TASTE-NUMBNESS MASKED ODT OF RILUZOLE INTERNAL TERNARY SOLID DISPERSION

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Abstract

Riluzole, a glutamate antagonist used in management of neurodegenerative disorder Amyotrophic Lateral Sclerosis (ALS) has low aqueous solubility and leaves a sense of intense and persistent numbness in the mouth. The purpose of present study was to optimize orally disintegrated tablets (ODTs) of Riluzole by solid dispersion technology using hydrophilic polymer PVP K30 and surface modifying carrier Syloid® 244 FP for solubility enhancement and effective taste and numbness masking. Saturation solubility of prepared solid dispersion showed increase in solubility as compared to Riluzole in water, pH 1.2, 4, 6.8, 7.4 and 0.1 N HCl. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and in vitro dissolution studies were done to characterize the solid dispersion system. Optimized taste masked ODTs showed 90% release of Riluzole in 45 mins comparable to that of the marketed film coated tablet. Thus, results conclusively demonstrated successful taste masking and rapid dissolution rate of the optimized ODT..

Keyword: Riluzole, Syloid® 244 FP, PVP K30, internal ternary solid dispersion, orally disintegrating tablets, taste masking

1.INTRODUCTION

Neurological disorders constitute a significant medical challenge; hence neuroprotective agents play pivotal role in managing this growing global burden of everlasting neurological care. Amyotrophic Lateral Sclerosis (ALS) is terminal and rare neurodegenerative disease identified by a slow deterioration of nerve cells accountable for controlling voluntary muscle movement. [1-3] Dysphagia is one of the most critical problems affecting people with ALS and leads to increased mortality in more than 85% of patients. [4-7]
Riluzole is the only licensed drug used in the management of ALS.[3,8] The marketed preparations of Riluzole are available as film coated tablets and oral suspensions. National Health Service (NHS) guideline for Riluzole tablets states that the tablets should be crushed and administered with a spoonful of sugar or yoghurt.[9] However, crushing of tablets increases the chances of inaccurate dosing, changes in drug product performance and safety concerns.[10] Crushing also disrupts film coating on the tablet that is designed to reduce anaesthetic effect and bitter taste of the drug.[4,10,11] The objective of present study was to develop taste masked orally disintegrating tablets (ODTs) of Riluzole that disintegrate rapidly so as to correct the above mentioned drawbacks or demerits. The USFDA has defined ODTs as "A solid dosage form containing medical substance or active ingredient which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue" therefore the disintegration time for ODTs are limited from seconds up to a minute. [10,11]
Riluzole,[2-amino-6-(trifluoromethoxy) benzothiazole] is a glutamate antagonist that slows the progression of the early disease. It has slight bitterness and prolonged local anaesthetic effect in the mouth (>20–30 minutes) and belongs to Biopharmaceutical Classification System (BCS) Class II, characterized as poorly soluble compound resulting in low bioavailability. [3,12,13]
Colloidal solid dispersion is a novel advancement that overcomes solubility issues of low solubility drugs by using a technology that prevents recrystallization, by forming strong hydrogen bonds between the drug and polymer complex that is adsorbed onto the porous

carrier for further stabilization apart from other novel techniques to improve dissolution.[14-17,18]

Another challenge when developing the formulation was to mask unpleasant taste of Riluzole. Melt granulation technique was employed to address unpleasant taste of Riluzole using glycerol monostearate (GMS) as a taste masking agent. Recent studies have also shown combined use of physical and organoleptic taste masking for effective and improved palatability, also application of pH modifying agents for taste masking of bitter drugs to produce an alkaline environment and hence decrease solubility and resultant taste perception of the drug. [18-23]

The aim of the present study was to enhance solubility of Riluzole using colloidal solid dispersion technique and mask its bitter taste by combined use of physical and organoleptic masking agents into an acceptable dosage form such as ODT using directly compressible co-processed excipients.

