e-ISSN - 2348-2184
Print ISSN - 2348-2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr

FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF PROPRANOLOL HCL

N.Sivaramaiah*, M.Alekhya, M.Anusha, CH.Bhargav, G.Harish, V.Nagaraju, G.Madhuri

Department of Pharmacology,Pharmaceutics and Pharmaceutical Analysis.
Nalla Narshima Reddy Education Society's Group of Institutions, Hyderabad, India.

Article Info

Received 14/11/2014
Revised 27/11/2014
Accepted 02/12/2014

Key words: -
Propranolol, Oral, Dispersible.

ABSTRACT

In the present work, oral dispersible tablets of Propranolol HCl were prepared by direct compression method. All the tablets were subjected to weight variation, drug content uniformity, hardness, friability, wetting time, dissolution, drug excipients interaction and short-term stability studies. It was found that the short-term stability studies of promising formulations indicated that there are no significant changes in drug content.

INTRODUCTION

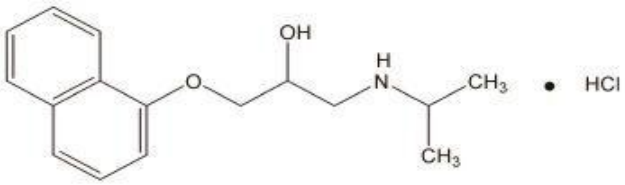
Propranolol is used in the treatment or prevention of many disorders including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety.

Chemically it is [2-hydroxy-3-(naphthalen-1-yloxy)propyl](propan-2-yl)amine having molecular Formula: $C_{16}H_{21}NO_2$ HCL and molecular weight average: 259.3434.It is Freely soluble in water and organic solvents having Melting point: 164 ^{0}C. Propranolol Hcl competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in reduction of resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension [1,2].

Corresponding Author

M.Alekhya
Email:- alekhyamadireddy09@gmail.com

Structure of Propranolol HCL



MATERIALS AND METHODS

Materials

Propranolol Hcl, Sodium starch glycolate, Crospovidone, Croscarmellose sodium, Aspartame, Magnesium stearate, Mannitol and talc are supplied by Spectrum Pharma.

Preparation of Propranolol Hcl Oral Dispersible tablets by Direct Compression Method

Raw material → Weighing → Screening → Mixing → Compression

Table 1. Formulation of Propranolol Hcl Oral Dispersible tablets

Ingredients (mg)	F1 (2%)	F2 (2%)	F3 (2%)	F4 (4%)	F5 (4%)	F6 (4%)	F7 (6%)	F8 (6%)	F9 (6%)	F10 (1:1)	F11 (1:1)	F12 (1:1)
Propranolol HCl	40	40	40	40	40	40	40	40	40	40	40	40
Mannitol	97	97	97	94	94	94	91	91	91	94	94	94
CCS	3	-	-	6	-	-	9	-	-	3	-	3
CP	-	3	-	-	6	-	-	9	-	3	3	-
SSG	-	-	3	-	-	6	-	-	9	-	3	3
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total tablet	150	150	150	150	150	150	150	150	150	150	150	150

EVALUATION PARAMETERS

Precompression Paramete

Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder.

Tapped Density (D_T):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$D_T = \frac{M}{V_1}$$

Where, M is the mass of powder, V_T is the tapped volume of the powder.

Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density.

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

Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\textbf{Tan } \theta = \textbf{(h/r)}$$

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

Where, θ is the angle of repose, H is the height in cms, R is the radius in cms

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$\frac{\text{Tappeddensity - Bulk density}}{\text{Tappeddensity}}$$

Post compression Parameters

1. Hardness:

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in Kg / cm^2.

Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (**%**). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing more than 325mg is ± 5%.

Thickness:

The thickness of the tablets was measured by screw gauge. It is expressed in mm.

Disintegration Time:

The *Invitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was

added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Content uniformity test:

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at 320nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

***In-vitro* dissolution studies:** The *In-vitro* dissolution study was carried out in USP dissolution test apparatus type 2 (paddle)

Dissolution Medium: 900ml of 6.8 pH Phosphate buffer

Temperature: 37 ± 0.5 ^{o}C , RPM: 50

Volume withdrawn & replaced: 5 ml every five minutes, $\lambda_{max:}$: 320nm .

