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Research Article

Formulation and evaluation of immediate release tablets of Imipramine hydrochloride

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Abstract

The aim of the present study is to develop and evaluate the immediate release tablet of Imipramine hydrochloride by direct compression method. The superdisintegrant crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) were used for immediate release of drug from tablet. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug-excipients interaction was investigated by FTIR. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F3 exhibits highest dissolution using crospovidone showed faster drug release 99.65 % over the period of 12 min while disintegration time of the tablet was showed 28 sec comparison to other formulations of Imipramine hydrochloride.

Keywords: Immediate release, polymers, superdisintegrant

1. Introduction

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques,[1,2] Immediate release and fast dispersing drug delivery system may offer a solution to these problems. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.[3,4]

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.

Imipramine is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as amitriptyline and doxepin. A tertiary amine, imipramine inhibits the reuptake of serotonin more so than most secondary amine tricyclics, meaning that it blocks the reuptake of neurotransmitters serotonin and noradrenaline almost equally. It binds the Sodium-dependent serotonin transporter and Sodium-dependent noradrenaline transporter, preventing or reducing the reuptake of norepinephrine and serotonin by nerve cells. Peak plasma levels are reached in 2 to 8 hours, and plasma half-life ranges from 11 to 25 hours. It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; small amount are excreted in the faeces via the bile. Imipramine is one of the less sedating tricyclics and has moderate antimuscarinic activity. Imipramine is used for the treatment of nocturnal enuresis in children. Tricyclic anti- depressants are not recommended under 6 years of age.

2. Material and Methods

2.1 Materials and Instruments:

All materials used during experiment are LR grade or the best possible pharma grades available were used as supplied by the manufacturer.

2.2 Manufacture of Imipramine Hydrochloride tablets

2.2.1 Direct compression technique

Imipramine Hydrochloride tablets were manufactured for nine batches F1 to F9 using different ratios of superdisintegrants mentioned in the (Table 3) keeping the total weight (100 mg) of the tablet constant in all the formulations. Imipramine Hydrochloride tablets were prepared by directs compression technique as per the formula given in the Table 3. The superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate were used in different proportions.

2.2.2 Procedure:

All the ingredients were passed through sieve #40 and were subjected for drying to remove moisture content at 40 to 45^{0C}. Weighed amount drug and excipients except magnesium stearate and talc were mixed properly by geometric addition method for 20 minutes manually. Talc and magnesium stearate were then passed through sieve #80, mixed and blended well with the initial mixture. The mixed blend of drug and the excipients were compressed on Karnavati 10 station rotary punching machine using 2 mm diameter round concave punch (force used: 58.5 kN).

Table No: 1 Formulation Table of Imipramine Hydrochloride Tablet

Ingredients(mg.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Imipramine Hydrochloride	10	10	10	10	10	10	10	10	10
Cross Povidone	6	9	12	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	6	9	12	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	6	9	12
MCC	30	27	24	30	27	24	30	27	24
Mannitol	47	47	47	47	47	47	47	47	47
Aspartame	5	5	5	5	5	5	5	5	5
Mg stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total Weight (mg)	100	100	100	100	100	100	100	100	100

2.3 Experimental Data

2.3.1 Preformulation Studies

The following Preformulation studies were performed for Imipramine Hydrochloride and excipients;

1. Determination of melting point of Imipramine Hydrochloride
2. Drug- excipients compatibility studies.

2.3.2 Determination of melting point

Melting point was determined by taking small amount of Imipramine Hydrochloride in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was calculated.

2.3.3 Drug-excipients compatibility studies

Excipients were integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage forms depends on the selection of excipients, which are added to facilitate administration of the drug and protect it from degradation.

2.3.4 FT-IR Studies

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. FT-IR spectroscopy was employed to ascertain the compatibility between Imipramine Hydrochloride and selected polymers. The pure drug, drug-polymers combinations and formulations were subjected to FT-IR 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 1:1 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 to1000 cm-1 wave number. FT-IR spectrum of Imipramine Hydrochloride was compared with FT-IR spectrum of Imipramine Hydrochloride with polymer. The pure drug and the drug with excipients were scanned separately. Disappearance of Imipramine Hydrochloride peaks or shifting of peak in any of the spectra was studied.