2. MATERIALS AND METHODS

Riluzole and Riluzole 50 mg film-coated tablets were obtained as gift samples from Alkem Laboratories Ltd., Baddi. Syloid® 244 FP was obtained as a gift sample from Grace Davison Chemicals India Pvt. Ltd., Mumbai. Geleol® (Glycerol monostearate) was provided as a gift sample by Gattefosse India Pvt. Ltd., Mumbai. Sucrex® (Sucralose) and F-Melt® Type C were provided as gift samples by Gangwal Chemicals Pvt. Ltd., Mumbai. Other ingredients were purchased from HiMedia, Mumbai, India.

2.1. Preparation of Riluzole-Internal Ternary Solid Dispersion Systems (Ril-ITSD)

Riluzole-Internal Ternary Solid Dispersions (Ril-ITSDs) were prepared using polymer PVP K30. A homogeneous clear solution of Riluzole and PVP K-30 in ethanol was prepared using two different ratios of Riluzole: PVP K-30 (1:1 and 1:2). The clear solution was heated gently on a water bath until half of the solvent evaporated at 60o C and then Syloid® 244 FP was suspended on top of this clear concentrated solution to make final ITSD systems in three different drug, polymer and carrier ratios (1:1:2, 1:1:3, and 1:2:2). After suspending the carrier, the system was mixed thoroughly and excess solvent was removed by gently heating it on the water bath at 60o C. The obtained complex was sieved through a 60 mesh SS screen. The Ril-ITSD system was stored in a dehumidifying chamber at room temperature.

Saturation Solubility of Ril-ITSD

Saturation solubility of Ril-ITSD was determined using orbital shaker at 200 rpm for 24 h at 370 C. Apparent solubility was determined in distilled water, pH 1.2, pH 4, pH 6.8, pH 7.4 and 0.1 N HCl. Excess amount of the samples was dispersed in 5 ml of distilled water, pH 1.2, pH 4, pH 6.8, pH 7.4 and 0.1 N HCl. After 24 h of shaking, the samples were centrifuged and the supernatant was collected and filtered using 0.2 µm membrane filter. The filtrate was diluted with the respective medium and absorbance was recorded using UV-visible spectrophotometer at λ 254 nm.

Differential Scanning Calorimetry (DSC)

A thermal analysis of all samples was conducted using DSC 7020 calorimeter, Hitachi Inc., equipped with DSC 7020 electric cooling unit. The freezing and heating measurements were performed in nitrogen atmosphere with a flow rate of 10 ml min−1, over a temperature range of 300C to 3000C and the thermal behaviour was studied by recording the thermograms.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of samples were performed on IRSpirit FTIR spectrophotometer. The scanning range was 500-4500 cm–1 and the resolution was 4 cm–1.

In Vitro Release Study of Ril-ITSD

In vitro release study was carried out using USP II Apparatus at 75 rpm in 900 ml of 0.1 N HCl as dissolution medium maintained at 37 ± 0.5 0C. ITSD samples corresponding to 50 mg of Riluzole were placed in each vessel. A 5ml aliquot was withdrawn at regular time intervals and replaced with an equal volume of dissolution medium to maintain the sink conditions. Samples were filtered and assayed using UV-visible spectrophotometer at λ 254 nm.

2.2. Preparation of orally disintegrating tablets of Ril-ITSD by melt granulation

Accurately weighed amount of Geleol (quantity based on the batches designed) was placed in a porcelain dish and melted over a thermostatically controlled water bath at 75 0C. When a uniform molten mass was obtained, accurately weighed amount of Ril-ITSD (equivalent to Riluzole dose 50 mg) was added to the molten lipid and mixed well. The molten mass was allowed to cool to room temperature. The cooled mass was sieved through 40 mesh SS sieve to obtain the matrix granules. Excipients (except directly compressible excipients) were sieved through 60 mesh SS sieve separately. Matrix granules of Ril-ITSD (equivalent to 50 mg) were added to weighed amounts of excipients and mixed by geometric dilution method for 10 min. Tablets were prepared by direct compression technique using Rotary Compression Tablet Press with 12 mm flat punch and total weight 700 mg per tablet and hardness 2.5-3.5 kg/sq.cm. Compressed tablets were evaluated for standard tablet evaluation parameters along with drug content, in vitro disintegration time, in vitro dissolution study. Composition of ODTs is shown in Table 1.

