



Formulation Development and *in vitro* Evaluation of Escitalopram Immediate Release Tablets

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Abstract

The aim of this study is to formulate and significantly improve the bioavailability and reduce the side effects of immediate release tablets Escitalopram. The precompression blends of Escitalopram were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicates good to fair flow ability and compressibility. Immediate release tablets were prepared with various polymers like PEG 6000, Croscarmellose sodium and Sodium-starch glycolate at different concentration ratios and were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all tests. Among all the formulations F7 formulation containing, drug and Croscarmellose sodium showed good result that is 98.12 % in 45 min. Hence from the dissolution data it was evident that F7 formulation is the better formulation. By conducting further studies like *in vitro* studies.

Keywords

Escitalopram, PEG 6000, Croscarmellose sodium and Sodium-starch glycolate, Immediate release.

INTRODUCTION

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the

maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more

preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release, the commonly Super disintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone (Manish Jaimini et al 2013). Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug delivery techniques and that utilizing in product development is critical for pharma companies to survive this century (Pandey V et al 2016, Gosh R et al 2012, Velivela S et al, 2016).

The term 'immediate release' pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption (Gabrielsson J et al 2002, Dedhiya MG, Rastogi SK et al, 2006, Patrik E, Barbro J, 2006).

Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease (Kaur V, Mehara N, 2016).

The main aim of the present study is to formulate and evaluate Escitalopram Immediate release tablets, to formulate Escitalopram Immediate release tablets for the improvement of Bioavailability and to perform various quality control evaluation parameters for the prepared tablets.

Escitalopram is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Escitalopram is mainly used to treat major depressive disorder or generalized anxiety disorder. It is taken by mouth.

MATERIALS AND METHODS

Buffer Preparation:

Preparation of 0.2 M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250 ml of 0.2 M potassium Dihydrogen ortho phosphate and 112.5 ml 0.2 M NaOH was taken into the 1000 ml volumetric flask. Volume was made up to 1000 ml with distilled water.

Pre formulation Studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Analytical method development for Escitalopram:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 240 nm. Hence all further investigation was carried out at the same wavelength.

b) Preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Escitalopram was dissolved in method 5 ml, volumetric flask makes up to 100 ml of Phosphate buffer of pH 6.8., from primary stock 10 ml was transferred to another volumetric flask made up to 100 ml with Phosphate buffer of pH 6.8, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 5, 10, 15, 20 and 25 $\mu\text{g/ml}$ respectively. The absorbance was measured at 240 nm by using a UV spectrophotometer.

Formulation Development: Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table 1: Formulation of Immediate Release tablets

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Escitalopram	10	10	10	10	10	10	10	10	10	10	10	10
PEG 6000	20	30	40	50	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	20	30	40	50	-	-	-	-
Sodium-starch glycolate	-	-	-	-	-	-	-	-	20	30	40	50
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
MCC	144	134	124	114	144	134	124	114	144	134	124	114
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Total weight of tablets = 200 mg

The tablets were prepared by using 7 mm flat surfaced punch. The hardness of the tablets was maintained as 3.1-3.9 kg/cm².

Evaluation parameters:

Pre compression parameters: Measurement of Micrometric Properties of Powders

Angle of repose: The angle of repose of API powder is determined by the funnel method. The accurately

weight powder blend are taken in the funnel. The height of the funnel is adjusted in way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$$\tan \theta = h/r \dots\dots\dots (1)$$

where, h and r are the height and radius of the powder cone.

Table 2: Flow Properties and Corresponding Angle of Repose

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

Bulk density: The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V₀ is noted. The bulk density is calculated in g/cm³ by the formula.

$$\text{Bulk density} = M/V_0 \dots\dots\dots (2)$$

M= Powder mass

V₀= apparent unstirred volume

Tapped density: The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml granulated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V₀ is noted. Tapping's are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two

tapping volume is less than 2%, V_b is considered as a tapped volume V_f. the tapped density is calculated in g/cm³ by the formula.

$$\text{Tapped density} = M/V_f \dots\dots\dots (3)$$

M= weight of sample power taken

V_f= tapped volume

Compressibility Index: The Compressibility Index of the power blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is an below: Carr's Index (%)=[(TD-BD)/TD]x100 (4)

Hauser's ratio: The Hauser's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hauser's ratio. It is calculated by the following equation.

$$H = pT / pB \dots\dots\dots (5) \text{ Where } pT = \text{tapped density, } pB = \text{bulk density}$$

Table 3: Scale of Flowability

Compressibility Index (%)	Flow Character	Hauser 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

