WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 13, Issue 1, 1994-2006. Review Article ISSN 2277–7105

AN EXTENSIVE REVIEW ON SUBLINGUAL MINITABLET OF RESPIRIDONE AND EVALUATION BY MELT-GRANULATION METHOD

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Article Received on
20 November 2023,

Revised on 10 Dec. 2023,
Accepted on 30 Dec. 2023

DOI: 10.20959/wjpr20241-30911

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ABSTRACT

Risperidone is an anti psychotic drug; mainly used to cure schizophrenia, bipolar disorder and autism spectrum disorder. Risperidone have short half life is 3 hours in extensive metabolizers and 20 hours in poor metabolizers. The oral bioavailability of risperidone is 70% due to highly bound to plasma protein and tissues and are extensively distributed. Risperidone is metabolized primarily into the liver and minimally through N-dealkylation. Required administration of frequent dosing of risperidone, maximum daily dose up to 1-3mg/day for the treatment of schizophrenia. The **aim of this work** to design and formulate and evaluation of sublingual tablets of risperidone as twice daily tablets, in order to speed up bioavailable time period and improve the patient compliance by **Melt-granulation method.** The **plan of work** is carried out the preformulation studies (Drug Characterization, Drug-Polymer Compatibility and Precompression Studies), formulation of sublingual tablet by direct compression method and evaluation of sublingual tablet (Uniformity of weight, Diameter and thickness, Hardness, Friability, Surface pH, Swelling Index, Drug content and *In- vitro* drug release) and determine the optimized formulation and the effect of polymers (PEG 4000, PEG 600), HPMC K100M and silicified MCC) and PVA used for easy dissolve in water due to its high melting point.

KEYWORDS: *Risperidone, sublingual, melt – granulation, PVA.*

INTRODUCTION

Melt granulation

Granulation is often required to ease handling of fine, poorly compressible, poor flowing, low bulk density materials. Pharmaceutical products tend to be made using either dry granulation by powder compression or wet granulation using a binder, typically a polymer, in solution that is dispersed among other ingredients and then dried to remove the solvent and leave polymer bridges that hold the granule together. Melt granulation is analogous to wet granulation though the binder, a polymer or lipid, is heated above a softening or melting point so it can form bridges amongst the dry particles that solidify to form an agglomerate. Melt granulation has been used in many industrial applications, including polymer, chemical, metal, glass, fertilizer and food production processes. It has been used as a pharmaceutical process for some time with the use of powdered or molten wax in a low shear mixer to achieve sustained release. Waxes and lipids like paraffin, glyceryl monostearate[6], glycerol palmitostearate[5], glyceryl behenate, stearic acid[7,8], hydrogenated oils[9] and polymers like polyethylene glycols[5] have been granulated using high-shear granulators with heat from jacketed bowls or frictional heating.

The melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder, which is added to the other components of the powder. Once in a molten state, the binder acts as a granulating liquid. The temperature of the mixture is raised to above the melting point of the binder, either by a heating jacket, or by the heat offriction generated by the impeller blades.

