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Research Article

DESIGN AND EVALUATION OF RAPIDLY DISINTEGRATING TABLETS OF RASAGILINE MESYLATE

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ABSTRACT

Rasagiline is an irreversible monoamine oxidase inhibitor indicated for the treatment of idiopathic Parkinson's disease. The aim of the present study is to improve quick on-set of action of Rasagiline Mesylate. Rapid disintegrating tablets were prepared by using 2% disintegrant such as povidone, 5% binders such Starch-1500. The excipients were used for this study was based on the compatibility studies. All the formulations were prepared by wet granulation method. Among all the formulations F8 was optimized batch. Preformulation parameters such as bulk density, tapped density, compressibility index, hausner's ratio, angle of repose were found to be within the limits. Hardness, friability, disintegration time of the F8 tablets were also with in limits with cumulative drug release 99.8% at 45th minute by HPLC method. Dissolution profile of F8 was compared with marketed formulation of Rasagiline and the results obtained were better than the marketed formulation. Stability studies showed no significant change in the F8 formulation.

INTRODUCTION

The tablet is the most widely used solid oral dosage form among the other dosage forms, because of its advantages like possibility of self administration, compactness, easy in manufacturing and cost effective[1, 2]. However Swallowing of tablet may produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia[3]. To overcome above problem rapid disintegrating dosage forms were developed which have many other advantages like improved bioavailability, reduced dosing[4]. Rapid disintegrating tablets are generally defined as tablets that are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques. The basic aim of rapidly disintegrating formulation is to allow an increase in systemic availability of drug. Rasagiline is an irreversible monoamine oxidase inhibitor indicated for the treatment of idiopathic Parkinson's disease. The conventional tablets available in market are not suitable where quick onset of action is required and also provide swallowing problems for the patients suffering from parkinsonism. To overcome these problems, there is a need to develop a rapidly disintegrating dosage form, particularly one that would rapidly disintegrate in saliva and could be administered without water anywhere anytime.

Present work

The aim of the present study is to design and evaluate rapidly disintegrating tablets of Rasagiline Mesylate which is pharmaceutically equivalent to the marketed product for the treatment of parkinsonism disease.

MATERIALS AND METHODS

Rasagiline Mesylate (Natco pharma LTD, Hyderabad), Aerosil (Signet Chemicals, Mumbai), Povidonek30, Pregelatinised Starch, Mannitol, Corn Starch , Starch-1500 (lycotab c) (Akin laboratories, Hyderabad), were used. All other chemicals and reagents used were of pharmaceutical or analytical grade.

Method

Wet granulation method

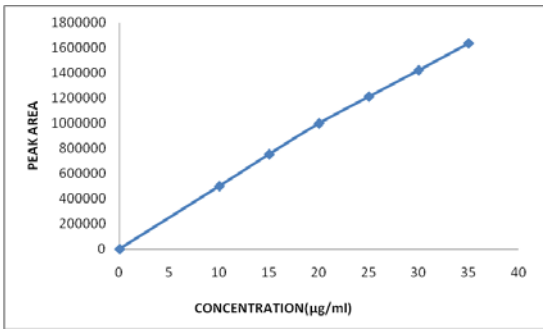

Fig. 1: Standard curve of Rasagiline Mesylate

Rasagiline Mesylate tablet were prepared by wet granulation method. Tablets containing 1mg of Rasagiline Mesylate were prepared and various formulations used in the study are shown in table: 1. Mannitol, starch-1500 were passed through 40# mesh and mixed in a poly bag. Povidone k-30, Rasagiline Mesylate was dissolved in water and above blend was granulated using this liquid. The wet mass was passed through 12# mesh and dried in tray drier at 60^{0}c.The dried granules were passed through 18# mesh. The dried granules were lubricated with starch-1500, talc and stearic acid which were previously passed through 40# mesh. The lubricated granules were compressed with 6mm round flat punches.