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The time required for water to reach upper surface of the tablet is noted as a wetting time. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured. The method was slightly modified by maintaining water at 37^{o} c. A tablet was placed on the tissue paper and small amount of amaranth powder was placed on upper surface of tablet. The time required for development of a red color on the upper surface of the tablet was recorded as wetting time[41].

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, Wa is weight of tablet before water absorption

Wb is weight of tablet after water absorption

R is water absorption ratio.

Stability Studies

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

METHOD

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40^{0}C / 75% RH for 3months and evaluated for their physical appearance, drug content and drug excipient compatibility at specified intervals of time.

RESULTS AND DISCUSSION

Table 2. Carr's Index limits

Carr's index (%)	Type of flow
5 – 15	Excellent
12 – 18	Good
18 – 23	Fair to passable
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Pre and Post Formulation Studies

Table 3. Pre-compression parameters of Propranolol HCl

Formulation number	Bulk Density	Tapped Density	Carr's Index	Hausner ratio	Angle of repose
F1	0.52	0.65	20.02	1.25	34.2
F2	0.55	0.64	26.21	1.16	35.5
F3	0.49	0.57	14.04	1.163	33.2
F4	0.48	0.55	12.72	1.14	32.4
F5	0.50	0.58	13.79	1.16	33.0
F6	0.53	0.61	13.11	1.15	32.1
F7	0.49	0.55	10.90	1.12	33.5
F8	0.53	0.61	13.11	1.15	32.1
F9	0.53	0.66	19.69	1.24	31.8

F10	0.51	0.65	21.53	1.27	35.4
F11	0.54	0.61	11.47	1.12	32.5
F12	0.52	0.65	20.00	1.25	33.1

Table 4. Post compression parameters of Propranolol HCl

Formulation	Hardness (Kg / cm^2)	Friability (%)	Thickness (mm)	Disintegration time (sec)	Weight variation (average weight) (mg)	Wetting time (sec)
F1	3.5	0.41	2.5	112	151	215
F2	3.8	0.46	2.4	115	148	198
F3	3.6	0.48	2.4	121	152	184
F4	4.1	0.42	2.3	124	150	201
F5	3.8	0.49	2.5	96	151	215
F6	3.5	0.45	2.5	124	150.2	214
F7	3.5	0.44	2.4	127	151.4	219
F8	3.6	0.47	2.5	114	150.1	225
F9	3.8	0.49	2.3	131	149.2	183
F10	3.9	0.48	2.5	98	151.2	214
F11	3.5	0.41	2.4	84	150.2	184
F12	3.2	0.42	2.5	124	151.1	214

Table 5. Dissolution Table of Formulations in phosphate buffer 6.8

Time in min/Form. code	5min	10min	15min	20min	25min	30min
F1	25.03	42.91	55.43	73.31	85.82	96.55
F2	28.6	41.12	59	80.46	87.61	92.98
F3	28.6	46.49	55.43	75.09	85.82	98
F4	32.18	46.49	51.85	64.37	75.09	97.9
F5	42.91	62.58	75.09	96.55	96.55	97.34
F6	46.49	62.58	76.88	94.76	98.34	96.34
F7	21.45	33.97	42.91	57.21	64.37	71.52
F8	25.03	32.18	46.49	71.52	76.88	85.82
F9	28.6	42.91	51.85	67.94	82.28	92.9
F10	33.97	48.27	60.79	78.67	85.82	94.76
F11	41.12	50.06	67.94	85.82	94.76	98.34
F12	19.66	30.39	41.11	64.37	73.31	85.82

Stability studies

Table 6. Stability Data of Formulation 11 at 40 ± 2^0C / 75 ± 5% RH.

