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Research Article

FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF ESCITALOPRAM OXALATE ORALLY DISINTEGRATING TABLETS

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ABSTRACT

The purpose of this research was to develop Orally disintegrating tablets of escitalopram Oxalate. Orally disintegrating tablets offers a solution for paediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. Selective serotonin reuptake inhibitors (SSRIs), which are broad spectrum antidepressants that are effective for major depressive disorder and several anxiety disorders. Escitalopram Oxalate is highly selective, more effective and better than other SSRIs. The aim is to formulate Orally disintegrating tablets of escitalopram oxalate using different ratios of Superdisintegrants LHPC-21, Kyron and Crospovidone, while Microcrystalline cellulose, Mannitol, Prosolv ODT used as fillers. Tablets were prepared by direct compression method. The tablets were evaluated for hardness, thickness, friability, and weight variation and disintegration time, dispersion times and %drug release studies were performed. Tablets containing Crospovidone, Kyron as disintegrants and Mannitol as filler were disintegrate rapidly below 20 sec and 100% drug release below 5mins.

Keywords: Escitalopram oxalate, orally disintegrating tablets, Kyron, Prosolv ODT.

INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to many other routes[1]. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are travelling or have little access to water are similarly affected[2, 3, 4]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orodispersible

Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms[5, 6, 7].

The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. ODT is one such dosage form which is useful for Geriatric patients mainly suffering from conditions like hand tremors and dysphasia[8].

- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Travelling patients suffering from motion sickness and diarrhea that do not have easy access to water.
- Especially for Patients with persistent nausea for a long period of time are unable to swallow.
- Mentally challenged patients, bedridden patients and psychiatric patients.

For treatment of depression various conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc are available in market but the major drawbacks with these are many patients find it difficult to swallow (dysphagia) tablets and hard gelatin capsules. The difficulty experienced in particular by paediatrics and geriatrics patients [9]. Other groups that may experience problems include the mentally ill, developmentally disable and patients who are uncooperative and hence do not take their medicines as prescribed leading to patient noncompliance.

Escitalopram oxalate [10] is selective serotonin reuptake inhibitor (SSRIs). SSRIs are broad spectrum antidepressants that are effective for major depressive disorder and several anxiety disorders. Escitalopram is highly selective, allosteric serotonin reuptake inhibitor. It has unique dual action mechanism involving allosteric and primary binding to serotonin transporter protein that explains the therapeutic superiority. Escitalopram Oxalate is highly selective, more effective and better tolerated than other SSRIs[11]. The concept of formulating orally tablets containing escitalopram oxalate offers a suitable and practical approach in serving desired objective of rapid disintegration and dissolution characteristics with increased bioavailability. Hence the aim is to formulate orally disintegrating tablet of escitalopram oxalate, using various Superdisintegrants and fillers

MATERIALS AND METHODS

Escitalopram oxalate (hetero drugs limited, Hyderabad),sodium starch glycolate(weiming pharmaceuticals.mfg.co.ltd) Crospovidone CL-F (shanhung industries Co.Ltd), LHPC-21 (SGN ETSU chemicals Co.Ltd), kyronT-314 (coral Pharma), Aspartame (neutrasweet company augusta), Orange, peppermint (Frimenich aromatics india PVT-LTD), lake sunset yellow (amerind colors& chemicals pvt.ltd), Aerosil 200 (wacker chemicals), Micro crystalline cellulosePh-112 (FMC biopolymer), ProsolvODT (JRS Pharma pvt ltd), Mannitol SD200 (Merck Pvt.ltd), Talc (Nandhu chemical industries, huble).

FORMULATION OF ESCITALOPRAM OXALATE ODT

The oral disintegrating tablets of escitalopram oxalate were prepared using Crospovidone, Kyron T-314, L-HPC-21, used as super disintegrants microcrystalline cellulose and Mannitol& Prosolv-ODT used as diluents, aspartame as a sweetening agent, powdarome orange and powdarome peppermint as flavour enhancer , aerosol and talc used as flow promoter .the composition of each batch shown in Table-1.

Direct compression technique was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration, in this process escitalopram oxalate,

aspartame, orange, peppermint, LHPC-21 were together passed through sieve no 40 (Blend-1).MCC& aerosil were together passed through sieve no 40 (Blend-2).lake sunset yellow was passed through the sieve no 80. The three blends are mixed and co shifted through sieve no 40 .blend for 5 mins magnesium sterate was added and blended for 10 mins. The final blend was compressed into tablets by using 8mm flat bowled edge punches with break line.