Post compression parameters:

a) Thickness: The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation: Twenty tablets randomly selected from each batch and individually. Weighed The average weight and standard deviation three batches were calculated. It passes the test weight variation test if not more than two of the individual tablets weights deviate from the average weight by more than the allowed percentage deviation and more deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability: The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25rpm for 4 min. Percentage friability was calculated using the following equation.

$$\text{Friability} = \left(\frac{[w_0 - w]}{w_0} \right) \times 100$$

d) Assay: The content of drug was carried out by five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder, this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 240 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid,

observe whether all of the tablets have disintegrated.

f) Dissolution test of Escitalopram tablets: Drug release from Escitalopram tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 phosphate buffer as the dissolution medium of quantity 500ml. the whole study is being carried out at a temperature of 37°C and at speed of 50 rpm. 5 ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25 and 30 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV Spectrophotometer. The concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies:

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

RESULTS AND DISCUSSION
Determination of λ max:

The Prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 240 nm.

Calibration curve of Escitalopram:

The standard curve of Escitalopram was obtained and good correlation was obtained with R^2 value of 0.999 the medium selected was pH 6.8 phosphate buffer.

Table 4: Standard graph values of Escitalopram at 240 nm in pH 6.8 phosphate buffer

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
5	0.126
10	0.241
15	0.352
20	0.461
25	0.581

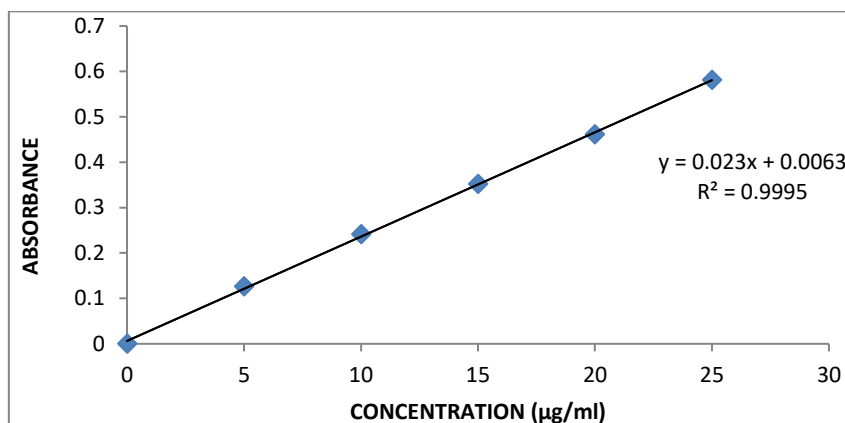


Fig 1: Standard curve of Escitalopram

Evaluation:

Characterization of precompression blend:

The precompression blend of Escitalopram were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than $34.0 \pm 0.05^\circ$,

Carr's index values were less than 22.5 for the precompression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.27 for all batches indicating good flow properties.

Table 5: Physical properties of precompression blend

Formulation code	Angle of repose (θ)	Bulk density (gm/cm ³)	Tapped density(gm/cm ³)	Carr's index (%)	Hausner's ratio
F1	40.4 ± 0.03	0.50 ± 0.09	0.62 ± 0.02	21.3 ± 0.07	1.26 ± 0.07
F2	34.0 ± 0.05	0.51 ± 0.08	0.64 ± 0.03	21.4 ± 0.14	1.23 ± 0.06
F3	29.5 ± 0.11	0.47 ± 0.11	0.56 ± 0.05	16.4 ± 0.13	1.15 ± 0.13
F4	31.8 ± 0.03	0.52 ± 0.08	0.64 ± 0.04	22.5 ± 0.09	1.27 ± 0.10
F5	37.7 ± 0.12	0.51 ± 0.10	0.62 ± 0.06	19.5 ± 0.06	1.23 ± 0.15
F6	36.2 ± 0.13	0.50 ± 0.07	0.62 ± 0.03	19.8 ± 0.06	1.24 ± 0.14
F7	40.1 ± 0.12	0.54 ± 0.09	0.65 ± 0.06	21.4 ± 0.06	1.26 ± 0.13
F8	33.4 ± 0.07	0.51 ± 0.05	0.63 ± 0.06	20.4 ± 0.12	1.23 ± 0.07
F9	26.2 ± 0.12	0.48 ± 0.04	0.57 ± 0.03	17.4 ± 0.07	1.15 ± 0.04
F10	31.4 ± 0.08	0.52 ± 0.06	0.64 ± 0.07	21.5 ± 0.03	1.23 ± 0.07
F11	29.6 ± 0.17	0.50 ± 0.02	0.62 ± 0.04	18.3 ± 0.04	1.20 ± 0.12
F12	30.3 ± 0.09	0.51 ± 0.06	0.64 ± 0.03	20.1 ± 0.08	1.23 ± 0.10