Sl. No.	Time in days	Physical changes	Percentage of drug content* ±SD	Moisture content	Percentage of drug release* ±SD (99.5% of release label claim in 10 min).
1.	1st day (initial)	Round flat shaped tablets, using 7mm punch	99.51±0.48	0.82	99.5%
2.	30th day (1 month)	No changes	99.35±0.11	0.78	99.3%
3.	60th day (2 month)	No changes	98.12±0.13	0.80	98.6%
4.	90th day (3 month)	No changes	97.81±0.28	0.78	98.2%

* SD- Standard deviation

Table 7. Standard graph results

Concentration in mcg	Absorbance at 320nm
1	0.016
2	0.041
3	0.064
4	0.098
5	0.124
6	0.151
7	0.19
8	0.227
9	0.257
10	0.274

Figure 1. Standard graph of Propranolol Hcl in 6.8 pH buffer

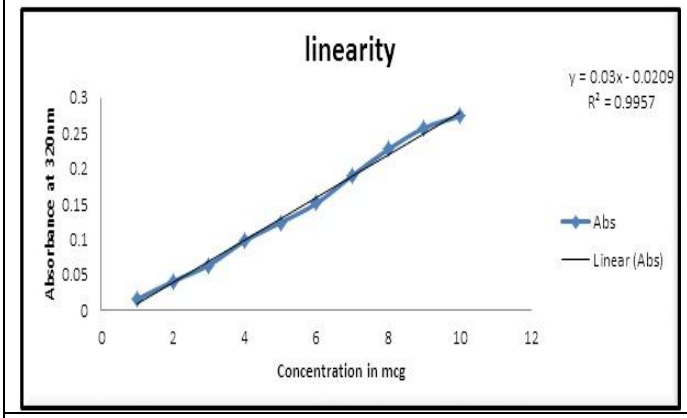