Table 1: Formulation trials of F1-F8 Batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Rasagiline Mesylate	1.56	1.56	1.56	1.56	1.56	1.56	1.56	1.56
Mannitol	-	78.54	78.54	78.54	80.34	76.74	73.94	78.54
Mannitol Spray dried	79.89	-	-	-	-	-	-	-
Starch-1500	4.5	4.5	-	-	2.25	6.3	8.1	4.5
Corn Starch	-	-	4.5	-	-	-	-	-
Pregelatinised Starch	-	-	-	4.5	-	-	-	-
Aerosil	0.45	-	-	-	-	-	-	-
Povidone K-30	-	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Purified Water	-	qs	Qs	qs	qs	qs	qs	qs
Talc	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Stearic acid	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

Preformulation Studies[5, 6]

Preformulation activity ranges from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can make us to develop successful dosage form. Preformulation testing is an investigation of physical and chemical properties of a drug substance.

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bio-available. Further the use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substances to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The granule mass should allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface .This forms a pile of granules on the paper.

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

Where, h= height of the pile

r=radius of the pile

Table 2: Physical parameters of Rasagiline Mesylate powder (pure)

Parameter	Rasagiline Mesylate
Bulk Density (gm/cm2)	0.480
Tapped Density (gm/cm2)	0.641
Compressibility Index	25.0
Hauser's Ratio	1.33
Angle of repose	25.594

Bulk density

An accurately weighed quantity of the Rasagiline blend (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured and it is tapped mechanically either manually or mechanical device till a constant volume is obtained. This volume is bulk volume (V_b) and it includes the true volume of the powder and void space among the powder particles

$$Db = M / V_b$$

Where, M is the mass of powder,

V_b is the bulk volume of the powder.

Tapped density

Tapped density is defined as the ratio between total mass of the powder taken to the tapped volume of the powder. The blend was tapped 750 times, the initial and final volume was noted if the difference between these two volumes is not less than 2% then tapping is continued for 1250 times. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus).

$$Dt = M / Vt$$

Where, M is the mass of powder,

Vt is the tapped volume of the powder.

Hausner's ratio: The relation between tapped density to the bulk density.

$$\text{Hausner's ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density,

Db is the bulk density.

Compressibility Index: It indicates powder flow properties that can be obtained from bulk and tapped density.

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder,

Db is the bulk density of the powder.

Drug – Excipients compatibility study: As a part of the product development, the compatibility of various excipients with active was evaluated. According to the functional category these excipients were mixed in different ratio with drug. These mixtures were kept in 40^0c / 75% RH and 25^0C / 60%RH in a 2-ml glass vial in exposed condition for 3month. Excipients are mixed with the drug in following ratio. At the interval of 2 weeks and 4 weeks, the samples were withdrawn and given to analytical development for analysis.

Table 3: Evaluation of powder blend

Formulation code	Bulk density	Tapped density	Compressibility Idex	Hausner's Ratio	Angle of repose
F1	0.492	0.548	15.46	1.19	31.31
F2	0.498	0.561	18.39	1.22	37.74
F3	0.486	0.596	19.43	1.26	38.63
F4	0.491	0.541	25.8	1.31	33.42
F5	0.472	0.581	21.36	1.33	26.61
F6	0.498	0.596	22.9	1.35	25.59
F7	0.472	0.578	22.8	1.35	25.62
F8	0.492	0.576	16.29	1.28	28.62

Evaluation of Tablets[7, 8, 9]

Physical appearance

The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test

Hardness of the tablet is determined by stock's Monsanto hardness tester which consists of a barrel with a compressed spring. The pointer moves along the gauge in the barrel fracture. The tablet hardness of 5kg is considered as suitable for handling the tablet.

Tablet size and Thickness

The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by vernier calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled to facilitate packaging.

Friability

This test is performed to evaluate the ability of tablets to withstand abrasion in packaging, handling ad transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at

25rpm for 4mins. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to1.0 percent.

