CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.345478

Available online at: http://www.iajps.com *Research Article*

MATRIX TABLET OF RASAGILINE MESYLATE: AN APPROACH FOR THE TREATMENT OF PARKINSON DISEASE

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Abstract:

Parkinson's disease is a common neurodegenerative disorder that can cause significant disability and decreased quality of life. It is a multidimensional disease and management needs to be holistic, incorporating the patient and family, utilizing a multidisciplinary team and addressing both medical as well as rehabilitation issues from diagnosis to advanced disease. In the present study, sustained release tablets of Rasagiline mesylate is designed using xanthan gum (XG), and hydroxyl propyl methyl cellulose K 100 M (HPMC) as release retarding polymers alone or in combination as Rasagiline is a better alternative and considered as drug of choice for effective treatment of Parkinson's disease with reduced side effects. Tablets were formulated in nine batches by using different ratios of drug and excipients. The drug release profiles of various formulations showed that these were successful in effectively sustaining the drug release from the matrix tablets, as set in objectives.

Keywords: *Rasagiline mesylate, matrix tablet, in vitro release*

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Please cite this article in press Reshu Virmani et al, ***Matrix Tablet of Rasagiline Mesylate: An Approach for the Treatment of Parkinson Disease****, Indo Am. J. P. Sci, 2017; 4(02).*

INTRODUCTION:

Parkinson's disease is a common neurodegenerative disorder that can cause significant disability and decreased quality of life. [1] Parkinson's disease is a disease of the elderly with a maximum incidence and prevalence in the 75 to 85 year old age groups. The impact of Parkinson's disease in this age group is greater because of their limited functional reserve and pre-existing co-morbidities [2, 3]. Characteristic neuropathologic features of the disease are dopaminergic neuron degeneration in the substantia nigra and the presence of eosinophilic intracytoplasmic inclusions (Lewy bodies) in the residual dopaminergic neurons [4]. The majority of pharmacological agents used in Parkinson's disease focus on restoring striatal dopamine by increasing the supply of dopamine with the dopamine precursor levodopa, directly stimulating post-synaptic dopamine receptors, impeding dopamine metabolism or inhibiting dopamine reuptake. [5].

The principal rationale for monoamine oxidase (MAO)-B inhibition in Parkinson's disease is enhancement of striatal dopamine activity, which is anticipated to result in symptomatic motor benefits [6]. A secondary rationale is based on evidence that selective MAO-B inhibitors exhibit antioxidant and antiapoptotic activity in experimental models, which may potentially translate into long-term clinical neuroprotective benefit (i.e, Disease modification). Physiologically, MAO is involved in oxidative deamination of monoamine neurotransmitters (e.g, dopamine, norepinephrine, serotonin) as well as biogenic amines, such as tyramine. Reactive hydrogen peroxide generated in this reaction may contribute to free radical-mediated neurotoxicity. Because the dopamine-producing SNpc is characterized by high intrinsic oxidative activity, it appears to be a particular target of free-radical activity [7].

Two isoforms of MAO, types A and B, have been described; they differ with respect to localization and substrate specificity MAO-A plays a crucial role in deactivating circulating catecholamines (e.g, epinephrine) and dietary vasopressors (e.g, tyramine), but it also deaminates dopamine, norepinephrine, and serotonin in the brain. However, peripheral inhibition of MAO-A has been associated with the risk for an acute syndrome consisting of hypertension, headache, nausea, palpitations and tachycardia when tyramine or other amines (e.g, levodopa) are ingested.

Because certain hard, aged cheeses contain tyramine, this acute reaction is often referred to as the "cheese reaction". Inhibition of MAO-A has also been associated with a risk for centrally mediated serotonin syndrome when administered with selective serotonin reuptake inhibitors (SSRls) or other serotonin-enhancing agents [8]. Because of the potential for such serious MAO-A-mediated interactions, use of nonselective MAO inhibitors (eg, phenelzine, tranylcypromine) are not desirable in patients with Parkinson‟s Disease, especially in levodopa-treated patients. MAO-B is the predominant isoform in the human brain, where it acts in the breakdown of dopamine to 3, 4-dihydroxyphenylacetic acid and homovanillic acid, as well as in the deamination of f3-phenylethylamine, an endogenous amine that stimulates release of dopamine and inhibits its neuronal reuptake. Selective inhibition of MAO-B results in elevations of synaptosomal dopamine concentrations and is thus pharmacologically appropriate for treating dopamine deficiency disorders such as [6].