2.4 Preparation of Buffers and Reagents[7]

2.4.1 Sodium hydroxide (0.2 M) solution

Eight gm of sodium hydroxide was dissolved in1000 ml volumetric flask containing about 700 ml distilled water and volume was made up to the mark with distilled water.

2.4.2 Potassium dihydrogen phosphate (0.2 M) solution

Potassium dihydrogen orthophosphate (27.218 gm) was dissolved in 1000 ml volumetric flask containing about 700 ml distilled water and volume was made up to the mark with distilled water. Phosphate buffer (pH 6.8) solution: Fifty ml of 0.2 M potassium dihydrogenorthophosphate solution was taken in a 500 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide solution was added. Then volume was made up to the 200 ml with distilled water and pH was adjusted to 6.8 with dilute sodium hydroxide solution.

2.4.3 Hydrochloric acid (0.1 N) solution

Concentrated hydrochloric acid solution 8.5 ml was placed in 1000 ml volumetric flask containing about 700 ml distilled water and volume was made up to the mark with distilled water.

2.5 Analytical Methods

2.5.1 Preparation of imipramine hydrochloride standard stock solution (100 µg/ml) in Phosphate buffer (pH 6.8) solution

A standard stock solution of imipramine hydrochloride was prepared by dissolving accurately weighed 10 mg of imipramine hydrochloride in phosphate buffer (pH 6.8) solution in a 100 ml volumetric flask and the volume was made up to 100 ml by using phosphate buffer (pH 6.8) solution to obtain a stock solution of 100 µg/ml.

From stock solution, appropriate aliquots were pipetted into different volumetric flasks and volumes were made up to 10 ml with phosphate buffer (pH 6.8) solution so as to get drug concentrations of 2, 4, 6, 8 and 10 µg/ml. The absorbances of these drug solutions were estimated at λ max 250.8 nm. This procedure was performed in triplicate to validate the calibration curve.

2.5.2 Calibration curve of imipramine hydrochloride in 0.1 N hydrochloric acid solutions

From stock solution, appropriate aliquots were pipetted into different volumetric flasks and volumes were made up to 10 ml with 0.1 N hydrochloric acid solutions so as to get drug concentrations of 2, 4, 6, 8 and 10 µg/ml. The absorbances of these drug solutions were estimated at λ max 250.8 nm.

3. Results

3.1 Evaluation of Tablets

3.1.1 Pre-compression parameters[8,9,10,11]

3.1.1.1 Melting Point:

The melting point of Imipramine Hydrochloride was determined by capillary tube method and it was found to be 270^0C -274^0C.

3.1.1.2 Angle of repose (θ)

Table 4 shows the results obtained for angle of reposes of all the formulations. The values were found to be in the range of 24.45 to 28.24. All formulations showed the angle of repose within 30^0. It indicates that all formulations showed good flow properties.

Table No: 2 Flow properties of granules prepared by different techniques

Batch Code	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner's ratio (HR)	% Carr's index (CI)
FT-1	26.20±1.51	0.535±0.02	0.635±0.02	1.18±0.034	15.74±0.04
FT-2	25.34±0.37	0.521±0.07	0.615±0.01	1.17±0.073	15.28±0. 51
FT-3	24.45±0.52	0.513±0.01	0.605±0.03	1.17±0.033	15.20±0.65
FT-4	27.36±1.15	0.543±0.15	0.645±0.02	1.03±0.061	15.81±0.56
FT-5	25.34±0.89	0.522±0.02	0.632±0.01	1.21±0.045	17.40.±0.42
FT-6	26.74±1.13	0.534±0.13	0.641±0.02	1.20±0.034	16.69±0.09
FT-7	26.98±1.32	0.524±0.02	0.609±0.01	1.16±0.055	13.95±0.23
FT-8	25.15±1.15	0.531±0.03	0.625±0.02	1.17±0.029	15.04±0.45
FT-9	28.24±1.13	0.545±0.04	0.635±0.01	1.16±0.026	14.17±0.24

3.1.1.3 Bulk density

Both loose bulk density LBD and tapped bulk density results are shown in table 4 the loose bulk density and tapped bulk density for all the formulations varied from 0.513gm/cm3 to 0.545gm/cm3 and 0.605gm/cm3 to 0.645gm/cm3respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped density. This result helps in calculating the % compressibility of the powder.