Table 1: Formulation composition for ODTs of Ril-ITSD

Ingredients	Formulation (mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Riluzole: PVP K-30: Syloid® 244 FP	200									
Geleol	-	-	-	-	-	-	-	64	105	140
L- Arginine	30	40	50	70	90	100	80	40	40	40
Sucralose	21	25	30	40	50	50	50	50	50	50
SSG	14	14	14	14	14	14	14	14	28	28
SSF	14	14	14	14	14	14	14	14	14	14
Flavour	-	-	5	5	5	5	7	7	7	7
Xylisorb	221	-	-	-	-	-	-	-	-	-
F-Melt C	-	207	207	207	207	207	285	311	256	221

Evaluation of orally disintegrating tablets

Uniformity of weight

Twenty tablets were selected randomly and average weight was determined. Individual tablets were then weighed and compared with average weight. [18]

Thickness

Thickness of the tablet was measured at 3 different points using a digital vernier caliper and the average thickness of three readings was calculated.

Hardness test

Hardness was determined using Monsanto hardness tester and expressed in kg/cm2. [19]

Friability test

Preweighed sample of ten tablets were placed In Roche Friabilator and operated for 100 revolutions at 25 rpm. The tablets were dusted and re-weighted. Friability was calculated by the following formula. [19]

Friability (%) = (Initial weight–Final weight/Initial weight) × 100

Wetting time and Water absorption ratio[21]

To determine wetting time, a piece of tissue paper folded twice was taken and placed in a petridish (d = 6.5 cm) containing about 6 ml of amaranth solution. ODT was placed on the paper and time elapsed in developing red colour on upper surface of the ODT was noted. For measuring water absorption ratio, weight of ODT before keeping in the petridish was noted (Wb). The wetted tablet from the petridish was taken out and reweighed (Wa). [29] The water absorption ratio, R can be the determined from following equation:

R = [(Wa-Wb) / Wb] x 100

In vitro dispersion time

ODT was placed in 10 ml of distilled water at 37± 0.5 0C and time required for complete dispersion of tablet was recorded. [18]

Drug content

Three tablets were randomly chosen and crushed. The blend equivalent to 50 mg of Riluzole was accurately weighed and transferred to 100 ml volumetric flask. Ethanol was added with continuous stirring and volume was made up to 100 ml. [20,21] After required dilutions with 0.1 N HCl, absorbance was determined at λ 254 nm.

In vitro dissolution studies[20-22]

In vitro dissolution study was carried out using six station USP Apparatus Type II in 900 ml of 0.1 N HCl at 75 rpm at 37±0.50C. Sampling was done at different time intervals of 5, 10, 15, 30, 45, and 60 minutes by withdrawing 5 ml of dissolution medium and replacing it with the same amount of fresh medium to maintain sink conditions. ODTs were placed in each of the vessels of the dissolution apparatus containing the medium. 5 ml aliquots were withdrawn at specified time intervals and same amount was replaced by fresh medium. The withdrawn aliquots were suitably diluted and analyzed through UV-visible spectrophotometer at λ 254 nm. All studies were carried out in triplicates.