Twin-screw melt granulation

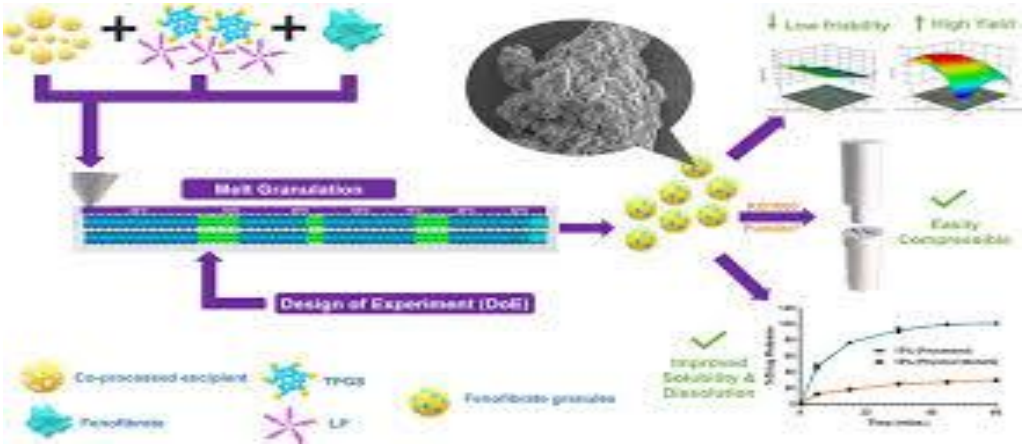


Fig.1: **About Melt-granulation involved.**

The expansion of twin-screw extrusion in pharmaceutical applications, generally for formulation of amorphous solid dispersions, has caused a large increase in interest for continuous granulation since the equipment can also be used for melt granulation. Continuous twin-screw melt granulation (TSMG) has been successful with the same binders used in high-shear melt granulation, for example, lipids, PEGs, and hydroxypropyl cellulose. These applications show the versatility of melt granulation for granulation of moisture sensitive APIs for immediate release, for improved dissolution, and for tastemasking and sustained release. Particularly in pharmaceutical applications, melt granulation is an underexploited process that may reduce product costs and improve process efficiency relative to other granulation techniques. It requires no drying step to remove solvents or water. This results in a more efficient process and allows for the use of excipients that are otherwise challenging to incorporate.

Objective

The objective of the present work has to design and evaluate the risperidone by melt granulation method in order to get rapid disintegration and dissolution.

To study the physio-chemical properties of silicified MCC.

To perform compatibility studies to investigate drug polymer interaction by FT-IR.

And also to study physical state of drug in granulation form by DSC.

MATERIALS AND METHODS

The chief material risperidone were brought from known person from kaushik therapeutics GMP where as PVA, Natrosl, mannitol, Prosolv, mcc were from our college. Electronic balance, bulk density apparatus, friability apparatus, etc. were brought from different companies.

Year of experimentation : 2023

Site : Adhiparasakthi college of pharmacy.

METHODS

The source of data for this journal review about in situ gel formulation and characterization are summarized and cited from several international journals, obtained from the net source using internet browser software and search engine. 30 international journals are used as a reference, obtained from various sources.

Excipients used

Drug Sample Risperidone and Excipients such Polyethylene glycol 400 and 6000, Granular Mannitol (Pearlitol), Silicified Microcrystalline Cellulose (Prosolv) and Natrosol (Hydroxyethyl Cellulose), gelatin, lactose, PVA (poly vinyl alcohol), Cros carmellose sodium.

Pre formulation and Formulation involved

Formulation of Sublingual Tablets by Melt Granulation Technique

Optimization of Blend of PEG 400 and PEG 6000 (Meltable binder)

PEG has been widely used in melt granulation because of its favorable solution properties, low-melting-point, rapid solidification rate, low toxicity, and low cost. PEG 400 was mixed with PEG 6000 at ratios of 1:1, 2:8, 3:7, 4:6, 5:5 weight ratios. These blends were melted on a water bath until homogeneous, then removed from the bath and triturated until congealed. The melting points of the resulting mixtures were determined using the capillary method. Mixtures which produced a melting point around 37 °C and 35 °C were being used for granulation preparation.

Optimization of Sugar

PEG Ratios

Sugars have not only good compatibility but also have good solubility, which will help in faster disintegration of the tablet. In the present formulation, directly compressible Mannitol (Pearlitol SD 200) was used as a diluent as well as a sweetener to enhance mouth- feel. Sugar was mixed with two PEG blends, i.e., Blend 1 with a melting point of 37 °C and Blend 2 with a melting point of 35 °C at the following weight ratios 1:1, 2:1, 3:1, 4:1, 5:1 respectively. PEG blends were heated at 40 °C in a water bath. Sugar was added to the molten mass and stirred at 100 rpm for 5 min using a High Shear Mixer. The mixture was continuously stirred until complete cooling.

Study of Compressibility of Prepared Meltable Granules

Granules obtained from the above procedure were mixed with other tablet additives geometrically. The amount of drug in each formulation was kept constant, i.e., 4 mg Risperidone per tablet, PEG as a meltable binder combination with sugar, Avicel pH 102 (Microcrystalline cellulose) as a diluent, Ac-di-sol (Croscarmellose sodium) as a super disintegrant and Orange flavor were used. The mixture followed by mixing for two minutes.