3.1.1.4 Percentage compressibility

The percent compressibility of powder mixture was determined by Carr's compressibility index. The table 6.4 Shows result obtained for percentage compressibility. The percent compressibility for all the nine formulations lies within the range of 13.95 to 17.40 %. All formulations are showing good compressibility.

3.1.1.5 Hausner's ratio

Hausner ratio of the powder was determined from the loose bulk density and tapped bulk density. Hausner ratio of all the formulation lies within the acceptable range. The Hausner's ratio of all the formulations is in the range of 1.03 to 1.21.

3.2 Post-compression parameters

All the formulations were subjected for Organoleptic, physical and chemical evaluations. Shape, thickness, hardness, friability, weight variation, *in vitro* disintegration time, wetting time, water absorption ratio, drug content, *in vitro* dissolution studies were carried out. All the formulations were passed the parameter.

3.2.1 Shape and Color of Tablets

Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for color. The tablet shows round shape, white in color. All ingredients used were white in color. There was no change in color and odor 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.

3.2.2 Thickness Test

The thickness of the tablets was measured by using Vernier caliper by picking the tablets randomly. The mean values are shown in table 5. The values are almost uniform in all formulations. Thickness was found in the range from 3.25±0.20 mm to 3.43±0.21mm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.

Table No: 3 Evaluation of physical parameters

Batch Code	Weight variation Average weight in (mg) ±SD (n=10)	Hardness (kg/cm2) ±SD (n=3)	Thickness (mm) ±SD (n=3)	Friability (%) (n=10)	Drug Content Uniformity (%) ± SD (n=3)
FT-1	98±0.14	3.0±0.10	3.38±0.09	0.56	98.31±0.68
FT-2	100±0.47	3.6±0.15	3.37±0.20	0.72	99.65±1.40
FT-3	101±1.14	4.0±0.21	3.43±0.21	0.52	99.50±1.31
FT-4	99±0.61	4.0±0.21	3.29±0.12	0.52	97.68±0.95
FT-5	98±0.42	3.5±0.05	3.27±0.17	0.47	98.41±1.33
FT-6	100±1.42	3.0±0.18	3.40±0.10	0.42	99.91±1.81
FT-7	98±0.60	3.0±0.14	3.27±0.13	0.67	98.65±0.57
FT-8	101±0.50	3.0±0.10	3.30±0.25	0.49	99.05±1.16
FT-9	102±0.43	3.5±0.10	3.25±0.20	0.73	98.56±1.42

3.2.3 Hardness test

The results of hardness are given in table 5 Hardness test was performed by Monsanto hardness tester. Hardness was maintained to be within 3.0±0.10 kg/cm2 to 4.0±0.21kg/cm2. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and posses good mechanical strength with sufficient hardness.

3.2.4 Friability

The results are tabulated in table 5 was found well within the approved range (<1%) in all the formulation. Friability was in between 0.42% to 0.73%. Results revealed that the tablets possess good mechanical strength.

3.2.5 Weight variation test

The percent weight variation for all the formulation is tabulated in Table 5. All the tablets passed weight variation test as the % variation was within the pharmacopoeia limit of ±10%. It was found to be from 95 mg to 105 mg. The weight of all the tablets was found to be uniform. This is due good flow property and compressibility of all the formulations.

3.2.6 Drug content uniformity

The content uniformity was performed for all nine formulations and results are shown in table 5 .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 97.68 % and 99.91 % of Imipramine Hydrochloride. The results indicated that in all the formulations the drug content was uniform.