Disintegration test

For most tablets the first important step toward solution is break down of tablet into small particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type sustained release tablets are tested for disintegration time.

Invitro-dissolution studies

In-vitro drug release studies were carried out using USP type II (paddle) dissolution apparatus in 500 ml 0.01N HCl medium at 50 rpm. 5ml of samples were withdrawn at intervals of 10, 15, 30, 45 min and replaced with fresh buffer. The samples were analysed by using HPLC at 254 nm.

Methodology

Instrument: High performance liquid chromatography equipped with UV-detector and data handling system.

Chromatographic conditions

Column: Purosphere star RP-18, (150 x 4.6mm), 5Mm

Flow rate: 1.5ml/minute

Wave length: UV-210nm

Column temperature: 30^{o}c

Injection volume: 20Ml

Run time: 15minutes

Standard preparation

Accurately weighed and transferred about 20mg of rasagiline mesylate working standard into 100ml volumetric flask. About 60ml of 0.01N Hydrochloric acid was added and sonicated to dissolve with occasional shaking the solution to room temperature and dilute to volume with 0.01N Hydrochloric acid. Transferred 5ml of the above solution to 50ml volumetric flask and dilute to volume with 0.01N Hydrochloric acid and mixture.

Sample preparation

One tablet was placed in each of six dissolution flasks containing 500ml dissolution medium, previously maintained at 37+1^{o}c, taking care to exclude air bubbles from the surface of each dosage unit and immediately operate the apparatus for 30minutes.

After completion of 10,15,30,45minutes a portion of solution was withdrawn from the zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1cm from vessel and filtered through 0.45Mm membrane filter.

Procedure

Separately equal volumes of diluents as blank (dissolution medium), standard preparation and sample preparations were injected into the chromatograph and the peak area/response for the analyte was recorded and the % content of rasagiline mesylate was calculated by using the formula.

% content of rasagiline mesylate dissolved/tablet:

$T_A/S_A \times S_W/100 \times 5/50 \times 500/I \times P/100 \times 100/L_A$

Where,

T_A = Peak area /response due to Rasagiline Mesylate in sample preparation.

S_A = Peak area response due to Rasagiline Mesylate in standard preparation.

S_W = Weight of Rasagiline Mesylate working standard, taken in mg.

P = Purity of Rasagiline Mesylate working standard taken as its basis.

L_A = Labeled amount of Rasagiline Mesylate, in mg.