EVALUATION PARAMETERS OF ESCITALOPRAM OXALATE ODT

Estimation of escitalopram oxalate

An UV Spectrophotometric method based on the measurement of absorbance at 239nm in methanol was used in the estimation of escitalopram oxalate. The method obeyed Beer's law in the concentration range of 2-10μg/ml. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of escitalopram oxalate content in various products and in vitro dissolution studies.

Evaluation of pre compression parameters of the powder

Prior to compression, granules were evaluated for their flow and compressibility parameters. Flow properties of granules were determined by angle of repose method. Compressibility index of granules were determine by Carr's index and Hauser ratio [12, 13].

Evaluation of post compressional parameters of the tablets[14]

Physical appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour etc.

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickhness should be controlled within a ± 5% variation of a standard.

Weight variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Average weight of tablet (mg)	% difference
130 or less	10 %
From 130 to 324	7.5%
> 324	5%

Hardness test

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Percentage friability

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping. **Method:** If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets were tested.

$$\%Friability = \frac{(Intial\ weight\ of\ tab - Final\ weightof\ tab)}{Final\ weightof\ tab} \times 100$$

Disintegration time

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±2^{0}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30seconds.

Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure[55]. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, *R* can be the determined according to the following equation. $R = 100 (Wa-Wb) / Wb$

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Dissolution studies

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions. **Method**: The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15 and 30 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

RESULTS AND DISCUSSION

The Escitalopram Oxalate API (10µg/ml) was scanned in the UV between 200-400nm observed that at 239 nm shows maximum absorbance. Shown in figure-1.

The flow properties of the drug show in table-2 shows drug posses poor flow property.

Standard Calibration curve of escitalopram oxalate was carried out at 239 nm of 2, 4, 6, 8, 10µgm/ml was shown in table-3, Figure-2.

Results of pre compression parameters shown in table-4 and post compression parameters were shown in Table-5.and dissolution profiles F9 formulations shown in table-6 and comparative dissolution profiles plotted shown in figure-3,4,5

F1 was carried Microcrystalline cellulose (Cyclocel pH112) as diluent, Crosspovidone XL (2.5%) & L-HPC (2.5%) as superdisintegrant. Aerosil is used as a glident the disintegration time was more than 3mins and in-vitro dispersion time was more than 7mins.

F2 was carried Microcrystalline cellulose (Cyclocel pH112) as diluent, Crosspovidone XL (2.5%) & L-HPC(2.5%) & KyronT314(5%) as superdisintegrant. Hence e disintegration time was reduced to 68 seconds but fails in the in-vitro dispersion time and wetting time.

F3 Formulation was carried out by increasing the concentrations of the super disintegrate Crosspovidone (5%), kyron (7.5%), L-Hpc (5%).and using the combination of the diluent Micro crystalline

cellulose and mannitol. Hence the disintegration time was reduced but still the wetting time was not yet improved

Formulation F4 was carried out with increased concentration of the mannitol (30%) as diluent results in good improvement in the disintegration time(65sec) and wetting time(45 sec).

F5 was carried out by using the Prosolv ODT (60%) as excipent specially designed for the orally disintegrating tablet here the disintegration time was increased and wetting time was also increased and the sticking problem was also observed during compression.

F6 formulation was carried out with addition of spray dried mannitol (25%) and Aerosil (2.5%) and crospovidone (5%) hence observed improvisation in the wetting time and disintegration time

F7 formulation was carried out with addition of spray dried mannitol (40%) and aerosil (7.5%) as a suspending agent hence observed improvisation in the wetting time (48sec) and disintegration time (21) hence concluded that Prosolv ODT does not show the impact on this formulation.

F8 formulation was carried out with mannitol as a filler and crospovidone, KyronT314 & L-Hpc 21 as a super disintegrates results in good wetting time (24sec)and disintegration time (14sec).

F9 is the reproducibility batch of F8 All the pre compression and the post compression parameters showed good results.