3.2.7 Wetting time

Wetting is closely related to inner structure of tablets and the hydrophobicity of excipients. The record of the wetting time was shown in table 6. The wetting time in all the formulation was very fast. This may be due to ability of swelling and also capacity of absorption of water.

Croscarmellose sodium, Crospovidone, Sodium starch glycolate and MCC absorbs water in all the formulations and shows fast wetting time. Apart from all the superdisintegrants formulations containing Crospovidone shows fast wetting time.

Table No 4: Wetting Time, Water Absorption Ratio and *in-vitro* Disintegration time

Formulation Code	Wetting Time (n=3) Mean ±SD (sec)	Water Absorption ratio (n=3) Mean ±SD (sec)	*In-vitro* Disintegration Time (sec)
FT-1	17 ±1.42	80 ±1.05	16 ±1.00
FT-2	22±1.89	67±1.16	20±1.70
FT-3	41±2.8	71±1.35	28±1.01
FT-4	73±1.35	48±1.73	60 ±1.28
FT-5	64±1.79	52±1.23	52±2.15
FT-6	54±1.41	63±1.37	34±1.55
FT-7	52±1.21	58±6.55	40±1.01
FT-8	51±1.15	59±1.14	39 ±1.00
FT-9	46 ±1.48	52±1.53	35±1.01

3.2.8 Water absorption ratio

The water absorption ratio results are tabulated in table 6. The ratio values of formulations found in the range of 48±1.73 to 80±1.05. The water absorption increased due to high swelling property. Crospovidone shows highest swelling property. So the water absorption ratio value of formulation F3 was high.

3.2.9 *In vitro* disintegration time

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. The results are shown in table 6 this was determined as per I.P for all the formulations. All the formulations show disintegration time less than 60 seconds. Crospovidone has high water uptake and swelling pressure which leads to faster disintegration. Sodium starch glycolate shows disintegration time in between and Croscarmellose sodium shows more disintegration time.

3.2.10 *In vitro* dissolution Studies

All the nine formulations were subjected for the *in vitro* dissolution studies using tablet dissolution tester (USP) TDT-08L, Electro lab. Solution having pH 6.8 was used as dissolution medium. The samples were withdrawn at different time intervals, filter and analyzed at 250.8 nm. Cumulative % drug release were calculated on the basis of mean amount of Imipramine Hydrochloride present in the respective tablet. The results obtained in the *In-vitro* drug release for the all formulations F1 to F9 are tabulated in Table 7. The plots are shown from figure 6.9 to 6.12. For % cumulative drug release vs. time. The superdisintegrants such as crospovidone (6%, 9% and 12%), sodium starch glycolate (6%,9% and 12%) and croscarmellose sodium (6%, 9% and 12%) were used in different proportions.

Table No. 5: *In-vitro* Drug Release Data batch F1-F9

Formulation code	After 3 min % Release	After 6min % Release	After 9 min % Release	After 12 min % Release	After 15 min % Release
F1	31.63	50.65	62.33	69.30	79.75
F2	34.51	49.92	66.03	88.12	99.28
F3	48.68	65.43	82.44	99.65	-
F4	44.21	53.46	65.90	73.94	88.15
F5	40.73	60.77	75.47	83.17	95.99
F6	30.15	45.84	65.01	87.21	99.17
F7	27.95	40.43	58.32	67.01	72.36
F8	27.31	50.90	63.08	71.95	85.82
F9	30.52	51.53	63.13	71.50	90.72

The rapid dissolution was observed in formulations F1, F2, release 79.75%, 99.28%, of drug respectively, at the end of 15 minutes and formulation F3 releases 99.65% at the end of 12 minutes. formulations F4, F5 and F6 which shows drug release 88.15%, 95.99%, 99.17% respectively at the end of 15 min. Formulations F7, F8, F9 releases 72.36%, 85.82%, 90.72% respectively at the end of 15 minutes. This rapid dissolution might be due to fast breakdown of particles and rapid absorption of drug. The drug release was completely achieved in a shorter duration of time. In all the formulations the drug release within 15 minutes. High dissolution may occur due to faster breakdown.