The obtained blend was compressed into a tablet of 100 mg using 8 mm round flat punches on 12 stations rotary tablet machine.

Preparation of Granules by using Meltable Binders

PEG Blend used as Meltable Binder

The optimized PEG blend: sugar ratio obtained from the above procedure. The granules were prepared in a laboratory-scale jacketed high shear mixer connected to a recirculating water bath to maintain a constant temperature. PCPM was mixed with either lactose or Avicel pH 102 (Microcrystalline Cellulose) with Ac-Di-Sol (Cross Carmellose Sodium) for 5 min at approximately 20,000 rpm. The temperature was then increased to 60 ºC and maintained at for the entire granulation. PEG blend: sugar ratio, was then added to the dry blend and mixed until a suitable granulation was obtained. At the end of the granulation process, the granules were allowed to cool at room temperature and then passed through a 30-mesh sieve. Granules contain 4% risperidone.

Table No. 1: Formulae for the Preparation of Risperidone Fast Dissolving Tablets as Per Experimental Design.

Compounds	F1	F2	F3	F4	F5	F6	F7	F8	F9
Risperidone	4	4	4	4	4	4	4	4	4
Silicified MCC	60	65	70	75	80	80	75	70	65
Croscarmellose sodium	5	10	15	10	10	5	15	15	5
Gelatin	-	-	-	36	48	78	-	-	-
PEG 400	8	8	8	-	-	-	-	-	-
PEG 8000	-	-	-	-	-	-	10	10	10
Mannitol	65	65	60	60	65				
HPMC									
Sucrose	-	10	10	-	-	-	-	10	10
Orange flavour	2	2	2	2	2	-	-	-	-
Lactose	3	3	3	3	3	3	3	-	-

Gelatin used as a Meltable Binder

Using Gelatin as a meltable binder, 3 formulations were prepared. The formulation compositions are as shown in Table. The granules were prepared in a laboratory-scale jacketed high shear mixer connected to a recirculating water bath to maintain constant temperature. Risperidone was mixed with either lactose or Avicel pH 102 with Ac-Di-Sol for 5 min at approximately 20,000 rpm. The temperature was then increased to 60 ºC and maintained at for the entire granulation. The binder, Gelatin, was then added to the dry blend and mixed until a suitable granulation was obtained. At the end of the granulation process,

the granules were allowed to cool at room temperature and then passed through a 30-mesh sieve. Granules contain 4% Risperidone.

Evaluations Involved

Fourier – Transform Infra red spectroscopy studies (FT-IR)

And Drug- Excipient comparability studies

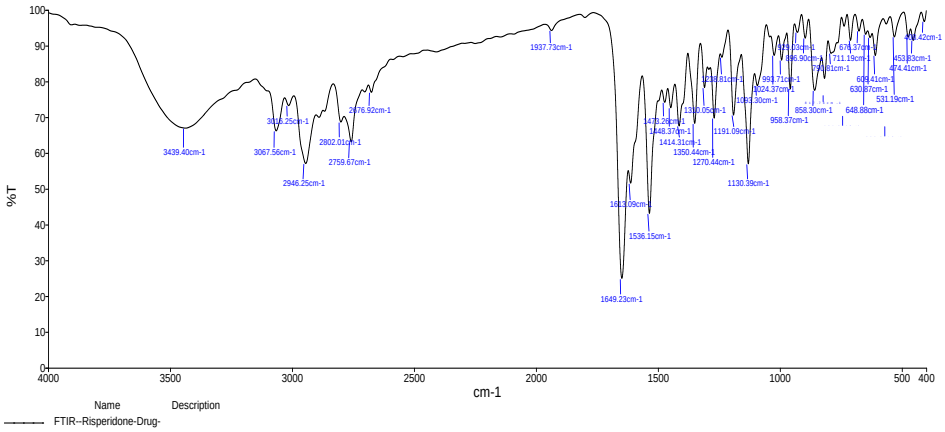


Fig. 1: FT-IR spectra of Risperidone drug alone.