MATERIALS AND METHODS:

Rasagiline mesylate was obtained as a gift sample from Orchid Chemicals & Pharmaceuticals Pvt. ltd. HPMC K100 M, Xanthan Gum was purchased from Sigma-Aldrich. All other chemicals and reagents used were of analytical grade.

Rasagiline Mesylate $C_{12}H_{13}N$ (CH_3SO_3H) (1H-Inden-1-amine, 2, 3dihydro-N-2-propynyl-, (1R)-, methane sulfonate). Rasagiline mesylate is an irreversible inhibitor of monoamine oxidase (MAO) and neuroprotective agent used for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa [9]. It is selective for MAO type B over type A by a factor of fourteen. 1.561 mg Rasagiline mesylate is equivalent to 1 mg of Rasagiline. The mean steady-state half life of Rasagiline is 3 hours.

Formulation Development of Rasagiline Mesylate Loaded Matrix Tablets

Formulation and characterization of granules

The wet granulation tableting method was chosen to prepare the matrix tablets because this method allows modification of various processing steps and produces tablets having good pharmaco-technical properties. The present work was designed to prepare sustained release tablets of Rasagiline mesylate using xanthan gum (XG), and hydroxy propyl methyl cellulose K 100 M (HPMC) as release retarding polymers alone or in combination where the drug: gum ratios were set at 1:10, 1:20 and 1:30. Matrix tablets were prepared using the formulations shown in Table 1.

Table 1: Formulation of matrix tablets, Tablets also contained 1% w/w each of magnesium stearate and talc. R= Rasagiline Mesylate, X= Xanthan gum, H= HPMC K100M. 1, 2 and 3 represent drug: polymer ratio 1:10, 1:20 and 1:30 respectively.

Formulation code	Rasagiline mesylate (mg)	Xanthan gum (mg)	HPMC K100M (mg)	Lactose (mg)	PVP K30 (mg)
RX1	1	10	-	67	20
RX2	1	20	-	57	20
RX3	1	30	-	47	20
RH1	1	-	10	67	20
RH2	1	-	20	57	20
RH3	1	-	30	47	20
RXH1	1	5	5	67	20
RXH2	1	10	10	57	20
RXH3	1	15	15	47	20

The prepared granules were characterized by drug content, angle of repose, bulk density & tapped density, Carr's compressibility index .[10].

Compression of Granules into Tablets and Characterization of Compressed Tablets [11]
The granules obtained were lubricated by adding magnesium stearate and talc by using blender. The granules were transferred into the hopper tablet press and weight and hardness of the tablets were adjusted. The theoretical weight of the tablets was calculated on the basis of the assay of the active constituent in granules. Hardness and weight variations were checked from time to time during compression. The compressed tablets were characterized by drug content, hardness and thickness, friability, weight variation and *in vitro* dissolution studies.

***In Vitro* Dissolution Studies**
Drug release studies were performed using USP apparatus II at a 100 rpm paddle stirring rate. The dissolution media were HCl buffer at pH 1.2 for the first two hours of the study, corresponding to the two hours average stay of food contents in stomach, and phosphate buffer at pH 6.8 mimicking the small intestine environment for the remaining time.

Preparation of the Simulated Gastric Fluid At pH 1.2
A volume of purified water was taken in a six liter conical flask and 12 g of sodium chloride (NaCl) were carefully weighed and transferred to the flask. Then 14 ml of 37% hydrochloric acid (HCl) were added to the flask. The volume was made up with-purified water. The flask was kept on a magnetic stirrer at 500 rpm until the contents were completely dissolved. The pH of the buffer was checked and adjusted with 0.1 N HCl and 0.1 N NaOH.

Preparation of the Simulated Intestinal Fluid at pH 6.8
A volume of purified water was taken in a six liter conical flask and 130.32 g of disodium hydrogen phosphate anhydrous (Na_2HPO_4) and 29.64 g of citric acid monohydrate were carefully weighed and transferred to the flask. The volume was made up with purified water and the flask was kept on a magnetic stirrer at 500 rpm until the contents were completely dissolved. The pH was checked and adjusted with 0.1 N HCl and 0.1 N NaOH.