In comparative study for the formulations F2, F3 and F6 drug releases 99.28%, 99.65% and 99.17% respectively at the end of 15 minutes and graphical representation is shown in fig. 11. Best optimized batch was F3 because of lesser disintegration time and highest percentage drug release at the end of 12 min among all the formulations.

Fig No. 1: Comparative *In-vitro* Release Profile of Imipramine Hydrochloride tablet for Formulations F1, F2 and F3

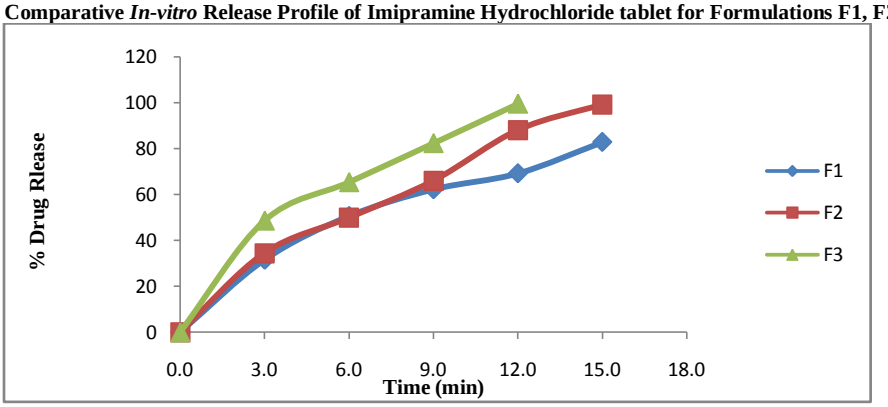


Fig No. 2: Comparative In-Vito Release Profile of Imipramine Hydrochloride tablet for Formulations F4, F5 and F6

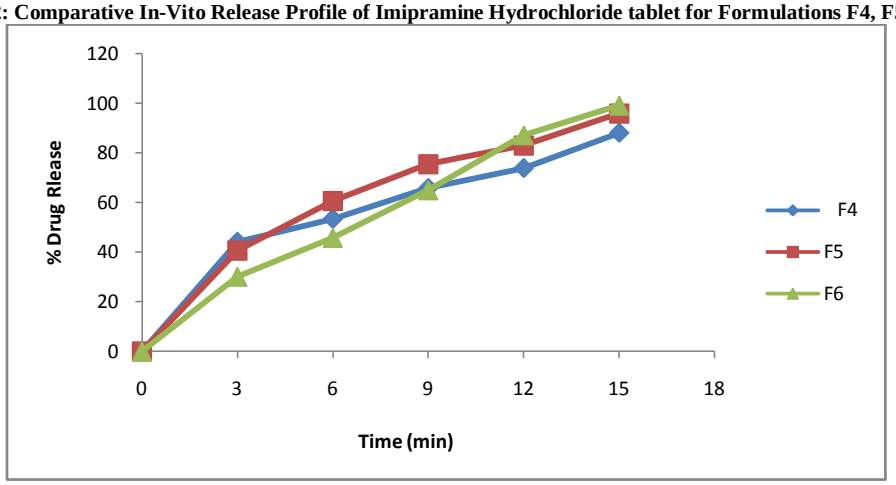


Fig No. 3: Comparative *in-vitro* Release Profile of Imipramine Hydrochloride tablet for Formulations F7, F8 and F9

