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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MATRIX TABLETS OF PROPRANOLOL HCL BY USING RELEASE RETARDING AGENTS

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ABSTRACT

The main aim of the present work is to formulate and develop matrix tablets of Propranolol HCl. Selected suitable method for preparation process of Direct compression method for matrix tablets of Propranolol HCl by using varying concentrations of HPMC K4M, HPMC K100M, sodium alginate and Xanthan gum as a release retarding agents, dibasic calcium phosphate, Microcrystalline cellulose as diluents, talc and magnesium stearate as glidant and lubricant. Excipients compatibility studies were carried out by Stability studies and FT-IR studies between API and selected excipients. All the matrix tablets of Propranolol HCl formulations were evaluated for Pre-compression and post-compression parameters. All the formulations were evaluated for the hardness, friability, thickness, weight variation, drug content uniformity, and in-vitro drug release studies. Based on in-vitro drug release the polymer Xanthan gum showed better dissolution control compared to the other polymers like HPMC K4M and HPMC K100M and sodium alginate. Release of Propranolol HCl from the tablets formulated by employing 25mg of Xanthan gum and 77 mg dibasic calcium phosphate showed that more drug release So, the formulation F- 10 was the optimized formula.

***KEYWORDS**: Propranolol HCl, HPMC, Sodium Alginate, Xanthangum, Dibasic Calcium Phosphate, Release Retarding agents, Diluents, Glidant, Release Kinetics.*

INTRODUCTION

Tablets are the solid dosage forms which contain active pharmaceutical ingredients with suitable diluents. Pharmaceutical manufacturers, physicians and patients prefer tablets as the wide form of medication for the treatment. Tablets offer excellent physico chemical stability properties with safe and convenient ways for administering the active pharmaceutical ingredients (API) with an exact dosage regimen. The tablets can be produced in a bulk with a robust quality control that offers different branding possibilities by means of change in the excipients, colour film coating, different shapes, sizes and logos. The Drug delivery system (DDS) provides an expansion in the markets/indications, with improving product stability and efficacy with no or very less side effects and thus generating opportunities [1].

The other reason for a wide range of solid dosage forms include that these products do not require any sterility problems as that of injections and are easy, less expensive to manufacture. High-precision dosing, and manufacturing efficiency make the tablets most desirable dosage forms. The sterile products like IM and IV injections are not generally preferred by the patients unless provided with sophisticated equipment that gives no or less pain. Many systemic diseases and some of the external diseases requires a quick onset of action immediately after administering a dosage form and thus an immediate release tablets provide a rapid drug release within the therapeutic dose [2].

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MATERIALS AND METHODS

The materials used in the present work as such propranolol HCl is an active drug, HPMC, sodium alginate, Xanthangums are as release retardants polymers, dibasic calcium phosphate, MCC as diluents, Magnesium stearate as glidant and talc as a lubricant [3].

Preformulation Studies:

Drug – excipient compatibility studies:

There is always possibility of Drug - Excipient interaction in any formulation due to their intimate contact. It is also necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies [4].

The excipients weighed according to mentioned ratio and shifted through BSS #30 and blended together. The mixture placed in Petri dish and kept at 40^0C/75% RH. The dishes were observed for every week up to 4 weeks for any physical incompatibility like lump formation, color change.

A) Preparation of pH 1.2 HCl media: Accurately measured8.5 ml of concentrated hydrochloric acid was added to 1000 ml of distilled water.

B) Preparation of pH 6.8 Buffer media: Accurately measured 50 ml of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200ml volumetric flask and 22.4 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 ml with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide.

*C) **Determination of maximum wavelength:*** Concentrations 5-20 µg/ml was prepared using pH 1.2 HCl media and pH 6.8 Buffer media. These concentrations were scanned between the wavelength 250nm to 330nm and the wavelength at which maximum absorbance was observed for each concentration was noted at 290 nm as maximum wavelength.

*D) **Preparation of Calibration Curve:*** Various concentrations of Propranolol HCl were prepared using pH 1.2 HCl media and pH 6.8 buffer media. The absorbance of these concentrations was noted at λmax and calibration curve was plotted taking Concentration on x-axis and Absorbance on y-axis. The equation for the calibration curve was determined and used for calculation of concentration of unknown samples.