All the values represent n=3

Evaluation of tablets:

Physical evaluation of Escitalopram Immediate release tablets: The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 8.3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 3.1-3.9 kg/cm² and the friability values

were 0.12 – 0.64 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.11 – 3.61 cm. All the formulations satisfied the content of the drug as they contained 97.15- 99.75 % of Escitalopram and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 6: Physical evaluation of Escitalopram

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm ²)	Friability (%)	Content uniformity(%)
F1	198.2	3.14	3.5	0.12	98.26
F2	199.4	3.52	3.1	0.29	97.15
F3	196.8	3.61	3.9	0.61	99.62
F4	195.2	3.42	3.4	0.24	98.35
F5	198.8	3.11	3.6	0.56	99.29
F6	197.1	3.28	3.1	0.35	98.61
F7	199.8	3.42	3.5	0.48	99.75
F8	197.5	3.51	3.6	0.64	97.82
F9	198.6	3.29	3.4	0.53	99.12
F10	199.0	3.18	3.2	0.42	97.49
F11	198.7	3.38	3.5	0.52	99.31
F12	198.9	3.16	3.7	0.39	97.86

In vitro release studies:

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 °C.

Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer .at 240 nm.

Table 7: *In vitro* data for formulation F1-F4.

TIME (MIN)	% DRUG RELEASE			
	F1	F2	F3	F4
0	0	0	0	0
5	19.32	22.15	34.91	28.62
10	25.39	32.47	41.82	36.56
15	46.75	45.32	56.94	45.84
20	67.28	63.79	68.66	59.42
25	73.41	78.34	82.24	78.82
30	79.63	82.47	87.11	89.94
45	83.82	89.68	93.23	96.44

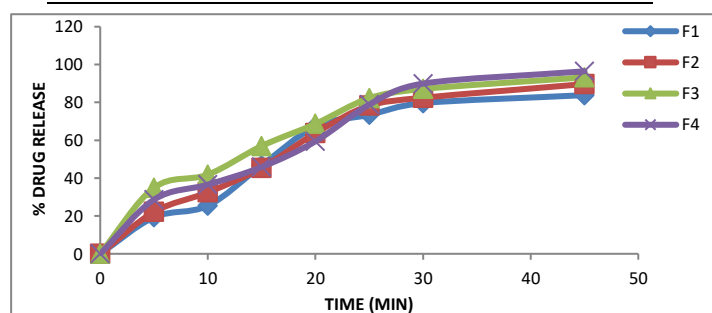

Fig 2: *In vitro* dissolution data for formulation F1-F4

Table 8: *In vitro* dissolution data for formulations F5-F8

TIME(MIN)	% DRUG RELEASE			
	F5	F6	F7	F8
0	0	0	0	0
5	23.62	32.91	30.52	25.47
10	35.11	41.63	43.33	36.94
15	47.25	54.28	53.75	44.79
20	59.41	65.15	75.85	65.57
25	67.37	68.82	82.54	72.64
30	73.85	73.65	88.76	84.84
45	76.65	84.56	98.12	91.32

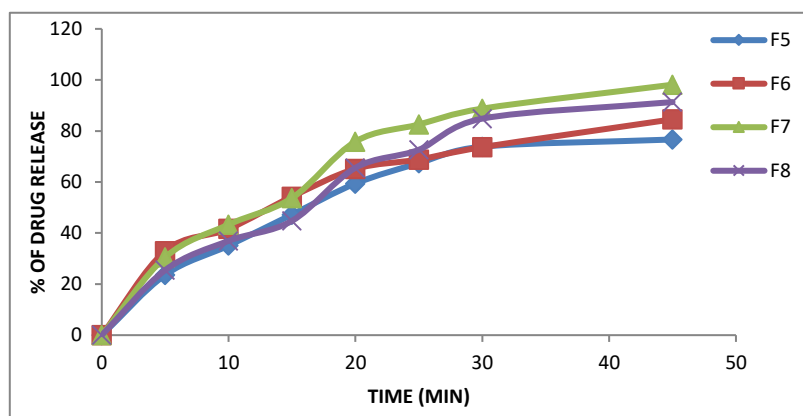


Fig 3: *In vitro* dissolution data for formulations F5-F8

Table 9: *In vitro* dissolution data for formulations F9-F12

TIME (MIN)	% DRUG RELEASE			
	F9	F10	F11	F12
0	0	0	0	0
5	25.91	21.62	18.85	15.59
10	37.15	29.10	29.68	34.41
15	45.20	45.81	38.92	38.98
20	57.38	58.99	46.58	49.12
25	79.82	67.38	58.28	58.78
30	86.73	74.87	65.96	63.93
45	95.19	86.56	72.48	68.56