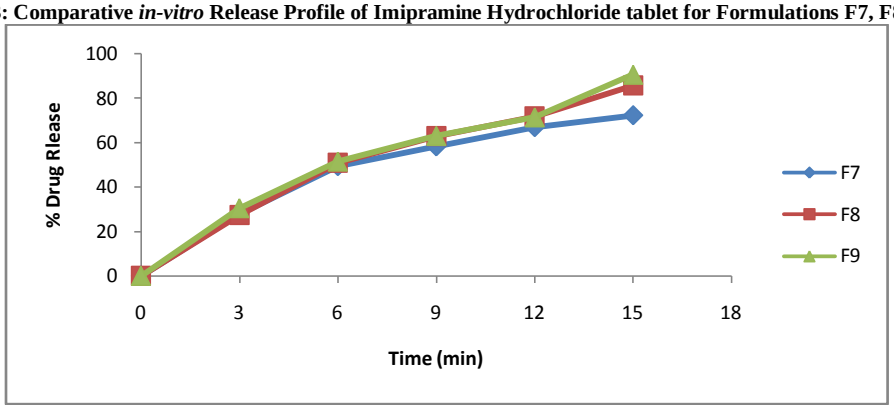
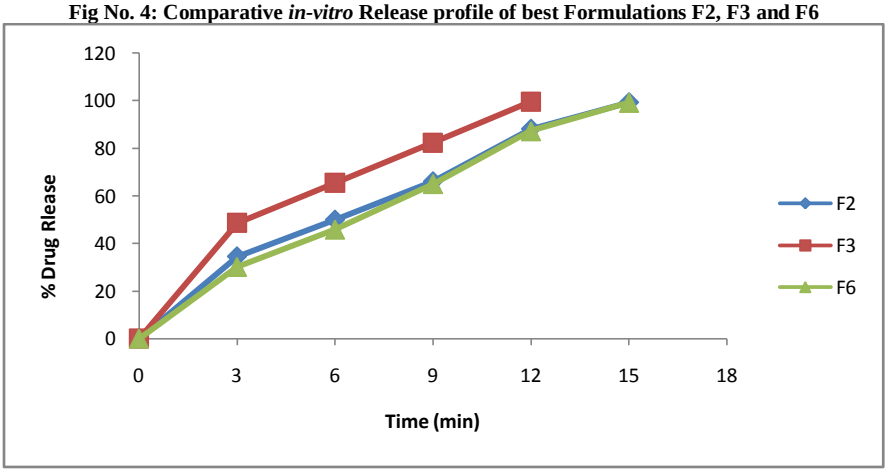


Fig No. 4: Comparative *in-vitro* Release profile of best Formulations F2, F3 and F6



3.3 Stability Studies

The formulations F3 was selected for stability studies on the basis of their high cumulative % drug release and also result of *in vitro* disintegration time studies. The stability studies were carried out at 25^0C/60% RH for the selected formulation up to 30 days. For every 10 days time interval the tablets was analyzed for drug hardness, *in vitro* disintegration time, % drug release up to 30 days. These formulations show not much variation in any parameter. The results obtained are tabulated in table 8 from these results it was concluded that, formulation F3 is stable and retained their original properties.

Table No 6: Selected Formulations for Stability Studies F3 Stored at 25^0C/60% RH

Formulation Code	Tested after time in days	Hardness (Kg/cm$^{2)}$	Disintegration Time (sec)	% Drug Release
F3	10	4.0±0.21	28±1.01	99.65
	20	4.0±0.16	28±1.17	99.60
	30	4.0±0.07	28±1.25	99.54

3.4 Drug- excipients compatibility studies:

To study the compatibility of the drug with various polymers, IR spectra of drug and formulation component were carried out. The FTIR spectra of drug and all excipients were shown in figure 6.3 to figure 6.8 and FTIR interpretation in table no.3 No major differences in the I.R. patterns of pure drug and excipients were observed. Therefore, the FTIR studies ruled out the possibilities of any drug excipients interaction during the preparation of tablets.

Fig No. 5: FT-IR spectra of pure Imipramine HCl.

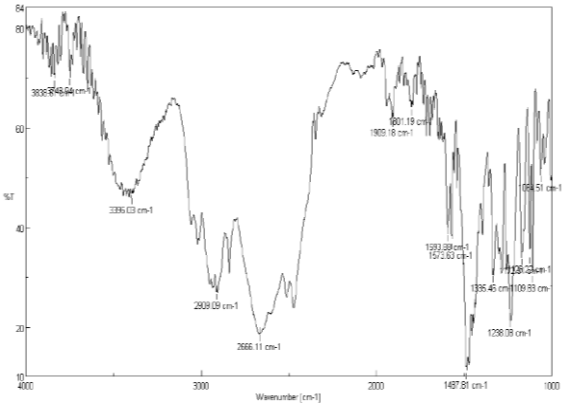


Fig No. 6: FT-IR spectra of pure Imipramine HCl and crosscarmellose sodium.