Formulations of Propranolol Hydrochloride matrix tablets:

Sifting: The required quantities of Propranolol Hydrochloride, Avicel PH 101 and HPMC were accurately weighed and passed through sieve no 40.

Mixing: The sifted material was mixed in Plastic bag for 5 minutes.

Sifting: The dried granules were passed through sieve no 30.

Lubrication: Sifted granules were lubricated with Magnesium stearate, which was passed through sieve no 40.

Compression: The total blend was poured into the hopper of 16-station compression machine and tablet weight was set to target weight of 240mg. The tablets were compressed using round shaped punches with 3.7 mm diameter with a hardness of about 4-6kg/cm^2.

Prepared formulations:

The formulations of propranolol HCl were prepared by direct compression technique using HPMC K4M, HPMC K100M, sodium alginate and Xanthan gum as release retarding agents in different ratios employing dibasic calcium phosphate, Microcrystalline cellulose as diluents, talc and magnesium stearate as glidant and lubricant.

Table No. 1: Shows that the composition of formulations F1-F12

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Propranolol	80	80	80	80	80	80	80	80	80	80	80	80
MCC101	50	50	50	50	50	50	50	50	50	50	50	50
DCP	77	64.5	52	77	64.5	52	77	64.5	52	77	64.5	52
HPMCK4M	25	37.5	50	-	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	25	37.5	50	-	-	-	-	-	-
Sodium Alginate	-	-	-	-	-	-	25	37.5	50	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	-	25	37.5	50
Mg.Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total tablet Weight	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**

Evaluation studies:

1) Pre-Compression Studies:

Certain methods are used to measure powder characteristics in order to monitor blend suitability for tableting. Good flow properties are essential for the transport of the material through the hopper into and through the feed frame and into dies [5].

a) Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the blend and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula.

$$\tan\theta = h/r$$

Therefore,

$$\theta = \tan^{-1}(h/r)$$

Where,
θ = angle of repose
h = height of the cone
r = radius of the cone base.

Table No. 2: Flow properties and corresponding angle of repose

Flow property	Angle of repose(degrees)
Excellent	25-30
Good	31-35
Fair (aid not needed)	36-40
Passable (may hang up)	41-45
Poor (must agitate, vibrate)	46-55
Very poor	56-65
Very, very poor	>66

b) Bulk density:

The bulk density is used as a measure to describe packing materials or granules.

$$\text{Bulk Density} = \frac{\text{Weight of the powder blend}}{\text{Untapped Volume of thepacking}}$$

Method: Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount (30gm) of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

c) Tapped Density:

Weighed quantities of granules were taken into graduated cylinder, was placed on the tapped density apparatus (Electro Lab USP II), volume occupied by granules was noted down. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

$$\text{Tapped Density} = \frac{\text{Weight of the powder blend}}{\text{TappedVolume of the packing}}$$

$$\text{Compessibility Index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped Density}} \times 100$$

d) Compressibility Index:

Compressibility is the ability of powder to decrease in volume under pressure. Using bulk density and tapped density the percentage compressibility of granules was determined, which is given as Carr's compressibility index.

It can also be expressed as

e) Hausner's Ratio (H):

It is an indication of the compressibility of a powder. It was determined by the ratio of tapped density and bulk density.

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

Table No. 3: Compressibility index and Hausner's ratio Limits

Compressibility Index (%)	Flow characters	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

2) Post Compression Studies:

The prepared matrix tablets were evaluated for general appearance, thickness, hardness, weight variation, friability and drug content.

a) General Appearance:

The tablets prepared were white, round, spherical shape. They were smooth, uniform and free from cracking and chipping.

b) Tablet Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

c) Weight Variation:

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table.

Table No. 4: Weight variation limits

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	>324	5

d) Friability test:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients [9, 10].