Taste masking evaluation

Determination of bitterness and numbness threshold of Riluzole

A panel comprising of ten healthy human volunteers (age 20- 25 years) were selected for the study. A series of aqueous solutions of Riluzole with different concentrations (5, 10, 20, 30, 40, 50, 60 and 70 µg/ml) were prepared. Formal written consent was taken from all human volunteers. The volunteers were asked to hold 10 ml of each solution in oral cavity for 30s and grade the taste on a scale from 0 to 4. The mouth was rinsed with distilled water and a gap of 30 min was allowed between successive tests. Based on the opinion of the volunteers, bitterness threshold concentration of Riluzole was determined. Numbness threshold was also determined using the same procedure. The threshold value was selected on the basis of the lowest concentration that produced bitterness and numbness.[23]

Gustatory Sensation Test

Ten healthy human volunteers of either sex, aged 20–25 years, participated in a gustatory sensation test. Formal written consent was taken from all human volunteers. Riluzole was used as the control for the test. The ODT was dispersed in 50 ml of water for 15 s and given to each volunteer to hold 1 ml of the dispersion in the mouth for 30 s. After expectoration, bitterness and numbness was evaluated using their respective scores, classified in eight grades as shown in Table 2.[23]

Scale	Taste	Numbness
0	No bitterness	No numbness
0.5	Very slightly bitter	Very slight numbness
1	Slightly bitter	Slight numbness
1.5	Slight to moderate bitter	Slight to moderate numbness
2	Moderately bitter	Moderate numbness
2.5	Moderate to strong bitter	Moderate to strong numbness
3	Strongly bitter	Strong numbness
4	Very strongly bitter	Very strong numbness

3. RESULTS AND DISCUSSION

FTIR

Riluzole gives characteristic peaks at 3300 and 3200 cm-1 corresponding to N-H stretching band. Presence of peak at 1600 and 1300 cm-1 in the spectra corresponds to N-H bending and C-N stretching, respectively. O-H and -C=O stretching corresponding to the carboxylic acids appear in the region of 3400-2400 cm-1 and 1720-1680 cm-1 respectively seen in Fig. 1. PVP K-30 showed a characteristic strong intensity band of –C=O stretching in the frequency range of 1,500–1,750 cm-1. Medium intensity band of –C–H bending was observed at 1,350–1,500 cm-1. Syloid® 244FP showed an intense Si–O linkage band at 1,106.5 cm-1, representing a silanol group. Ril-ITSD showed absence of N–H stretching bands between 3300 and 3200 cm-1 hence, confirming the formation of complex as seen in Fig. 2.

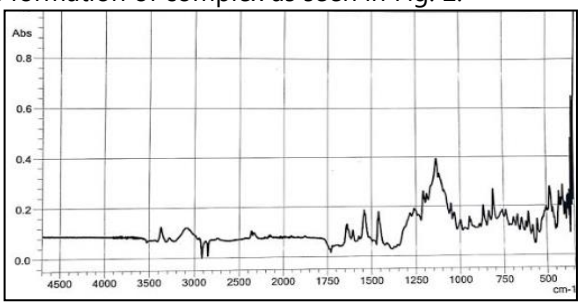

Fig 1. FTIR of Riluzole

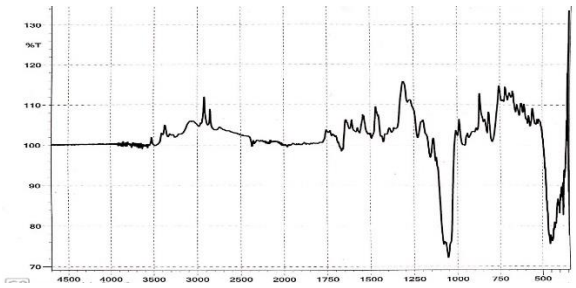

Fig 2. FTIR of complex

DSC

DSC thermograms of Riluzole and Ril-ITSD are shown in Figs. 3 and 4 respectively. The DSC thermogram of Riluzole showed a single endotherm at 116.5°C. 1:1:2 ITSD showed absence of the characteristic melting endotherm of Riluzole, confirming a solid solution of an amorphous form of Riluzole dispersed in the polymeric porous carrier matrix at the molecular level.