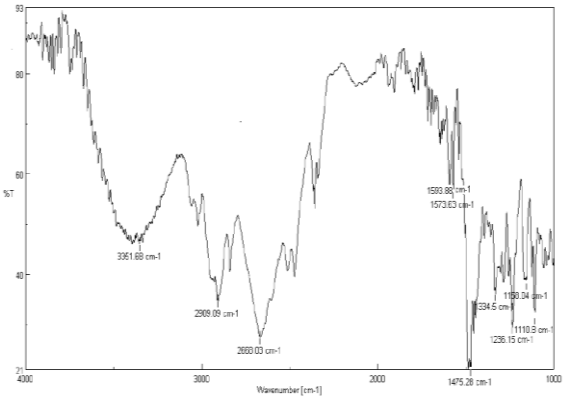


Fig No. 7: FT-IR spectra of pure Imipramine HCl and sodium starch glycolate.

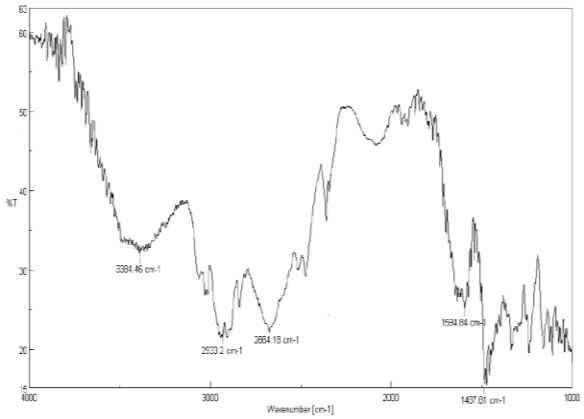


Fig No. 8: FT-IR spectra of pure Imipramine HCl and Cross Povidone

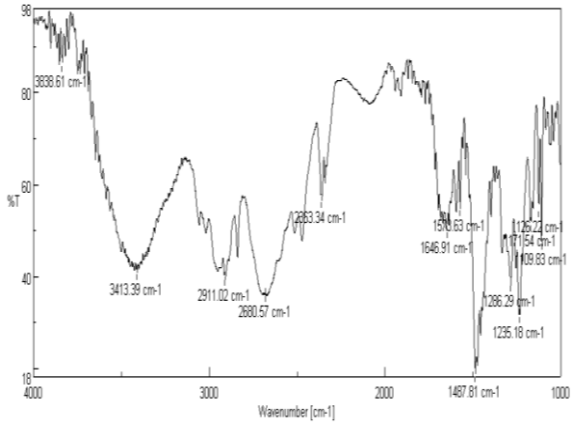


Fig No. 9: FT-IR spectra of pure Imipramine HCl and MCC

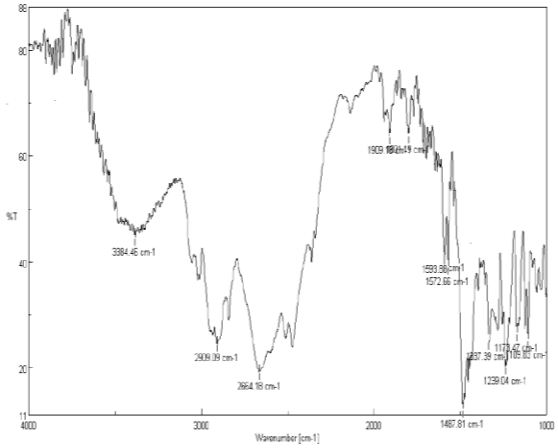
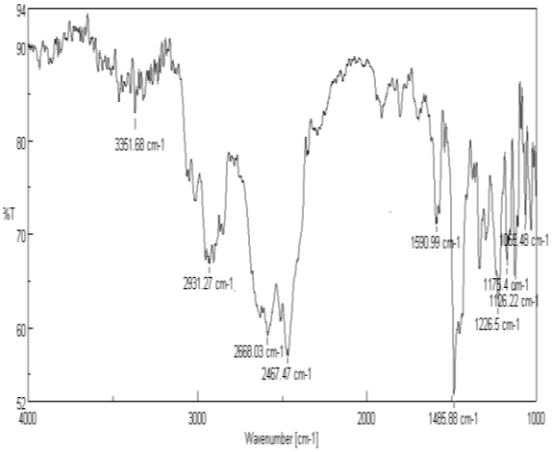