Method: 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{friability} = \frac{(w_1 - w_2)}{w_1} \times 100$$

Where: w_1= weight of the tablet before test.
w_2 = weight of the tablet after test

e) Content of active ingredient:

To ensure the consistency of dosage units, each unit in a batch should have active substance content with in a narrow range around the label claim. Dosage units are defined as dosage form containing a single dose or a part of a dose of an active substance in each dosage unit. Ten tablets from each formulation were powdered. The powder equivalent to 50mg of propranolol HCl was weighed and dissolved in 5ml of water and 60ml of methanol in 200ml standard flask shake for 30min and then make up with 0.1N HCl and then centrifuge it from that take 5ml of solution in 50ml standard flask make up with buffer. Generally the drug content in any formulation should fall within the limit of 90-110%.

f) In-vitro drug release studies:

Dissolution method for Propranolol Hydrochloride matrix Tablets: *In Vitro* drug release was performed for the matrix tablets according to the USP, dissolution for 24 hours. Automated Electro Lab type II apparatus were used. Dissolution was done at 100rpm and 37±0.5°C in type-II apparatus. For the first 1.5 hour, 900ml of pH 1.2 Buffer media was used in the dissolution vessels followed by 900ml of pH 6.8 buffer media for the rest 22.5 hours. Samples withdrawn (1ml) were replaced with an equal amount of fresh dissolution medium at particular time intervals, samples were immediately filtered through filter paper and diluted to 5ml with dissolution media. The absorbances of these diluted samples were noted at maximum wavelength 290 nm using Shimadzu UV-Visible Spectrophotometer. The amount of drug present in the samples was calculated using the calibration curve constructed from reference standards. Cumulative % drug release was plotted against time was calculated [6-8].

Dissolution parameters:

Apparatus: USP Type II (Paddle) for matrix tablets.
Medium: 900 ml of pH 1.2 HCl (degassed) for 1.5 hours
900 ml of pH 6.8 Phosphate buffer (degassed) for 22.30 hours
Temperature: 37 ± 0.5^{0}C

Preparation of primary stock solution of Propranolol Hydrochloride:

10mg of Propranolol Hydrochloride was accurately weighed and transferred into the 100 ml volumetric flask, and volume was makeup using water.

Preparation of standard solution of Propranolol Hydrochloride:

1ml of the standard stock solution was diluted to 10 ml using the dissolution media. The solution was filtered through 0.45mm Nylon 66 member filter and absorbance of this was noted.

RESULTS AND DISCUSSION

Drug Excipient Compatibility:

Table No. 5: Data for drug excipient compatibility studies

Ingredients	Ratio	Initial	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks
			40°C & 75%RH	40°C & 75%RH	40°C & 75%RH	40°C & 75%RH
Propranolol HCl	1	White powder	No change	No change	No change	No change
Propranolol HCl + Xanthan Gum	1:1	Cream Color	No change	No change	No change	No change
Propranolol HCl + MCC	1:1	White powder	No change	No change	No change	No change
Propranolol HCl + HPMC K4M	1: 1	White powder	No change	No change	No change	No change
Propranolol HCl + HPMC K100M	1: 1	White powder	No change	No change	No change	No change
Propranolol HCl +Sod. Alginate	1: 1	White powder	No change	No change	No change	No change
Propranolol HCl + Talc	1: 1	White powder	No change	No change	No change	No change
Propranolol HCl + DCP	1: 1	White powder	No change	No change	No change	No change
Propranolol HCl + Magnesium stearate	1:1	White powder	No change	No change	No change	No change

There is no change in color, hence it was concluded that there is no interaction between drug and excipients.

Calibration Curves of Propranolol HCl In pH 1.2 HCl buffer:

The calibration curve of propranolol HCl was carried out in pH 1.2 HCl in different concentrations (5, 10, 15, 20) and absorbance was observed or recorded at 290nm.Graph was plotted by taking absorbance on X-axis, concentration on Y-axis. The straight line appeared passing through the origin connecting all the five points indicates that the drug is following Beer's-Lambert's law which is suitable for the UV-Spectrophotometric analysis.