Figure 2. Graphical Representation of Disintegration Time of Tablets

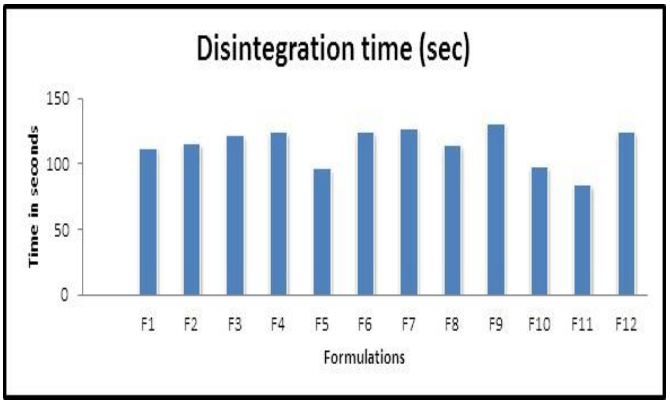


Figure 3. Dissolution Profile of all formulations

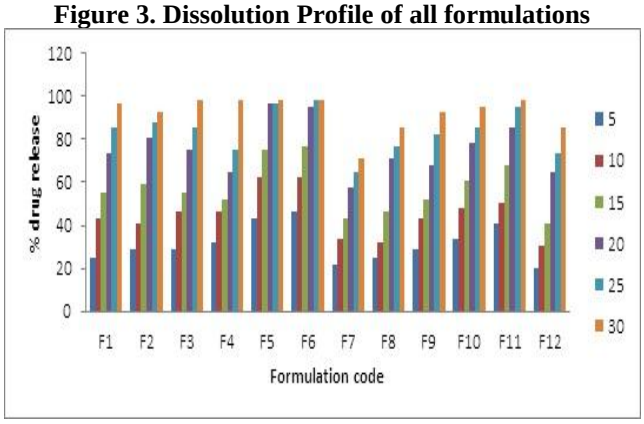


Figure 4. Dissolution profile of Formulation F1 to F3

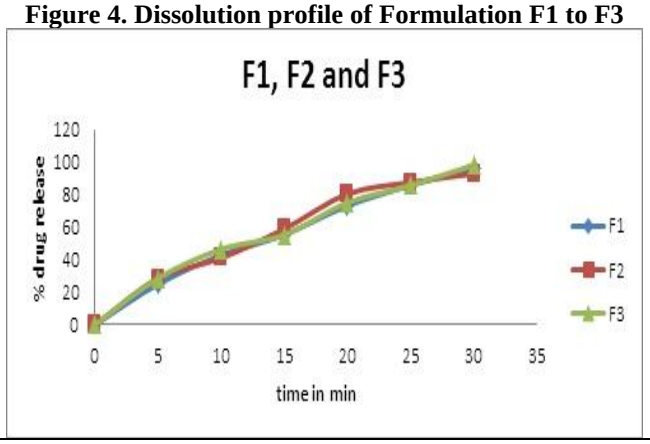


Figure 5. Dissolution profile of Formulation F4 to F6

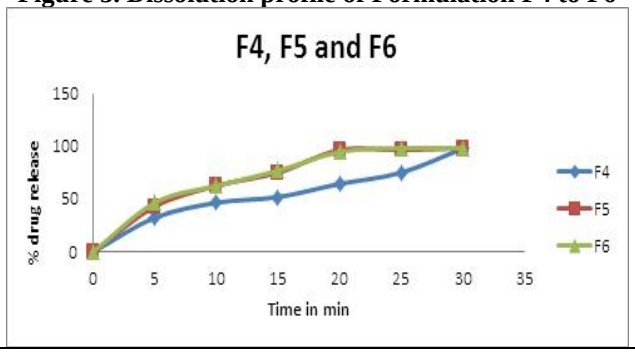


Figure 6. Dissolution profile of Formulation F7 to F9

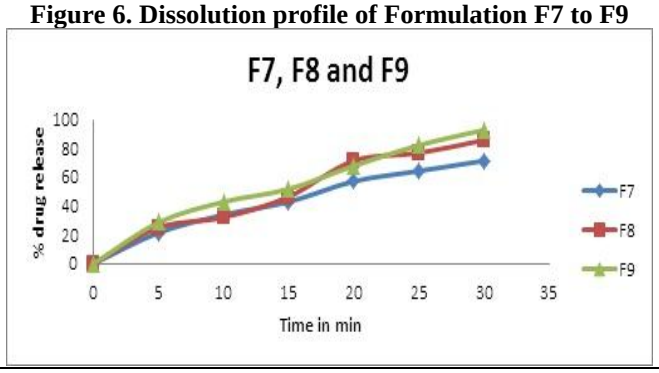


Figure 7. Dissolution profile of Formulation F10 to F12

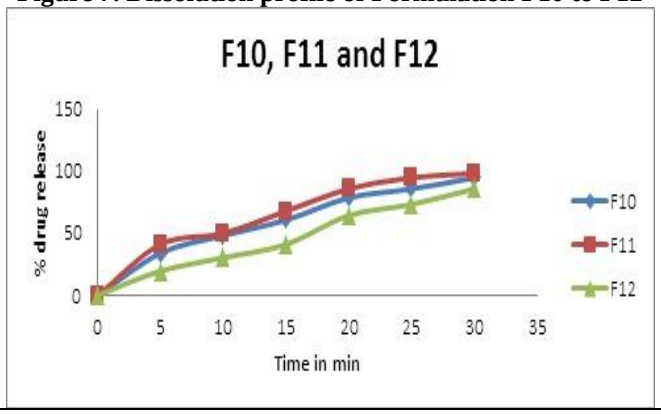
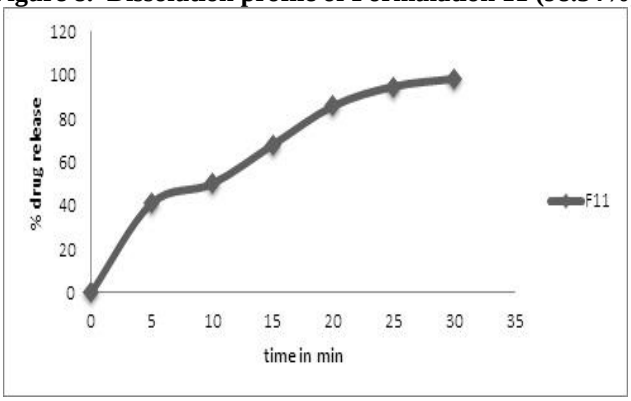


Figure 8. Dissolution profile of Formulation 11 (98.34%)