RESULT AND DISCUSSION:

The granules prepared via a wet granulation method were examined for angle of repose, Carr's compressibility index, and other properties. The results of various characterization parameters of granules are summarized in Table no.2.

Table No. 2: Physical properties of granules prepared using different polymers alone or in combination in different ratios

Formulation Code	Granules Properties		
	Angle of repose	Carr's Compressibility Index	Drug Content (%)
RX1	24.0 ± 0.98	22.0 ±0.82	99.7 ± 1.35
RX2	27.5 ± 0.84	20.2 ± 0.99	101.3 ± 1.22
RX3	28.5 ± 0.92	22.8 ± 1.02	98.3 ± 1.40
RH1	24.5 ± 0.84	21.8 ± 0.64	100.6 ± 1.11
RH2	25.5 ± 0.75	20.2 ± 0.74	101.5 ± 0.96
RH3	27.5 ± 0.88	21.4 ± 0.61	99.7 ± 1.21
RXH1	21.5 ± 1.13	18.2 ± 0.77	98.7 ± 1.22
RXH2	22.5 ± 0.99	16.3 ± 0.64	98.6 ± 1.41
RXH3	24.0 ± 1.25	17.0 ± 0.55	99.6 ± 0.89

The angle of repose ranged from 24.0 to 28.5 degrees showing fair to good flow properties in all the batches. A gradual increase in angle of repose shows that it may be due to increase in polymer concentration in the blend because the polymer is increasing in linear fashion (table 5.7). The values of the angle of repose were 21.5, 22.5 and 24 for the batches RXH1, RXH2 and RXH3, respectively, showing excellent flow of the granules even with maximum polymer concentration.

The values of Carr's index of granules comprised of xanthan gum and HPMC alone lies between fair to passable range, while those comprised of combination of - polymers showed good flow properties. Thus, better compressibility of the granules containing xanthan gum and HPMC was confirmed.

The tablets were prepared by a wet granulation method and evaluated for friability, thickness, hardness, weight variation, drug content and *in vitro* drug release.

All the results of evaluation parameters of tablets were summarized in table no.3.

Table No. 3: Physical properties of tablets prepared using different polymers

Formulation code	Tablet properties				
	Friability (%)	Thickness (mm)	Hardness (Kg)	Weight (mg)	Drug content (%)
RX1	0.64± 0.24	3.94 ± 0.03	5.24 ± 0.84	96.8 ± 3.99	99.0 ± 1/02
RX2	0.25 ± 0.35	3.98 ± 0.04	5.38 ± 0.48	103.4 ± 3.84	101.0 ± 1.30
RX3	0.30 ± 0.39	4.03 ± 0.03	5.36 ± 0.64	110.3 ± 4.01	97.5 ± 0.97
RH1	0.29 ± 0.22	3.88 ± 0.057	5.62 ± 0.19	92.3 ± 3.76	99.3 ± 1.08
RH2	0.11 ± 0.18	3.94 ± 0.049	5.66 ± 0.21	102.9 ± 4.23	100.2 ± 1.52
RH3	0.42 ± 0.25	4.17 ± 0.05	5.58 ± 0.22	105.7 ± 4.18	101.2 ± 1.33
RXH1	0.30 ± 0.19	5.85 ± 0.08	5.41 ± 0.21	101.7 ± 4.15	99.6 ± 1.42
RXH2	0.27 ± 0.25	6.10 ± 0.11	5.49 ± 0.18	100.3 ± 3.88	98.1 ± 1.52
RXH3	0.29 ± 0.31	6.20 ± 0.94	5.51 ± 0.24	107.2 ± 4.42	99.1 ± 1.11

Friability of the tablets were found within limits of 1% and ranged between 0.11 - 0.64%, showing good mechanical strength of the matrix system. Hardness and content uniformity of the tablets were also in accordance with pharmacopoeial limits. Moreover, hardness is not the only parameter indicative of tablet ruggedness. Friability has an important role to play in physical properties of the tablets. Usually it is believed that when hardness is above a certain value characteristic of the system, the friability is increased. No such interdependence was observed here between hardness and friability attributes. Indeed it has been pointed out earlier for similar matrix tablets containing HPMC as release rate retarding component that friability and hardness values were shown independent of each other [12].

More die filling will lead to a harder tablet because a greater quantity of powder is compressed into the same volume, but it may cause the tablets so produced to chip or cap. For easier and more uniform die filling, larger size dies were used that avoided chipping and capping with matrix tablets. In this study, with 12 mm concave punches and dies, no such problems were encountered. The hardness of the matrices varied from 5.24 to 5.66 kg.