Table No. 2: FT-IR interpretations of Risperidone drug only.

Types of vibrations.	Wave number
C=N Stretching	1613.09 cm^{-1}
C-N Stretching	1270.44 cm^{-1}
C-O Stretching	1191.01 cm^{-1}
C=C Stretching	1649.23 cm^{-1}
C-C Stretching	1238.81 cm^{-1}

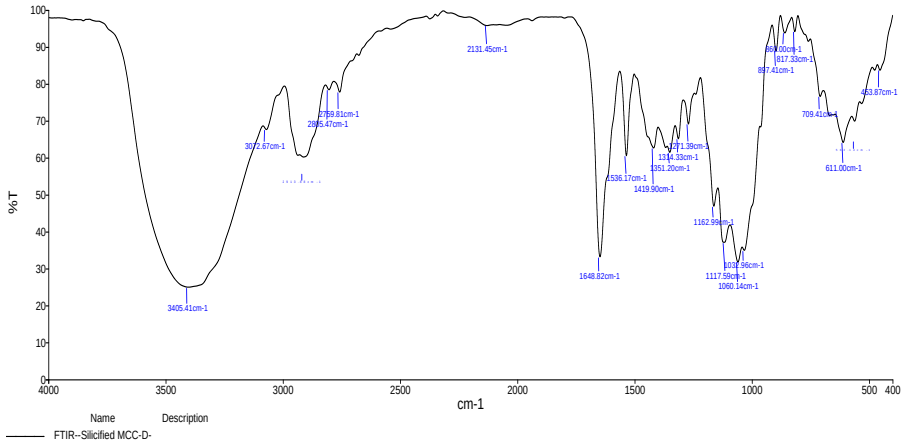


Fig. 2: **FT-IR spectra of Risperidone drug with silicified MCC.**

Table No. 3: FT-IR interpretations of Risperidone drug and Silicified MCC.

Types of vibrations	Wave number
C-O Stretching	1162.99 cm^{-1}
O-H Stretching	3405.41 cm^{-1}
C-H Stretching	3072.67 cm^{-1}

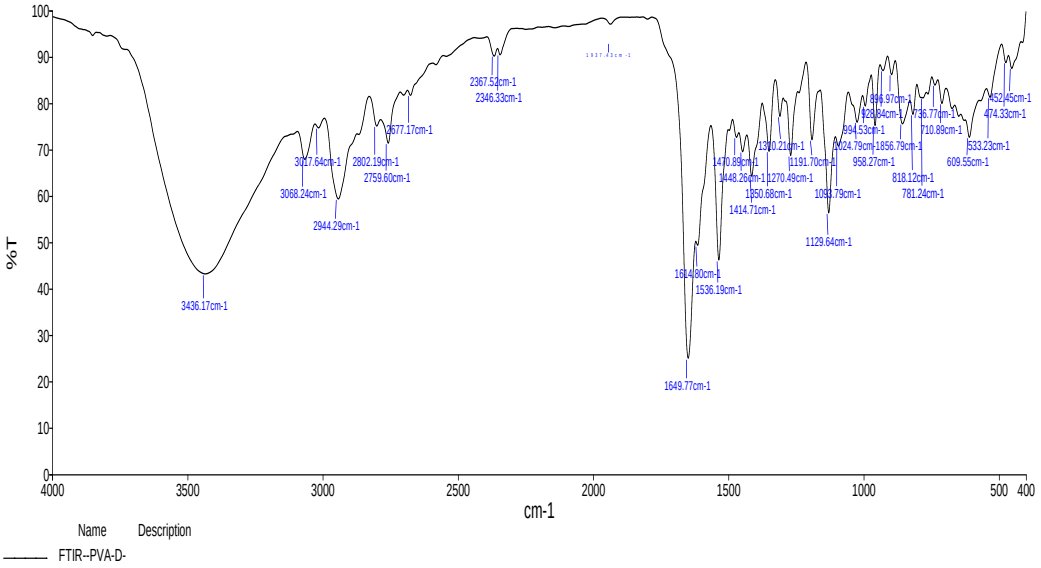


Fig. 3: **FT-IR spectra of Risperidone drug with PVA.**

Table No. 4: FT-IR interpretations of Risperidone drug and PVA.

