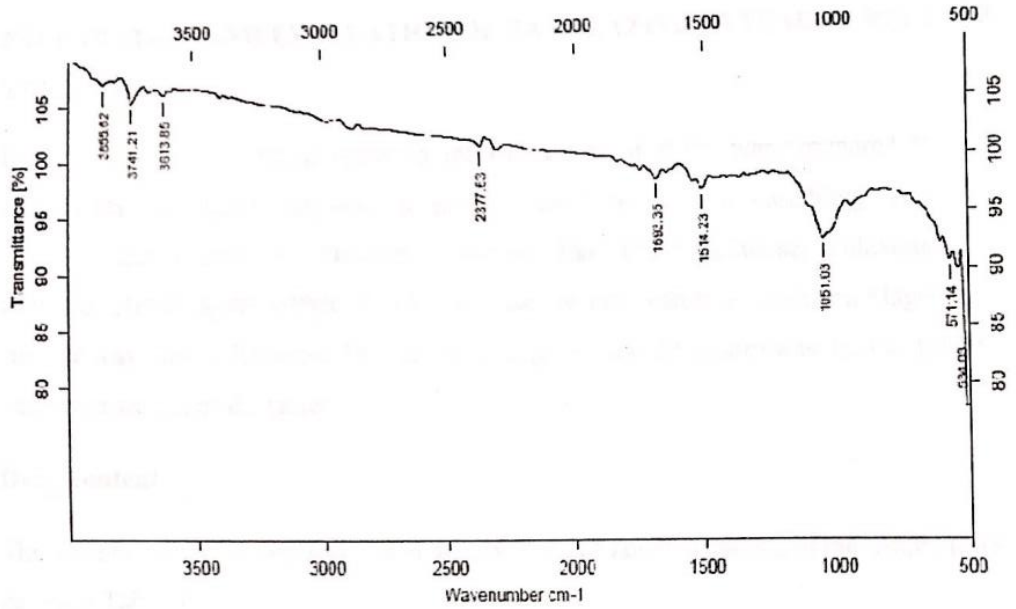

Fig.6. FTIR spectrum of HPMC K15M

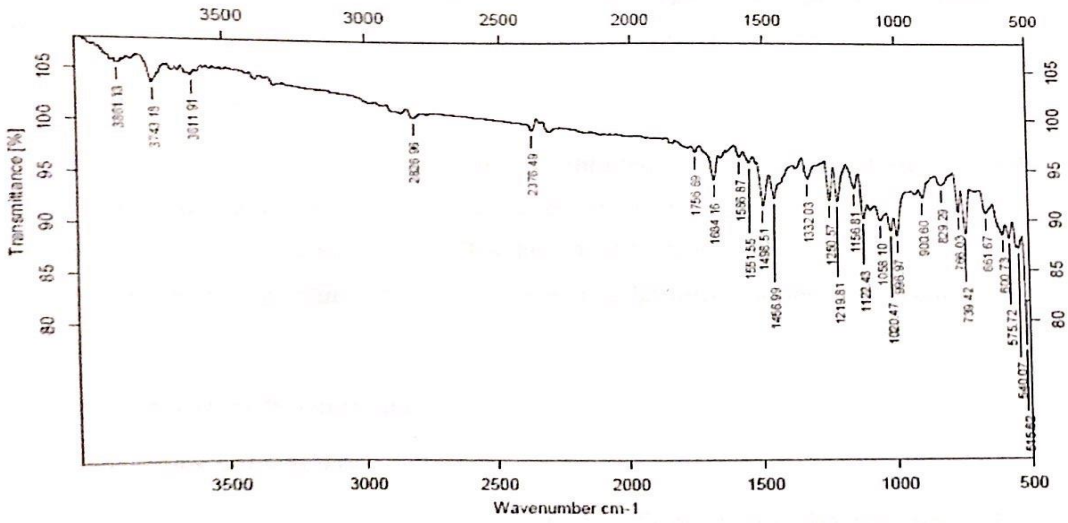

Fig.7. FTIR spectrum of Ranolazine-HPMC K15M (1:1)

Fig.5 shows that the IR spectrum of pure Ranolazine and **Fig.6** shows the IR spectrum of HPMC K15M. **Fig.7** shows the IR spectrum of 1:1 ratio of drug and polymer. From the FTIR studies the characteristic absorption bands for important functional group of pure drug were identified. IR spectra at 1688.2 cm^{-1} (C=O ketone stretch), 1655.8 cm^{-1} (C=O carboxylic acid stretch), 1437.8 cm^{-1} (C=C stretch aromatic), 1335.8 cm^{-1} (N-H stretch), 1295.1 cm^{-1} (C-N stretch) and 1257.5 cm^{-1} (C-O stretch).FTIR spectra shown in the figures showed that the characteristic bands of Ranolazine were not altered without any change in their position, indicating no chemical interactions between the drug and polymer.

DISCUSSION

The linearity results of Ranolazine standard in dissolution medium i.e., 0.1 N HCl shown in the above graph was found to be satisfactory since the correlation coefficient was 0.999. The present analytical method obeyed beers law in the concentration range of 10-50 µg/ml and suitable for estimation of the drug showed at fig.2

Calibration curve for Ranolazine was constructed in different buffer solutions as the solubility studies were carried out the drug in all these buffers. The solubility experiment we clearly observed at more soluble in 0.1N HCl compare to other buffer mediums given in a fig.1 and table.3.

Flow properties of granules, prepared from all the formulations are good except for F1 formulation as obtained from the Bulk density, Tapped density, Hausner's ratio, Compressibility index and angle of repose values indicated.

Table.6. Mean ± SD percent of Ranolazine dissolved from formulations F1 – F12

Time (hr)	Cumulative percent drug dissolved mean ±SD											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
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
0.5	26.22	21.66	16.02	54.96	26.22	20.74	14.91	54.96	11.27	13.056	11.24	11.12
1	37.37	28.2	20.22	74.88	36.78	30.43	22.97	74.88	17.64	19.716	17.18	16.75
2	47.22	34.97	28.8	96.36	46.71	40.71	33.94		28.26	22.152	22.86	27.90
4	65.31	50.65	40.97		56.83	51.09	41.57		33.48	31.560	28.56	38.28
6	83.42	61.88	52.2		64.29	58.46	49.80		40.80	45.840	35.52	46.08
8	98.48	77.82	65.48		73.46	65.83	58.80		47.76	54.120	44.40	53.76
10	92.42	97.54	77.8		83.40	74.31	66.26		58.20	63.720	52.32	64.44
12		87.68	96.25		92.91	85.03	75.43		68.76	69.00	59.76	72.24
18						77.91	87.00		87.60	82.320	73.20	86.16
24						66.94	65.66		81.12	97.080	91.20	96.84

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