FOURIER TRANSFORM INFRARED SPECTROSCOPY OF PROPRANOLOL HCl

Figure 9. FT-IR of pure drug

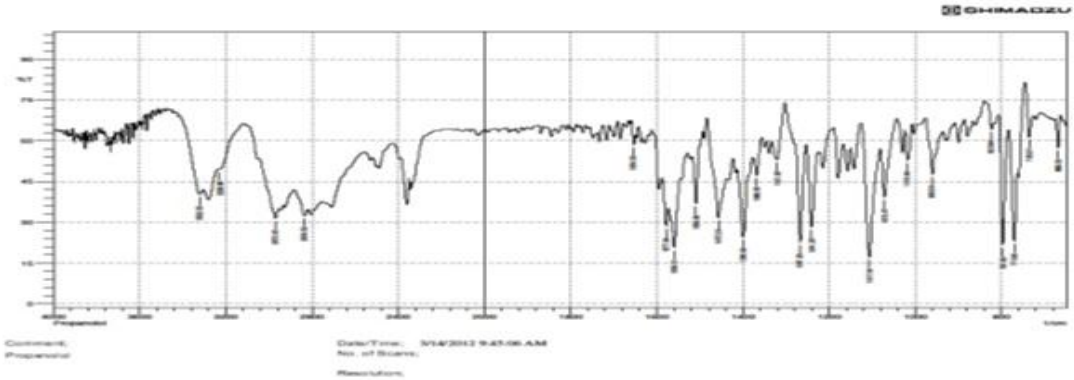


Figure 10. FT-IR of Drug with Croscarmellose sodium

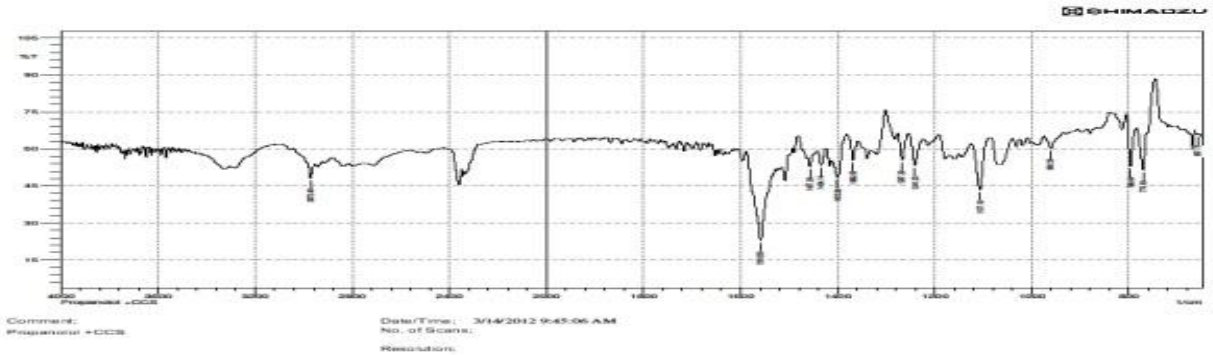


Figure 11: FT-IR Drug with sodium starch glycolate and cross povidone

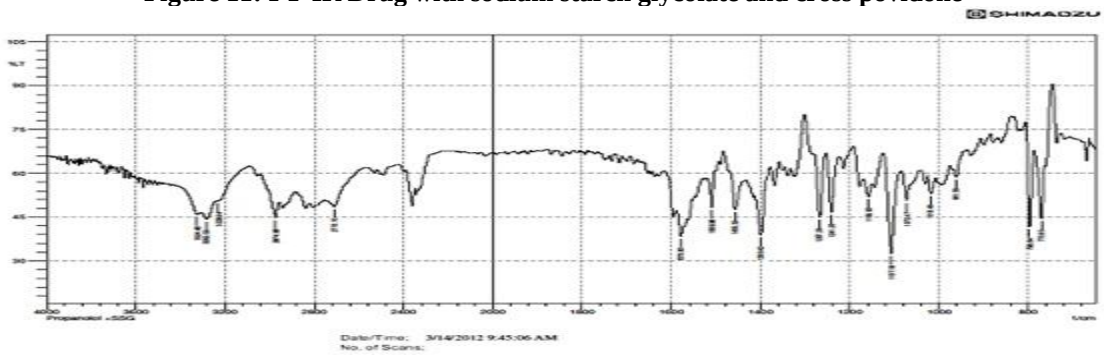


Figure 12. FT-IR of Drug with crospovidone

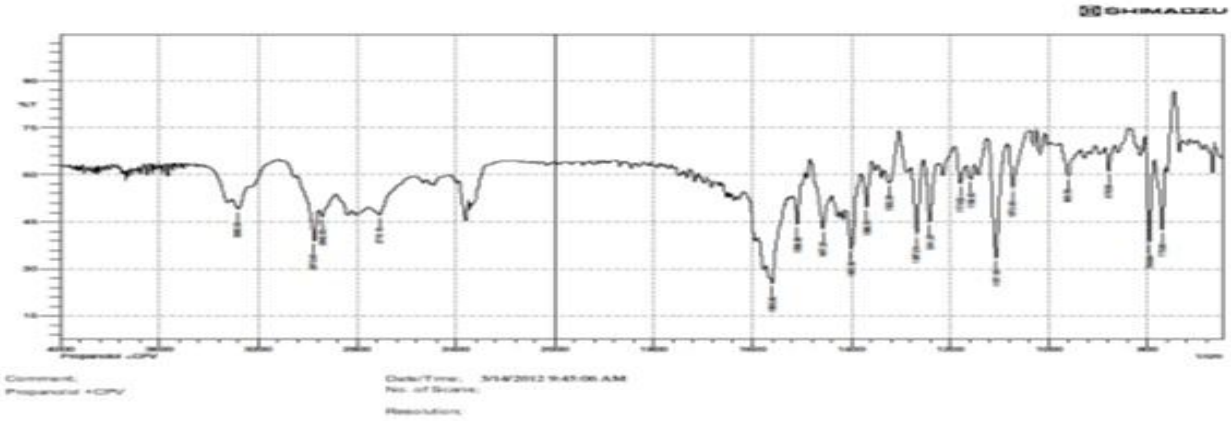