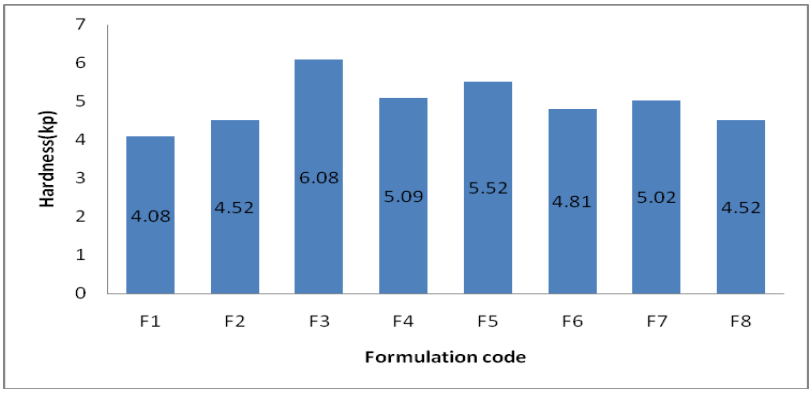

Fig. 2: Graph of the Hardness of various batches

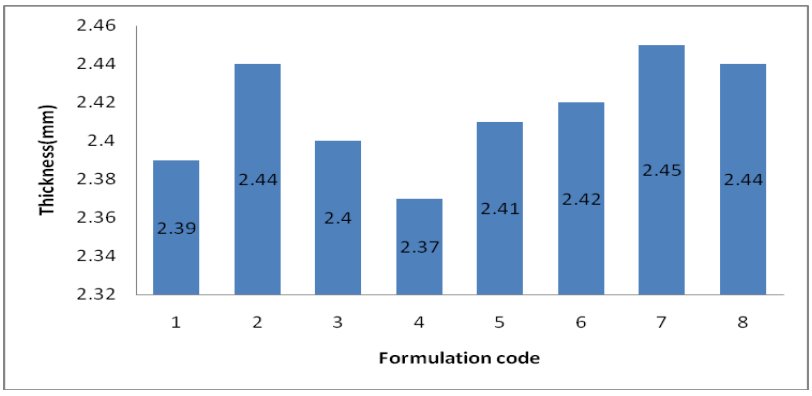

Fig. 3: Graph of the Thickness of various batches

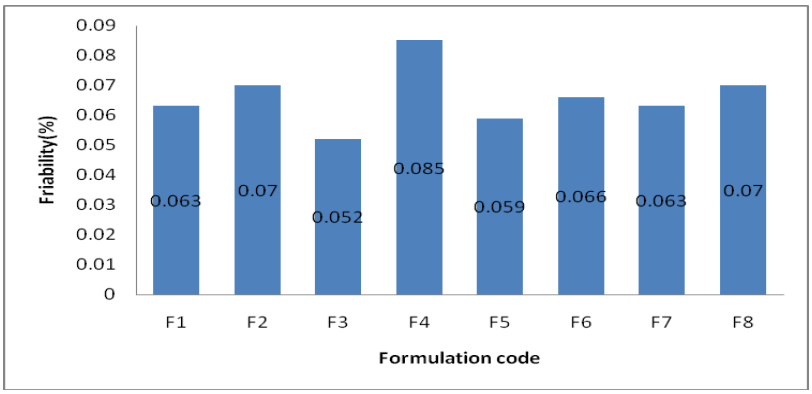

Fig.4: Graph of the Friability of various batches

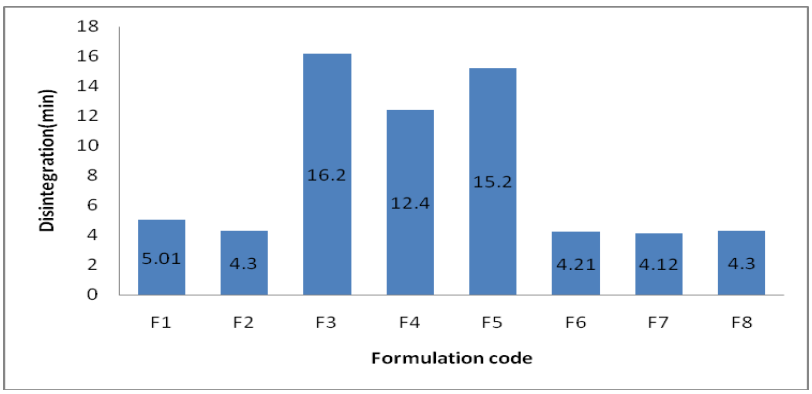

Fig. 5: Graph of the Disintegration time (min) of various batches

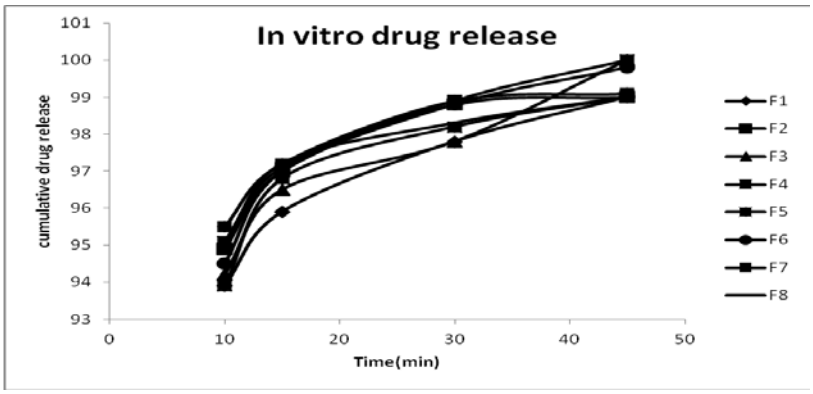

Fig. 6: Cumulative drug release profile of batch F1 to F8

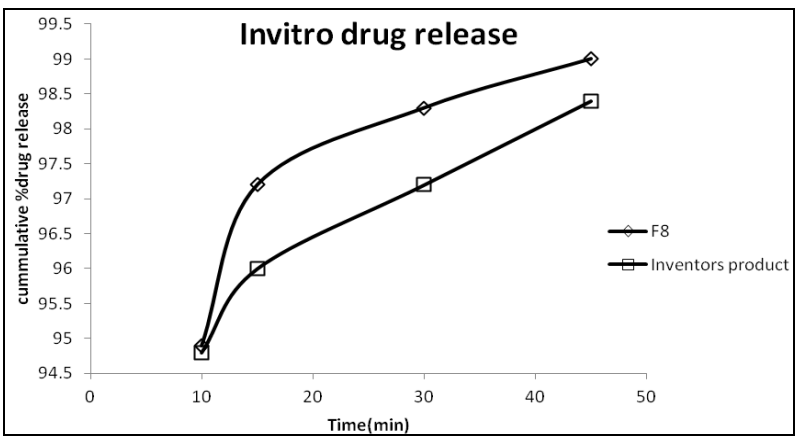

Fig. 7: Comparison of *in-vitro* dissolution of F8 with marketed tablet

Stability studies of Rapid disintegrating tablets

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behaviour and properties of the drug substance and formal stability studies on the drug substance.

Selection of batches

Data from stability studies should be provided on at least three promptly batches of the drug product. The primary batches should be of the same formulation and packaged in a same type of package as proposed for marketing. The manufacturing process used for primary batches should simulate that, to be applied to production batches and should provide product of the same quality and making the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller.

Specifications

Specification, which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH CS L6AS and IS6B.

Stability studies should include testing of these attributes of the drug product that are susceptible to change during storage and likely to influence quality, safety and efficiency. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes/ preservative content and functionality tests (for a dose delivery system). Analytical procedures should be fully validated and stability indicating.

Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For a product with a prolonged shelf life of at least 12 months, the frequency of testing at long term storage condition should normally be 3 months over the first year, every 6 months over the second year and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three points, including the initial and final time point (e.g. 0, 3, and 6 months), from a 6 month study is recommended. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage conditions, a minimum of four time points, including the initial and final points (e.g. 0, 6, 9, and 12) from a 12-month study is recommended.

Storage conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time cover the proposed shelf life.

Table 4: Physical and chemical parameters of Rasagiline Mesylate tablets of formulation F8 after one month at 40^{0}c/75% RH:

Parameter	Initial	After 1st month	After 2nd month	After 3rd month
Description	**Off white coloured, round shaped tablets**	**Off white coloured, round shaped tablets**	**Off white coloured, round shaped tablets**	**Off white coloured, round shaped tablets**
Avg. weight (mg)	92.3	91.8	91.6	91.6
Hardness(kp)	4.52	4.25	4.21	4.20
Thickness(mm)	2.54	2.53	2.53	2.53
Friability (%)	0.070	0.069	0.068	0.068

Table 5: Physical and chemical parameters of Rasagiline Mesylate tablets of formulation F8 after Third month at 25^{0}C/60%RH:

Parameter	Initial	After 3rd month
Description	Off white coloured,round shaped tablets	Off white coloured,round shaped tablets
Avg. weight(mg)	92.3	92.6
Hardness(kp)	4.52	4.50
Thickness(mm)	2.54	2.53
Friability (%)	0.070	0.071