Table1: Formulation Developmental Trails

Excipients /Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Escitalopram Oxalate	20	20	20	20	20	20	20	20	20
Crospovidone CL-F	5	5	10	10	10	10	10	10	10
LHPC-21	5	5	10	10	10	10	10	10	10
Kyron T314	0	10	15	15	15	15	15	15	15
aspartame	5	5	5	5	5	5	5	5	5
orange	5	8	8	8	8	8	8	8	8
Peppermint	0	8	8	8	8	8	8	8	8
Lake sunset yellow	1	1	1	1	1	1	1	1	1
Aerosil	20	20	20	20	0	5	15	20	20
Prosolv ODT	0	0	0	0	120	65	25	0	0
MCC(CyclocelpH112)	136	81	50	40	0	0	0	0	0
Mannitol SD200(Peritol)	0	40	50	60	0	50	80	100	100
Talc	3	3	3	3	3	3	3	3	3
Total weight(mg)	200	200	200	200	200	200	200	200	200

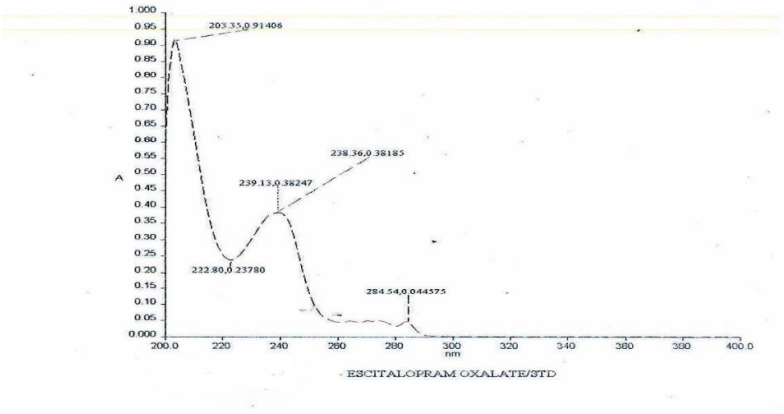

Fig. 1: UV Spectroscopy of Escitalopram oxalate API

Table 2 Flow properties of Escitalopram oxalate API

S. No.	TEST	RESULT
1	Bulk density(g/ml)	0.200gm/ml
2	Tap density(g/ml)	0.384
3	Compressibility Index (%)	48%
4	Hausner Ratio	0.1923
5	Angle of Repose	44.645

Table 3: Standard calibration curve of the Escitalopram oxalate

Concentration (µg/ml)	Absorbance at 239nm
0	0
2	0.0813
4	0.1586
6	0.2349
8	0.3087
10	0.3824
Slope(m)	0.381
Intercept	0.003
Correlation	0.999

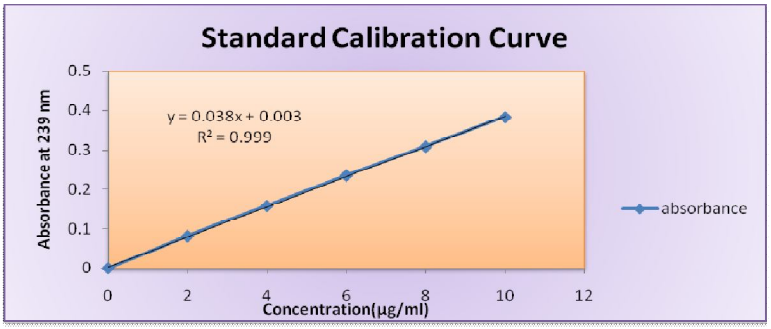

Fig. 2: Standard calibration curve of the Escitalopram oxalate

Table 4: Results of Pre Compression Parameters

BATCH NOS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	48.32	37.45	34.76	32.98	40.5	38.04	32.56	29.65	28.98
Bulk density	0.25	0.605	0.631	0.586	0.387	0.59	0.384	0.486	0.463
Tap density	0.384	0.741	0.728	0.681	0.54	0.74	0.45	0.532	0.509
Compressibility index	34.89	18.35	13.32	13.95	28.33	20.27	14.66	8.64	9.03
Hausner ration	1.53	1.22	1.15	1.16	1.39	1.254	1.17	1.09	1.09