Since there is increase in absorbance with increase in concentration and R^2 value as indicates 0.9997 that line was linear and nearer to 1

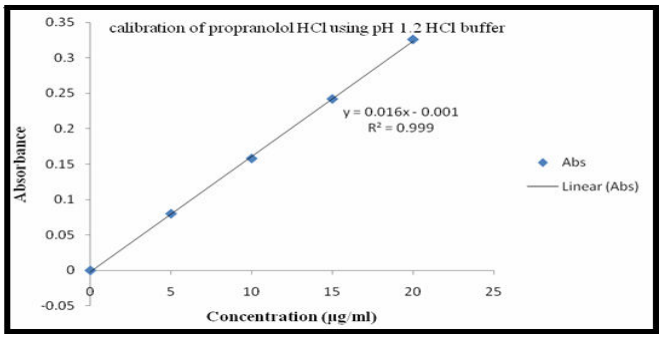

Fig. 1: Calibration curve of Propranolol HCl using pH 1.2 HCl media at 290nm In pH 6.8 phosphate buffer

The calibration curve of propranolol HCl was carried out in pH 6.8 phosphate buffer in different concentrations (5, 10, 15, 20) and absorbance was observed or recorded at 290nm.Graph was plotted by taking absorbance on X-axis, concentration on Y-axis. The straight line appeared passing through the origin connecting all the five points indicates that the drug is following Beer's-Lambert's law which is suitable for the UV-Spectrophotometric analysis.

Since there is increase in absorbance with increase in concentration and R^2 value as indicates 0.9991 that line was linear and nearer to 1.

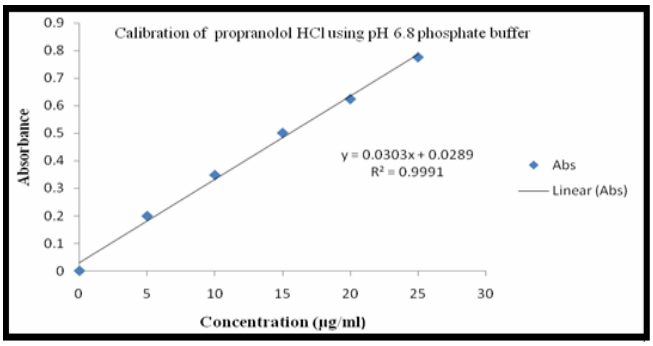

Fig. 2: Calibration curve of Propranolol HCl using pH 6.8 media at 290nm

Table No. 6: Calibration equations and Regression values of different media

Media	λmax	Calibration equation	Correlation coefficient	Std abs
pH 1.2	290	y = 0.0163x + 0.0016	0.9997	0.624
pH 6.8	290	y = 0.0303x + 0.0289	0.9991	0.326

1) Pre compression studies:

The powder blends was prepared as planned shown in table 11 and used for characterization of blend for various flow properties.

i) Bulk Density (BD):

The powder blends of formulations F1-F12 have the bulk density ranged between 0.48±0.03to 0.61 ±0.030 g/ml.

ii) Tapped density (TD):

The powder blends of formulations F1-F12 have the tapped bulk density ranged between 0.55±0.030 to 0.65 ±0.042 g/ml. These values indicate good packing characteristics and the powder was not bulky.

Table No. 7: Results of Pre compression parameters

Formulation code	Weight variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	251.0 ± 3.323	4.8 ± 0.633	3.8 ± 0.458	0.52 ± 0.227	99.50
F2	249.1 ± 1.155	5.6 ± 0.284	3.6 ± 0.065	0.55 ± 0.070	100.01
F3	250.6 ± 0.922	5.1 ± 0.156	3.9 ± 0.083	0.51 ± 0.071	100.62
F4	250.0 ± 0.727	5.2 ± 0.136	3.8 ± 0.111	0.51 ± 0.049	99.31
F5	250.1 ± 0.773	5.1 ± 0.247	3.8 ± 0.198	0.64 ± 0.085	100.41
F6	250.9 ± 1.097	5.2 ± 0.177	3.8 ± 0.139	0.67 ± 0.069	100.32
F7	250.0 ± 0.970	5.1 ± 0.189	3.7 ± 0.183	0.56 ± 0.085	99.10
F8	251.0 ± 0.774	5.2 ± 0.360	3.6 ± 0.226	0.54 ± 0.059	99.62
F9	251.0 ± 0.583	5.1 ± 0.212	3.8 ± 0.216	0.40 ± 0.069	99.99
F10	250.0 ± 1.040	5.5 ± 0.191	3.7 ± 0.174	0.49 ± 0.092	99.12
F11	252.0 ± 1.298	5.4 ± 0.229	3.8 ± 0.210	0.54 ± 0.038	99.62
F12	251.0 ± 0.843	4.8 ± 0.264	3.8 ± 0.145	0.55 ± 0.098	99.86