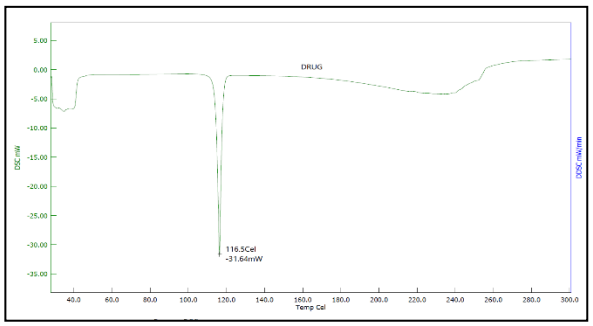

Fig 3. DSC thermogram of Riluzole

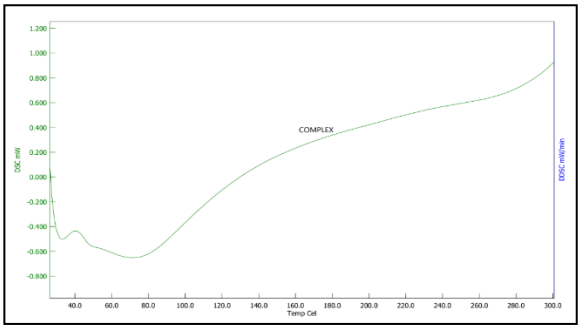

Fig 4. DSC thermogram of complex

Saturation solubility

Saturation solubility of Ril-ITSDs showed an exponential increase in solubility as compared to Riluzole in all the media as shown in Table 3. Solubility profile was dependent on both PVP K30 and Syloid® 244FP concentrations.

Table 3: Saturation Solubility of Ril-ITSDs

Media	Saturation solubility (µg/ml)			
	Riluzole	Ril-ITSD (1:1:2)	Ril-ITSD (1:1:3)	Ril-ITSD (1:2:2)
Distilled Water	0.214	12.66	14.75	20.44
0.1 N HCl (pH 1.2)	0.612	20.93	24.13	31.22
pH 4.0	0.271	14.83	15.31	21.98
pH 6.8	0.165	7.23	12.56	14.25
pH 7.4	0.209	11.49	12.09	19.43

In vitro release study of Ril-ITSD

Ril-ITSD with Riluzole: PVPK30: Syloid 244 FP 1:1:2 showed an improved dissolution profile with 95% drug release within 30 min. Increasing the polymer fraction in 1:2:2 Ril-ITSD further enhanced the dissolution profile. This can be explained by the phenomenon of increasing solubility of a drug at molecular level with an increasing amount of polymer.[41] Increasing Syloid 244 FP fraction from 1:1:2 to 1:1:3 resulted in a slower dissolution rate profile. However, 1:1:2 Ril-ITSD showed effective taste masking of the drug compared to the other two ratios of Ril-ITSD. Hence, optimum drug: polymer: carrier ratio with enhanced drug solubility and acceptable taste masking was found to be 1:1:2.

Pre-compression parameters of optimized blend

The results of bulk density, tapped density, Carr's index and Hausner's ratio are summarized in Table 4. The results indicated that the tablet blend possessed good flow property.

Table 4: Evaluation of flow properties of the blend

Sr. No.	Pre-compression parameters	Result
1.	Bulk Density (g/ml)	0.5169± 0.037
2.	Tapped Density (g/ml)	0.5822 ± 0.029
3.	Compressibility Index or Carr's Index (%)	11.21 ± 0.126
4.	Hausner's ratio	1.126 ± 0.031

Post-compression parameters of optimized ODTs

The results of uniformity of weight, drug content, in vitro disintegration time, wetting time, water absorption ratio, hardness, thickness and friability are summarized in Table 5. The results indicated that bitter taste of Riluzole could get masked when mixed with L- Arginine HCl and sucralose in formulations F1 and F2. But formulations F3, F4 and F5 showed reduced numbness but not complete taste masking. Formulation F6 showed increased numbness when concentration of L- Arginine HCl was increased. In F7, L- Arginine HCl was reduced but numbness still persisted but disintegration time was less. When Geleol was used in formulations F8 and F9 with increased concentration of disintegrant, it was observed that there was better taste masking. Formulation F10 was selected as the optimized formulation since it gave satisfactory taste masking and palatability with improved in vitro disintegration time as desired.