Table 5: Results of Post Compressional Parameters

Physical Appearance: - slight orange coloured tablets with break line

Formulation Code	Average weight (mg) ±7.5%	Thickness (mm) ±5%	Hardness (kp)	Percentage Friability (%) 0.1-0.9%	In vitro Disintegration Time (sec)	In vitro dispersion time(sec)	Wetting time (sec)
F1	201	3.55	2.5	0.31	180	>7min	240
F2	199.6	3.54	2.3	0.20	68	132	118
F3	202.5	3.71	2.0	0.22	55	110	97
F4	200	3.89	2.2	0.10	49	65	45
F5	198.5	3.45	2.1	0.60	54	165	120
F6	202.1	3.56	2.7	0.34	32	121	104
F7	200	3.67	2.5	0.11	21	45	48
F8	200	3.71	3.4	0.09	14	34	24
F9	200	3.70	3.5	0.09	16	31	28

Table 6: Dissolution study of Escitalopram Oxalate Oral Disintegrating Tablets

Cumulative percentage of drug release (%)									
Time (min)	**F 1**	**F 2**	**F 3**	**F4**	**F5**	**F6**	**F7**	**F 8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	92.99	98.66	99.44	102.59	101.28	102.48	103.14	103.04	103.13
10	96.3	98.74	100.71	102.37	102.46	102.66	103.65	103.54	103.65
15	96.49	100.77	101.72	102.33	103.59	103.2	103.51	103.29	103.71
20	98.83	102.14	102.27	101.47	101.02	101.22	102.75	101.79	103.75
30	101.79	102.04	102.25	101.26	101.87	101.4	102.84	101.85	102.84

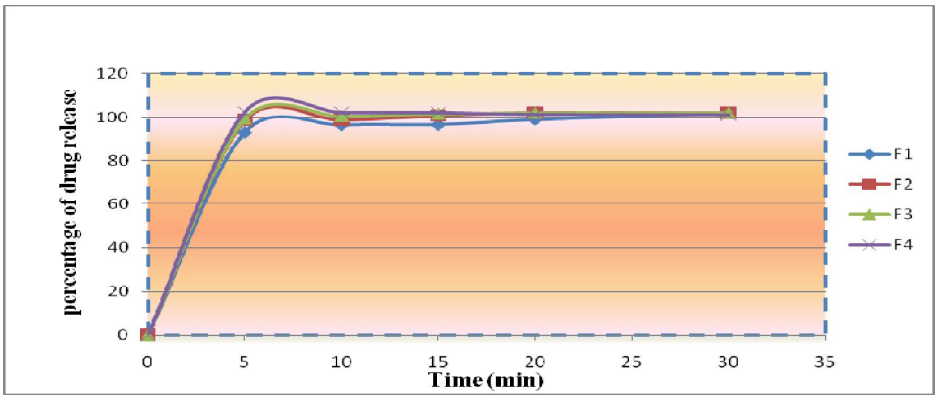

Fig. 3: Comparative dissolution profile of Different Formulations (F1, F2, F3, F4)

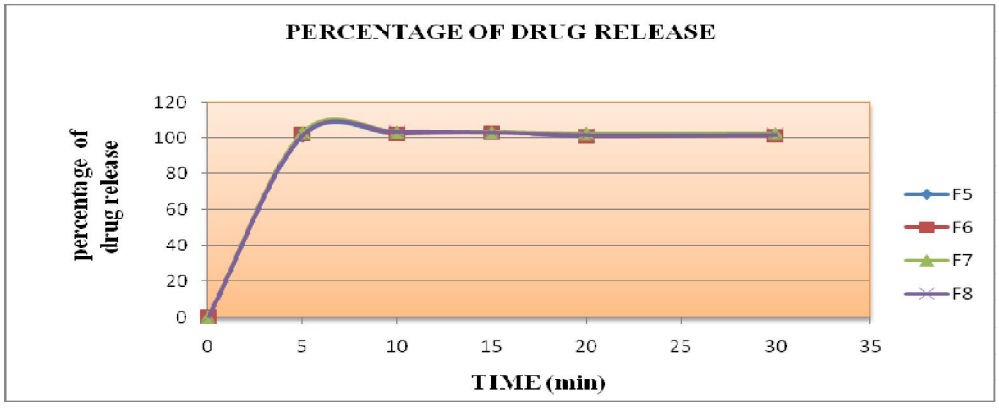

Fig. 4: Comparative dissolution profile of Different Formulations (F5, F6, F7, F8)