Figure 13. FT-IR of Drug with Mg.Stearate

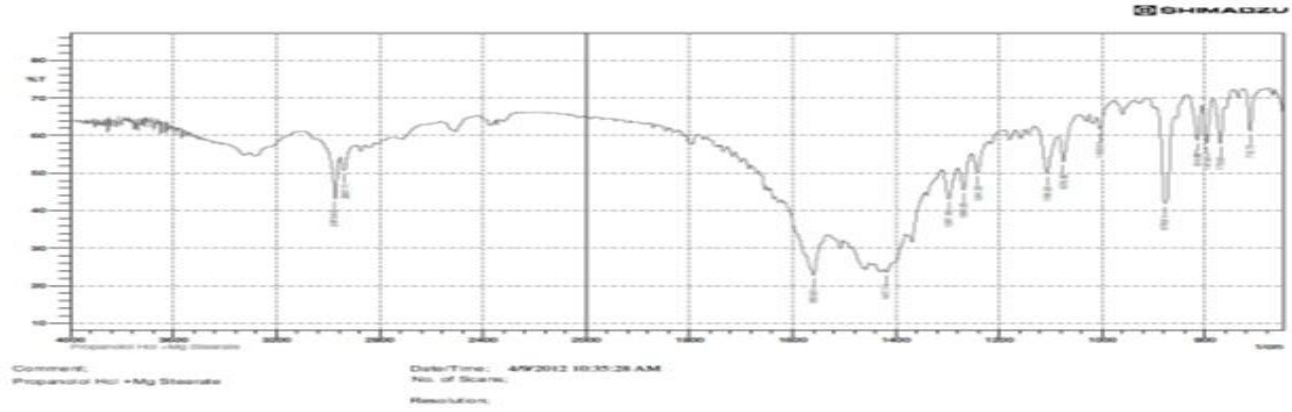


Table 8. FT-IR Studies

S.No	Peaks	Functional group
1	3668.62 & 3346.30	OH (Alcohol)
2	3051.96	Aromatic C-H Stretching
3	3015.42	Alkene C-H Stretching
4	2950.80 & 2893.72	Alkane C-H Stretching
5	1730.91 & 1709.46	Ketone
6	1621.74	NH (Amine)
7	1396.31, 1372.09, 1351.93 & 1325.98	C-O (Phenol)
8	1081.22, 1159.04, 1182.78	C-N Vibrations
9	600-900	C-H Bending (Aromatic)