Fig No. 10: FT-IR spectra of Optimized Formulation



Standard Plot

The standard calibration curve of Imipramine Hydrochloride was obtained by plotting Absorbance vs. Concentration. Table 9 and 10 shows the absorbance values of Imipramine Hydrochloride. The standard curve is shown in figure 6.1 and figure 6.2. The standard calibration curve shows the correlation coefficient of 0.9991 and 0.9992. The curve was found to be linear in the concentration range of 2 to 10µg/ml (Beer's range) at 250.8 nm. The calculations of drug content, *in vitro* drug release and stability studies are based on this calibration curve.

Fig. 11 Std. Calibration Curve of Imipramine HCl in Phosphate Buffer (pH 6.8).

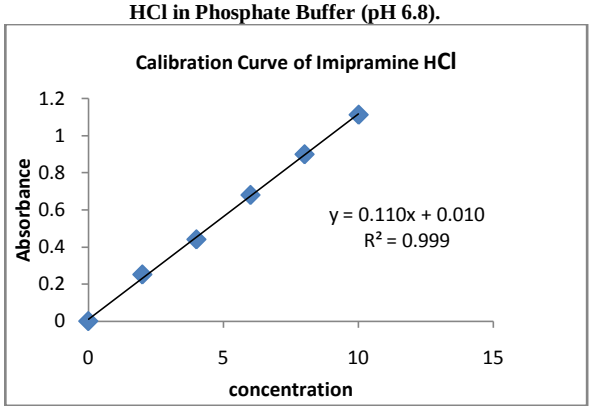
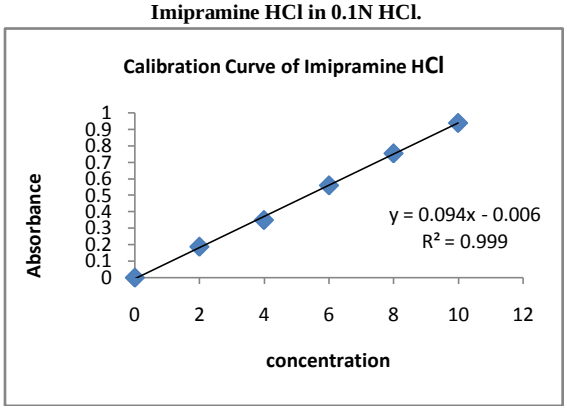


Fig. 12 Std. Calibration Curve of Imipramine HCl in 0.1N HCl.



4. Conclusion

Preformulation studies of Imipramine Hydrochloride were performed; the FT-IR analysis revealed that the superdisintegrants and excipients used were compatible with Imipramine Hydrochloride Immediate release tablets of Imipramine Hydrochioride is to be prepared by direct compression technique using superdisintegrants, namely crospovidone, sodium starch glycolate and croscarmellose sodium.

Amongst all the formulations, formulation containing crospovidone as superdisintgrants is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration compared to other superdisintegrants.

Combines multiple mechanisms to achieve disintegration at low levels wells without forming gel i.e. require slow dissolution and disintegration and Provides rapid disintegration in direct compression tablet as well increases tablet breaking force and reduces friability; enhances the dissolution of poor soluble drugs**.**

Apart from all the formulations, F3 formulation showed maximum drug release (99.65%) at the end of 12 min.

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