Table 6: Physical and chemical parameters of Rasagiline Mesylate tablets of formulation F8 after one month at 40^{0}c/75% RH and third month at 25^{0}C/60%RH

Time Interval	Percentage Drug Release		
(Min)	**Initial**	**1st month**	**3rdmonth**
0	0	0	0
10	94.9	94.3	93.3
15	97.2	97.0	96.8
30	98.3	98.2	97.9
45	99.8	98.8	98.6

DISCUSSION

Rasagiline Mesylate tablets were formulated by using wet granulation method using mannitol as diluent, povidone as disintegrant, Starch-1500 as binder and stearic acid as lubricant.

Preformulation studies

Preformulation studies of Rasagiline Mesylate granules prepared by wet granulation method were carried out. The parameters such as bulk density, tapped density, compressibility index, hausner's ratio, angle of repose were found to be within the limits.

Drug – Excipients compatibility study

The drug and excipients compatibility studies were performed by means of physical mixture of drug and excipients in different ratios and were kept at 40^{0}C for 28days and no changes were observed. This indicates that the drug is compatible with the formulation excipients.

Angle of repose

Angle of repose of all batches was found to be in the range of 25.59^0 to 38.63^0. Optimized batch formulated with starch-1500 showed angle of repose 28.62^0 indicating excellent powder flow.

Hausner's ratio

Hausner's ratios of all batches were found to be in the range of 1.19 to 1.38. Optimized batch formulated with starch-1500 showed 1.28 which shows good flow properties of all prepared batches.

Compressibility Index

Compressibility index of all granules were found to be in the range of 15.46% to 25.8%. F8 showed compressibility index of 16.29% indicating good flow properties of granules.

Evaluation of tablets

Hardness test

Hardness of prepared batches were found to be in the range of 4 – 7 kg/cm^2 .Formulation F8 showed hardness of 4.52 kg/cm^2 which is found to be within the acceptable range.

Tablet size and Thickness

The maximum thickness of the tablet was found to be 2.45 mm and the minimum thickness is 2.37mm. Optimized batch showed thickness of 2.44mm.

Friability

The friability range of all tablets was found to be 0.052% - 0.08%. Best formulated batch showed 0.070%. The friability of all tablets was found to be less than 1% indicating that the tablets are mechanically stable.

Disintegration test

Disintegration time of all batches were found to be in the range of 4.12 min to 16.2 min. F8 batch showed less disintegration time 4.3 min.

Invitro-dissolution studies

In-vitro dissolution studies of all formulated batches were carried out. In-vitro release of all formulated batches were found to be in the range of 99% to 100% at the end of 45 min. Best formulated batch F8 showed in-vitro release of 99.8%.

Comparison of optimized batch with innovator

The best formulated tablet (F8) was compared with marketed tablet. Cumulative drug release of formulation F8 was 99.8% at the end of 45 min which is more than the innovator product i.e 98.4%.

Stability studies

Physical and chemical parameters of Rasagiline Mesylate tablets was carried out for the optimized formulation F8 according to ICH guide lines for one month at 40^0c/75% RH and third month at 25^0C/60%RH. The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable.

CONCLUSION

Rasagiline Mesylate tablets were formulated by using wet granulation method using mannitol as diluent, povidone as disintegrant, Starch-1500 as binder and stearic acid as lubricant.

The drug and excipients compatibility studies were performed by means of physical mixture of drug and excipients in different ratios and were kept at 40^0C for 28days and no changes were observed. This indicates that the drug is compatible with the formulation excipients.

The blends were analysed for the parameters such as bulk density, tapped density, compressibility index, hausner's ratio, angle of repose and the results were found to be within the limits for the optimized batch. The rapidly disintegrating tablets of F8 batch showed disintegration time 4.3min.

In-vitro dissolution study was performed by vary USP XII with 0.01N hydrochloric acid for 45minutes. The *in-vitro* dissolution study of optimized batch was found equal to the innovator product compared to the other formulations.