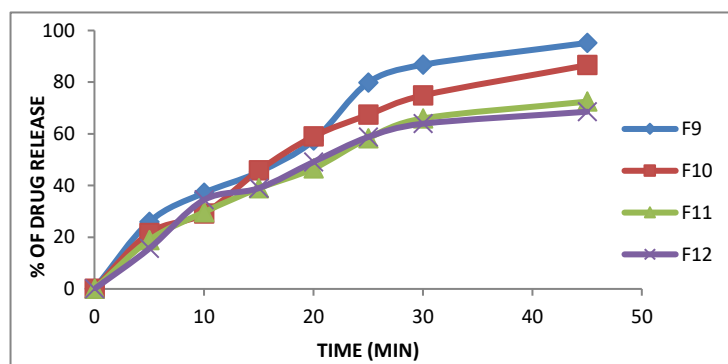


Fig 4: *In vitro* dissolution data for formulations F9-F12

Among all the formulations F7 formulation containing drug and Croscarmellose sodium showed good result that is 98.12 % in 45 minutes, at the concentration of 40 mg. Hence from all the formulations it is evident that F7 formulation is the better formulation.

Drug-Excipient compatibility studies by FTIR studies:

Escitalopram was mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug –excipient interactions.

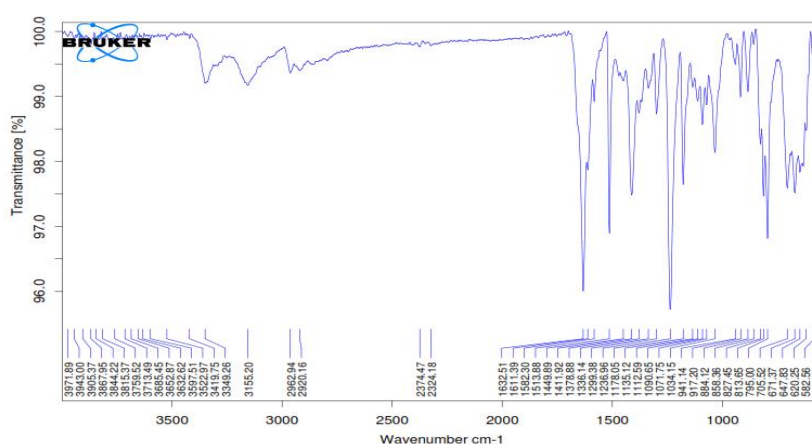


Fig 5: FTIR spectra of pure drug

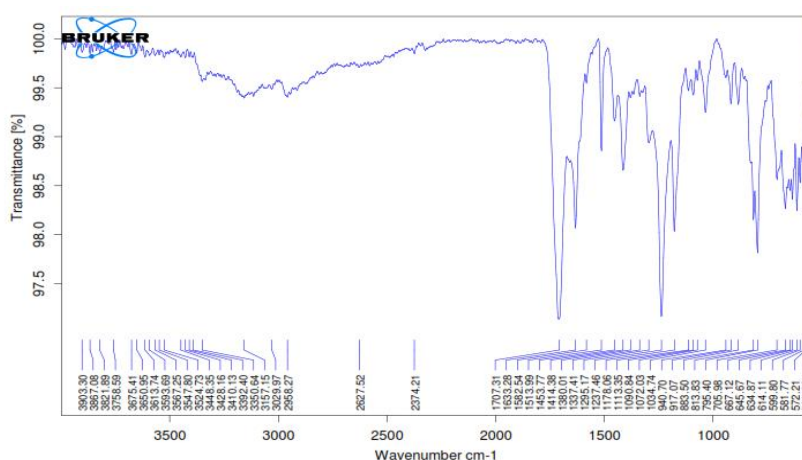


Fig 6: FTIR spectra of optimized formulation

CONCLUSION

The standard curve of Escitalopram was obtained and good correlation was obtained with R^2 value of 0.999. The medium selected was pH 6.8 phosphate buffer. Escitalopram was mixed with various proportions of excipients showed no colour change at the end of 2 months, proving no drug-excipient interactions. The pre compression blend of Escitalopram immediate release tablets using super disintegrants were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend or all batches indicating good to fair followability and compressibility. Immediate release tablets were prepared with various concentrations of polymers and were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. The formulations (F7) prepared with Croscarmellose sodium polymer showed drug release in increasing order. The formulation (F7) containing drug and Croscarmellose sodium showed good drug release at 40 mg concentration. Among all the formulations F7

formulation containing drug and Croscarmellose sodium (40 mg concentration) showed maximum and good result that is 98.12% drug release in 45 min. Hence from dissolution data it was evident that F7 formulation is the better formulation.

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