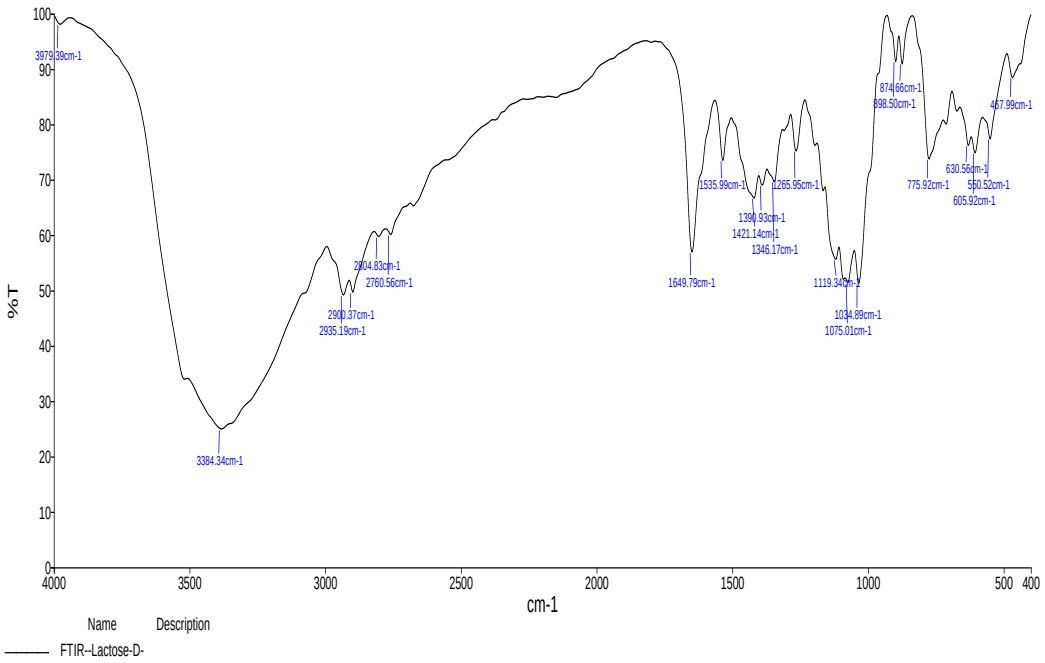


***Fig. 4*: FT-IR spectra of Risperidone drug with Lactose.**

Table No. 5: FT-IR interpretations of Risperidone drug and Lactose.

Types of vibrations	Wave number
C-H Stretching	2935.19 cm^{-1}
O-H Stretching	3384.34 cm^{-1}
C-O Stretching	1119.34 cm^{-1}

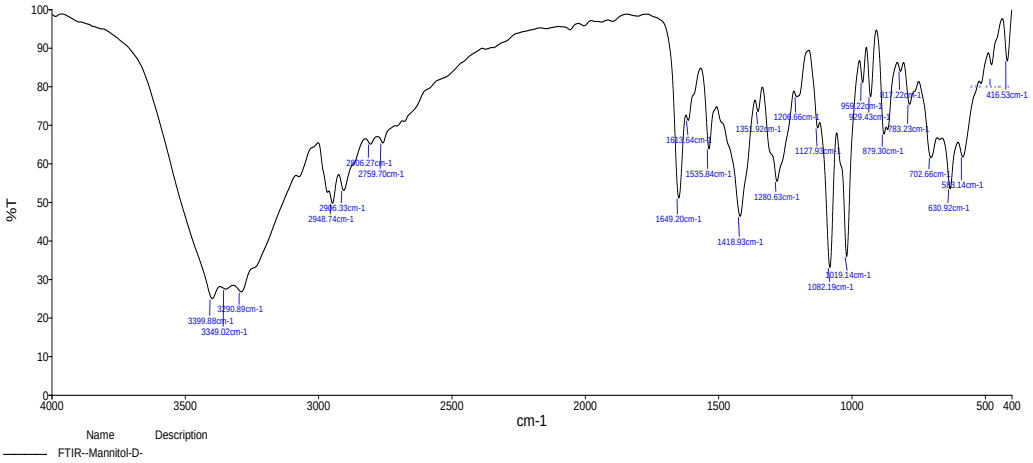


Fig. 5: **FT-IR spectra of Risperidone drug with Mannitol.**

Table No. 6: FT-IR interpretations of Risperidone drug and Mannitol.