Table 5: Evaluation results of optimized ODT F10

Evaluation Parameters F10

Evaluation Parameters	F10
Uniformity of weight (mg)	699.1 ± 0.901
Thickness (mm)	6.3 ± 0.014
Hardness (kg/cm^2)	2.5 ± 0.254
Friability (%)	0.12 ± 0.0381
Water absorption ratio	95.56 ± 0.843

Wetting Time (s)	8.82 ± 0.506	
In vitro disintegrating time (s)	40 ± 0.612	
Drug content (%)	98.24 ± 0.654	
In vitro drug release	F10	Marketed film coated tablet
$t_{50\%}$ (minutes)	10.39 ± 0.2481	15.44 ± 0.5939
$t_{90\%}$ (minutes)	44.24 ± 0.5574	51.69 ± 0.4927

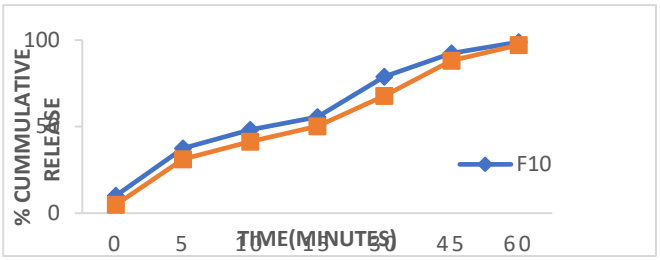

Fig. 5: Dissolution Profile of optimized ODT F10 and Marketed film coated Tablet

Taste Masking Evaluation

Determination of bitterness and numbness threshold of Riluzole

The threshold concentration of Riluzole with respect to evaluation of palatability was determined referring Table 6 and Table 7. The bitterness and numbness threshold concentrations were found to be 70 µg/ml and 20 µg/ml respectively.

Table 6: Bitterness threshold determination of Riluzole

Concentration (µg/ml)	No. of volunteers									
	1	2	3	4	5	6	7	8	9	10
5	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0
70	0.5	0.5	1	1	0.5	1	0.5	1	1	1
80	0.5	1	1	1	0.5	1.5	1	1	2	1.5

Table 7: Numbness threshold determination of Riluzole

Concentration (µg/ml)	No. of volunteers									
	1	2	3	4	5	6	7	8	9	10
5	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
20	0	0.5	0.5	0	0.5	0	0	0.5	0.5	0.5
30	0.5	1	1	1	1	1	0.5	1	1.5	1
40	1.5	2.5	2	2.5	2	2	1.5	2.5	2	2
50	2.5	3	3.5	3	3	3.5	2.5	3	3	3

Gustatory Sensation Test

In vitro taste assessment of ODT batches (F8-F10) was carried out to determine the release of Riluzole from phosphate buffer pH 6.8. The results showed that release of Riluzole decreased with increase in the amount of lipid carrier in the formulations F8, F9 and F10 respectively.

4. CONCLUSION

Riluzole used in management of neurodegenerative disorder Amyotrophic Lateral Sclerosis (ALS) is a BCS Class II drug having low aqueous solubility and leaves a persistent anaesthetic effect on the tongue. It is available in the market as a film coated tablet and oral suspension. Difficulty in swallowing tablet is a major problem especially for patients suffering from ALS. In the present work, orally disintegrating tablets of Riluzole were prepared by direct compression method using colloidal solid dispersion technology for solubility enhancement and a combination of physical and organoleptic taste masking agents to mask unpleasant taste. The mechanism of solubility enhancement was investigated using multiple methodologies, including DSC, FTIR and in vitro dissolution studies. The optimized formulation gave satisfactory results in pre- and post-compression characterization parameters.

5. CONFLICT OF INTEREST

There is no conflict of interest.

6. ACKNOWLEDGMENT

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