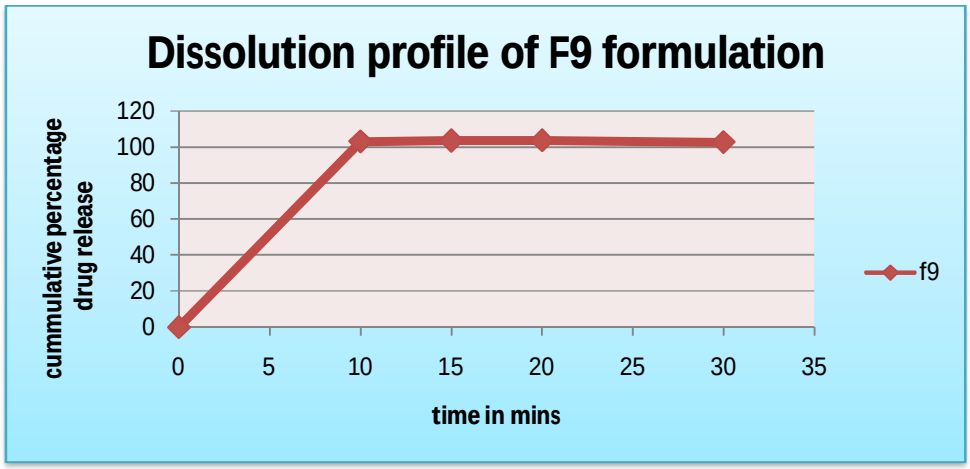

Fig. 5: Dissolution profile of F9 formulation

SUMMARY

A recent advance in Novel Drug Delivery System aims to enhance safety to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is Orally Disintegrating Tablet.

The present study was to formulate and standardize of an Anti depressant drug Escitalopram Oxalate. Escitalopram Oxalate orally disintegrating tablets formulated in the present study are beneficial to the paediatrics and elderly patients. It is also beneficial to the person having Dysphagia, mentally ill and several anxiety disorders.

Preformulation studies were carried out during the early stages of this work. It was found that Escitalopram oxalate is having maximum absorbance at wavelength 239 nm. The drug-polymer compatibility study was carried out to determine the interactions between the drug and the polymers used in the study.

The orally disintegrating tablets were formulated using the above mentioned difrent super disintegrants by direct compression technique. Crospovidone, LHPC-21 and Kyron T-314 were used as super disintegrants .

Prepared tablets were evaluated for Pre-Compression Parameters and Post compression Parameters.

Flow properties –Angle of repose, Bulk density, Tap Density and also %compressability was determined to all formulations which showed good flow property.

Formulation F1 was carried Microcrystalline cellulose (Cyclocel pH112) as diluents, Crosspovidone XL (2.5%) & L-HPC (2.5%) as Superdisintegrants. Aerosil is used as a glident here shows the DT more than 3mins to improve the disintegration time the addition of the super disintegrants KYRON T-314 ,the disintegration time was improved but still the wetting time and the invitro dispersion time were not improved for this reason the Spray dried Mannitol was used as diluents and concentration of super disintegrants was increased in F3.As the increasing the concentration of the diluents Mannitol results in the good wetting time and invitro dispersion.

F5,F6,F7 were prepared by using Prosolv ODT which does not give good results so the increasing concentration of Mannitol and the cross provide were used again gives the best result. F8 were carried out with Mannitol as filler and Crospovidone, Kyron T-314 &L-HPC 21 as super disintegrates results in good wetting time 24 sec and disintegration time 14 seconds.

The final trials F8, F9 were optimized with various tablet parameters like Thickness (3-4) mm; Hardness (3-4) kp; Percentage Friability (<1%) and Disintegration time (14±3 seconds), which were within the specified limits. The Dissolution and Assay results of F8 and F9 were good

CONCLUSION

Escitalopram Oxalate used as Antidepressant. They are formulated as oral disintegrating tablets which show better patient acceptability and compliance with improved efficacy when compared with conventional dosage forms.

Direct compression was the preferred technology for the preparation of oral disintegrating tablets of Escitalopram Oxalate. Based on the preliminary studies various formulation trials (F1-F9) were carried out with different concentrations of Superdisintegrants, filers and lubricants. From the various formulations it was concluded that the formulation F9, the reproducibility batch of F8 was finalized as the optimized formula.

Formulation F9 showed satisfactory results with various physicochemical evaluation parameters like Hardness, Percentage weight loss, Disintegration time, Dissolution profile, Assay and Moisture content. When subjected to accelerated stability studies the tablets were found to be stable.

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