Types of vibrations	Wave number
C-H Stretching	2948.74 cm^{-1}
C-O Stretching	1127.93 cm^{-1}
O-H Stretching	3349.02 cm^{-1}

Effect of Meltable Binders on In-vitro Dissolution Profile of Risperidone

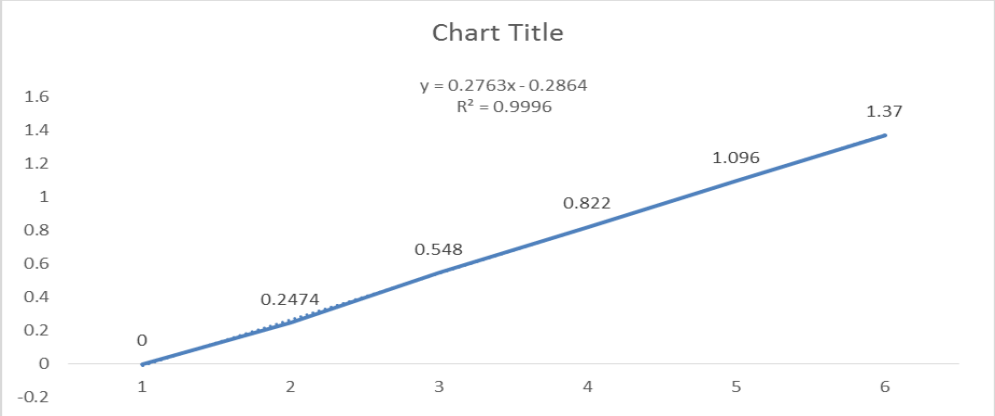
The prepared granules of PEG blend & Gelatin were subjected to an in-vitro dissolution test. Weighed accurately a quantity of the Granules equivalent to about 4 mg of Risperidone for dissolution testing. The dissolution test was performed in a USP XXI Dissolution Test Apparatus-II (Electrolab) paddle method in 900 ml Phosphate buffer pH 6.8 maintained at 37 ± .5 ºC, at 50 rpm. 5 ml sample was withdrawn at each predetermined time interval. The volume withdrawn at each interval was replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted and absorbance was measured spectrophotometrically at 280 nm. The percentage of Risperidone released at various time intervals was calculated and plotted against time.

Effect of Various Excipients on Compression Properties of Granules

Once the granules were prepared using the melt granulation method, various excipients for improving flow properties, as well as various sugars, were used in the formula and their

effects were observed on the compression properties of granules. From the literature survey, we found that Sucrose is hygroscopic, especially at elevated temperatures and high humidity. Mannitol, however, has low hygroscopicity and allows a short disintegration time, yet possesses low compressibility and results in a soft tablet. Granulation of mannitol improves its compressibility. Consequently, the tablets were formulated using granular mannitol alone or in combination with sucrose. A mixture of mannitol and sucrose has excellent flow and compression properties: produced tablets are hard, with smooth surfaces and low friability. Also, inclusion of Prosolv® into formulation improves flow properties, yet causes an increase in the disintegration time.

Linearity (calibration curve) of the Risperidone drug



CONCLUSION

MDT's found to be brilliant drug delivery system for geriatric, pediatric, bed ridden, psychotic patients and those patients who are busy in travelling, has difficulty in swallowing and may not have access to water, MDT's offer many advantages over the conventional oral tablets. They require small amounts of active ingredients to be effective. The major advantages are quick absorption, rapid onset of action, improved bioavailability than regular tablet and capsule.

FUNDING

Nil.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none.

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