***In Vitro* Drug Release**

In vitro drug release studies were performed using USP apparatus II at a 100 rpm paddle stirring rate. The dissolution media were HCl buffer at pH 1.2 for the first two hours of the study, corresponding to the two hours average stay of food contents in stomach, and phosphate buffer at pH 6.8 mimicking the small intestine environment for the remaining time.

The formulations RX1, RX2 and RX3 released approximately 27, 23 and 18% of drug by the end of the first hour. This is in accordance with USP limits for sustained release formulations. While RH1, RH2 and RH3 released approximately 10, 11 and 12%-of the drug respectively, showing a negligible effect of a higher concentration of HPMC on the rate of release. The burst release effect was observed in the formulations which-contains only 10% of release retardant polymer especially in RX1. This initial burst release effect was not seen in the tablets RX2 and RX3 having 20 and 30% of the gum.

Thus it can be concluded that the relatively low concentration (10% of the tablet weight) of the xanthan gum or a higher relative concentration of drug is responsible for the initial quick release. The drug release was complete from all the xanthan gum formulations.

Formulations RH2 and RH3 each released ~20% and ~30% at the end of the first and second hour, respectively. These results reflect a small effect of HPMC level on the drug sustaining behavior. The drug release is governed by polymer swelling/relaxation and dissolution/erosion when HPMC is involved. The polymer swelling provides a basis for developing a gel structure which makes a tortuous pathway for slower drug release and the latter mechanism shortens the diffusion path-length, besides dissolution of the polymer itself.

The comparable drug release from formulations RH2 and RH3 to that from RH1 may be explained by erosion of HPMC which was evident visually when eroded particles of tablet were seen in the dissolution vessels in the present study. The erosion of the polymer creates more particles resulting in an overall increased surface area thereby increasing the release rate. Also, the decrease in drug release due to an increase in the diffusion path length that is typically observed with an intact matrix tablet is compensated by the erosion process.

The matrix tablets incorporating xanthan gum and HPMC as a combined rate retarding material showed a somewhat biphasic drug release. The drug release rate declines after the first four hour of the study thus providing the loading for the patient. Release from the formulations RXH1 and RXH2 is nearly same in the first two hours of the release study but it is slower with RXH3, apparently due to a higher percentage of rate retarding polymers. Drug release from the three formulations suggests that xanthan gum has the major contribution in drug release pattern. Drug release from tablets having 10% of only xanthan gum as release retardant (RX1) was 91% in 12 h and that from RXH1 was 83% in 12 h, although there is also present a high viscosity grade HPMC K100M. RXH1 contains 5% of each of xanthan gum and HPMC. It is suggested that when 5% of xanthan gum was replaced with 5% of HPMC in RXH1, the release was-affected. The batch RH1 has 10% of HPMC and it released 96% of drug in 12 h whereas the replacement of 5% of HPMC with xanthan gum decreased the release to 82% in 12 h. This shows a synergistic effect of xanthan gum on HPMC. This is apparently due to a more viscous and more tortuous gel structure developed by the two combined polymers. The same phenomenon exists in the other two batches RXH2 and RXH3 for which the drug release at 12 h was 77 and 65%, respectively, whereas it was 83 and 80% for RX2 and RX3. The Batch RXH3 was thus optimized.

CONCLUSION:

Matrix tablets prepared incorporating either single or combinations of release rate retarding materials were shown to possess good pharmacotechnical properties. The drug release profiles of various formulations showed that these were successful in effectively

sustaining the drug release from the matrix tablets, as set in objectives. There are various formulations in this study which can be used to prepare commercially available oral sustained release dosage forms with desirable pharmaceutical properties and drug release profile. If a 12h release profile is desired any formulation containing the HPMC alone as rate retardant can be used. If seeking a 24h release profile the formulations containing xanthan gum alone or in combinations can be used to design such dosage form.

In the future this study can be continued by conducting clinical trials for the formulations showing promising results. More polymers and gums can be examined in the preparation of these products showing more even and desirable release profiles.

Ideally a sustained release dosage forms should provide a loading dose followed by a zero order release pattern over a predicted time frame. More work is needed on prospective and promising materials and methodologies to achieve these targets.

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