Based on all parameters F8 batch was concluded as optimized batch and gave a compressibility index (16.29%), hausner's ratio(1.28), hardness test(4.52KP), thickness(2.44mm), friability test(0.070%), disintegration time(4.30min).

REFERENCES

1. Rai V.K, Pathak N, Bhaskar R, Nandi B.C, Dey S, Tyagi L.K. Optimization of Immediate Release Tablets of Raloxifene Hydrochloride by Wet Granulation Method. International J of Pharm Sci and Drug Rese 2009; 1(1) : 51 – 54.
2. Syed Azeem, Shaweta Sharma. Immediate Release Drug Delivery Systems. International J of Biopharm & Toxico Rese 2011; 1(1): 24 – 46.
3. Jigar A Patel, Jitendra S Patel, Arjun Sony, Hemangi J Patel. Formulation and Evaluation of Immediate Release Tablet of Azithromycin by Dry Granulation Method using Super Disintegrants. American J of Pharmtech Rese 2011; 1 (4): 211-218.
4. Indhumathi D, Surya Prabha K. Formulation and Evaluation of Orodissolving Tablet of Fluoxetine using Super Disintegrants. International J of Pharma and Bio Sci 2011; 2 (1): 833 -847.
5. Leon Lachmann, Herbert A, Liberman and Joseph L, Kani. The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese publishing house, Bombay, 1987, 67- 71.
6. Indian Pharmacopoeia, Fourth edition, Controller of publications, Govt. of India, New Delhi. 1996, A-86.
7. Leon Lachmann, Herbert A, Liberman Joseph. L, Kani, The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese publishing house, Bombay, 1987, 297.
8. Alfred martin, AHC Chun. Physical pharmacy, Fifth Edition, Lippincott Williams and Wilkins, 1994, 286-289.
9. Rudnic E Schwartz JB. Oral solid dosage forms In: Remington's Pharmaceutical Sciences, Eigthen Edition, Gennaro A R Mack PublishingCompany, Easton Pennsylvania USA, 1990, 1633-1665.
10. Anupama Kalia, Shelly Khurana, Neena Bedi . Formulation and evaluation of mouth dissolving tablets of oxcarbazepine. Int. J. Pharma 2009; 1 Suppl 1:12-23.
11. Kevin M, Biglan MD, Steven Schwid. Rasagiline Improves Quality of Life in Patients with Early Parkinson 's Disease. Mov Disord 2006; 21(5): 616-623.
12. Kimberly, JBK, David Y, Sonia PT. Drug-Excipient Interactions and their affect on Absorption. Pharm Sci Tech 2000; 10(3): 336-345.
13. Rang. H P, Dale. M M, Ritter. J M, and Moore P K. Pharmacology. Fifth edition, Churchill Livingstone, 441.
14. Parikh. M. Handbook of Pharmaceutical Granulation Technology. Edited by Dilip; Volume 81, 7-9.
15. Late SG, YU YY, Banga AK. Effects of Disintegration Promoting Agent, Lubricants and Moisture Treatment on Optimized Fast Disintegrating Tablets. Int J pharm 2009; 365(1-2): 4-11.
16. Mohico L Dumant. Probability of Passing Dissolution Acceptance Criteria for an Immediate Release Tablet. Int J Pharm 1992; 97: 119-131.
17. Jagadeesh Induru, Padmaja Bhukya. Excipient screening and development of formulation design space for Diclofenac Sodium fast dissolving tablets .Int J Pharm Pharm Sci,2012;4(1): 241-248.
18. Sandeep D Jadhav, Rahul N Kalambe, Chetan M Jadhav, Bharat W Tekade, Vijay R Patil .Formulation and evaluation of fast dissolving oral film of Levocetirizine Dihydrochloride. Int J Pharm Pharm Sci, 2012;4(1): 337-341.