All are within the specified limits.

iii) Thickness:

Thickness specifications may be set on an individual product basis. There were no marked variations in the thickness of tablets within each formulation indicating uniform behavior of blend throughout the compression process. The thickness of all formulations F1-F12 ranged between 3.6 ±0.065to 3.8 ±0.111.

iv) Tablet hardness:

A difference in tablet hardness reflects difference in tablet density and porosity. Which in turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of F1-F12 tablets was found to be in the range of 4.8 ± 0.264 kg/cm^2 to 5.6±0.284kg/cm^2. This indicates good tablet strength.

v) Percent friability:

Percentage friability of all the formulations F1-F12 was found between 0.40 ± 0.069 to 0.55 ± 0.070 %. The pharmacopoeial limit for percentage friability is 1%. This indicated good handling property of the prepared matrix tablet.

vi) Weight variation:

A tablet is designed to contain a specific amount of drug. When the average masses of the tablet is 240 mg the pharmacopoeial limit for percentage deviation is ±5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the USP specifications.

vii) Drug content of Propranolol HCl:

The content of active ingredients in the formulation F1-F12 was found to be between 99.10 to 100.62 % w/w, which was within the specified limit.

Kinetics of *In-vitro* Drug Release:

The kinetics of *In-Vitro* drug release was determined by applying the drug release data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

Table No. 8: It shows *In-Vitro* drug release profile of formulations containing HPMC K4M (F1 to F3)

Formulation code	1.5hr	4hr	8hr	14hr	24hr
F1	27.88	52	65	78	89.63
F2	24.22	43	56	69	85.81
F3	21.2	39	48	62.5	82.7

Table No. 9: It shows *In-Vitro* drug release profile of formulations containing HPMC K100M (F4 to F6)

Formulation code	1.5hr	4hr	8hr	14hr	24hr
F4	22.7	53.5	61	72	85.17
F5	21.91	44.5	61	73	82.04
F6	20.88	29	37.6	50.12	76.35

Table No. 10: It shows *In-Vitro* drug release profile of formulations containing Sodium alginate(F7 to F9)

Formulation code	1.5hr	4hr	8hr	14hr	24hr
F7	21.6	32.1	40.05	48.09	71.87
F8	21.15	35	43.45	61.25	70.5
F9	22.42	33.56	42.82	63.04	72.58

Table No. 11: It shows *In-Vitro* drug release profile of formulations containing xanthan gum (F10 to F12)

Formulation code	1.5hr	4hr	8hr	14hr	24hr
F10	**22.91**	**56.89**	**75**	**81**	**99.92**
F11	**21.43**	**52.56**	**72.09**	**82.36**	**97.05**
F12	**21.12**	**42.23**	**69.56**	**83.25**	**95.92**

When cumulative % drug release (Table 8-11), it was observed that, for three of the polymers used, an increase in polymer concentration from 25% to 50%, induce a decrease in the release rate. The drug release rate from xanthan gum matrix was found to be more as compared to HPMC K15M, HPMC K100M and sodium alginate. This might be due to fast hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. Whereas formulation containing HPMC K4M (F1-F3) gave higher drug release as compared to formulation containing HPMC K100M (F4-F6),sodium alginate (F7-F9) and Xanthan gum (F10- F12), which may be due to quick hydration of polymer matrix, after which matrix might get started to erode.

CONCLUSION

In the present work, an investigation was made to use Xanthan gum as a natural polymer in the design of extended release oral drug delivery systems. Propranolol HCl was chosen as the model drug with the view of formulating extended release tablets to improve its bioavailability. Release of propranolol HCl from the tablets formulated by employing 25mg of Xanthan gum and 77 mg dibasic calcium phosphateshowed that more drug release So,the formulation F-10 was the optimized formula. The polymer Xanthan gum showed better dissolution control compared to the other polymers like HPMC K4M and HPMC K100M and sodium alginate.

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