Peaks obtained at 3668.62 & 3346.30 are due to the presence of OH (Alcohol) group
Peak obtained at 3051. Is due to the presence of Aromatic C-H Stretching
Peak obtained at 3015.42 is due to the presence of Alkene C-H Stretching
Peaks obtained at 2950.80 & 2893.72 are due to the presence of Alkane C-H Stretching
Peaks obtained at 1730.91 & 1709.46 are due to the presence of Ketone group
Peak obtained at 1621.74 is due to the presence of NH (Amine) group
Peaks obtained at 1396.31, 1372.09, 1351.93 & 1325.98 are due to the presence of C-O (Phenol)
Peaks obtained at 1081.22, 1159.04, 1182.78 are due to the presence of C-N Vibrations
Peaks obtained from 600-900 are due to the presence of C-H Bending (Aromatic)

DISCUSSION

Hardness and friability: The hardness of the tablet formulations was found to be in the range of 3.5 to 4.1 kg/cm^2 (Table 5). The friability values were found to be in the range of 0.52 to 0.41 %. (Table 5).

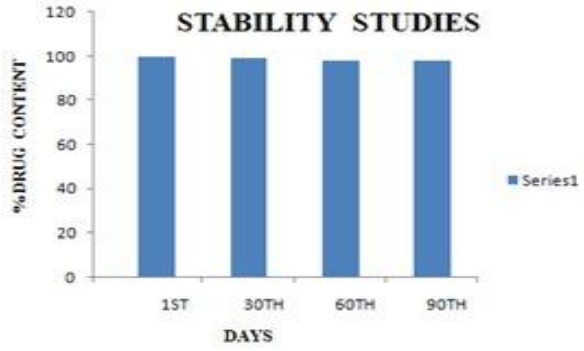
Disintegration time: The disintegration time of formulation 11th was 84 sec which is the best result obtained than the rest of the formulations.

Uniformity of weight: All the prepared tablets of Propranolol Hcl were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±5%.

Uniformity of drug content: The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 95.74 to 103.94 percent (which was within the acceptable limits of ±5%.)

***In vitro* dissolution study:** *In vitro* dissolution studies were performed in pH 6.8 phosphate buffers.

Figure 14. Graph showing % Drug content



CONCLUSION

The ODTs have potential advantages over conventional dosage forms, with their improved patient compliance; convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of Fast dissolving tablets, which in turn prolongs the patent life of a drug. Keeping in view of the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular. Thus ODT may be developed for most of the available drugs in ODTs has increased as it has significant impact on patient compliance and is used to improve the bioavailability and stability. ODTS are alternative for drug delivery to paediatrics and geriatric patients. The basic approach in the formulation of ODTs tablets are to increase porosity of tablet and incorporate super disintegrants in optimum concentration to achieve rapid disintegration and instantaneous dissolution of tablet along with good taste masking properties and excellent mechanical strength. Thus ODT has tremendous scope for being the delivery system for most of the drugs in near future.

Based on the above study following conclusions can be drawn:

- Tablets prepared by direct compression method were found to be good without any chipping, capping and sticking.
- The hardness of the prepared tablets was found to be in the range of 3.2 to 4.1kg/ cm^2.
- The friability values were found to be in the range of 0.41 to 0.49%.
- Disintegration time was found to be in the range of 84sec to 131sec.
- Formulation 11^{th} showed good results than rest of the 12 formulations in pre and post compression studies.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- Formulations 11^{th} displayed faster drug release when compared to remaining 12 formulations considered in pH 6.8 phosphate buffers.
- Short-term stability studies of promising formulations indicated that there are no significant changes in drug content.
- IR-spectroscopic studies indicated that there are no drug–excipients interactions.

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