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Formulation and Evaluation of Risperidone Sub-Lingual Tablet By Melt Granulation Method for the Treatment of Schizophrenia

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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 timeperiod 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.

I. INTRODUCTION

Melt granulation

Melt granulation is analogous to wet granulation though the binder, a polymer or lipid, is heated above a softening or melting pointso it can form bridges amongst the dry particles that solidify to form an agglomerate. 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.

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 ona 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 SugarPEG 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 witha 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

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(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.

ORGANOLEPTIC PROPERTIES.

The organoleptic properties of Risperidone (API) was given in the below table

Table: 6. Organoleptic properties of Risperidone (API)

Tests	**Specifications**	**Observation**
Colour	White to off white, yellow	White to off white
Odour	Odourless	Odourless
Taste	Bitter	Bitter

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

	QUANTITY PER TABLET (mg)							
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Risperidone	4	4	4	4	4	4	4	4
Silicified MCC	200	200	200	200	200	200	200	200
Croscarmellose sodium	20	20	20	20	20	20	20	20
PEG 8000	20	-	-	-	20	-	-	-
PEG 400	-	10 ml	-	-	-	-	20	-
Gelatin	-	-	20	-	-	-	-	20
Mannitol	-	-	-	20	20	-	-	20
Sucrose	-	-	-	-	20	20	20	20
Lactose	40	40	40	40	40	40	40	20
Orange flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

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II. RESULTS AND DISCUSSION

1.

.DRUG- EXCIPIENT INTERACTION STUDIES :

Fourier – Transform Infra red spectroscopy studies

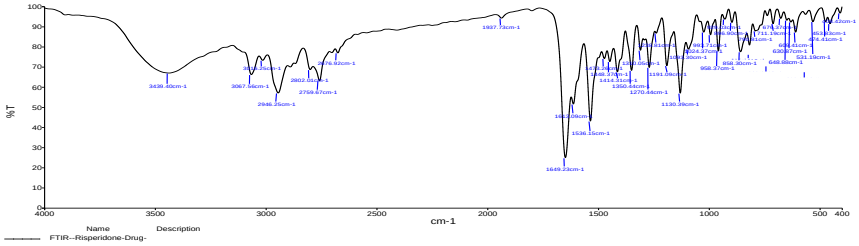

FIG.3..FT-**IR spectra of Risperidone drug alone**

DISCUSSION

The FT-IR spectral studies shows that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture shows all the characteristic peaks of Risperidone, thus confirming that no interaction of drug occurred with the components of the formulation.

1.3.PRE COMPRESSION PARAMETERS

Table:13. Precompression parameters

Formulations	Loose bulk density g/cm^3	Tapped bulk density g/cm^3	True density	Porosity (%)	Compressibility Index (%)	Haussner's ratio	Angle of repose
I	0.4323	0.4645	1.3477	65.53%	13.02%	1.296	36°13'
II	0.3505	0.3689	2.3045	75.62%	9.8%	1.0650	19°04'
III	0.3889	0.4297	5.1302	91.62%	15.6%	1.281	12°19'
IV	0.3831	0.4201	7.4946	10.61%	10.1%	1.101	28°05'
V	0.3765	0.4657	4.2567	84.86%	6.15%	1.142	15°49'
VI	0.4028	0.4438	4.0388	89.02%	10.15%	1.322	22°26'
VII	0.4000	0.4545	2.3434	80.60%	14.23%	1.020	26°62'
VIII	0.3831	0.4286	4.2345	88.86%	8.15%	1.506	24°54'

The above results in the term of micromeritic properties reveals that the flow property of the Formulation-VIII was good and other was fair.

1.4.POST COMPRESSION PARAMETERS

1.4.2.EVALUATION OF RISPERIDONE SUB LINGUAL TABLETS

Table:16. Evaluation of Risperidone Sub lingual tablet

Formulation code	Wetting time (in sec <105)	Dispersibility test	Disintegration time (>120 sec)	Fineness of dispersion	In-Vitro dispersion time
I	58	Pass	75±2.51	Pass	56±0.54

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II	101	Pass	98±1.52	Pass	52±0.12
III	100	Pass	63±1.52	Pass	50±0.25
IV	98	Pass	65±1.26	Pass	55±0.75
V	65	Pass	29±1.0	Pass	57±0.89
VI	72	Pass	98±2.0	Pass	52±0.23
VII	89	Pass	105±3.21	Pass	51±2.33
VIII	63	Pass	28±2.0	Pass	54±1.55

All the values are expressed as mean± SD, n=3

DISCUSSION

The In Vitro dispersion time of the best formulation (F VIII) at different time intervals (20, 38, 70, 96 seconds) were shown in figure.

1.4.2.2.Estimation of drug content :

Table.17. Percentage purity of respiridone tablets

S.no.	**Formulations**	**% Drug content**
1.	F 1	88.22±1.02%
2.	F 2	85.01±0.23%
3.	F 3	92.64±2.4%
4.	F 4	90.43±1.47%
5.	F 5	95.07±1.75%
6.	F 6	89.47±1.20%
7.	F 7	91.89±1.45%
8.	F 8	98.62±2.01%

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Table:27. The In Vitro drug release profile of the Risperidone sublingual tablets

All the values are expressed as mean± SD, n=3

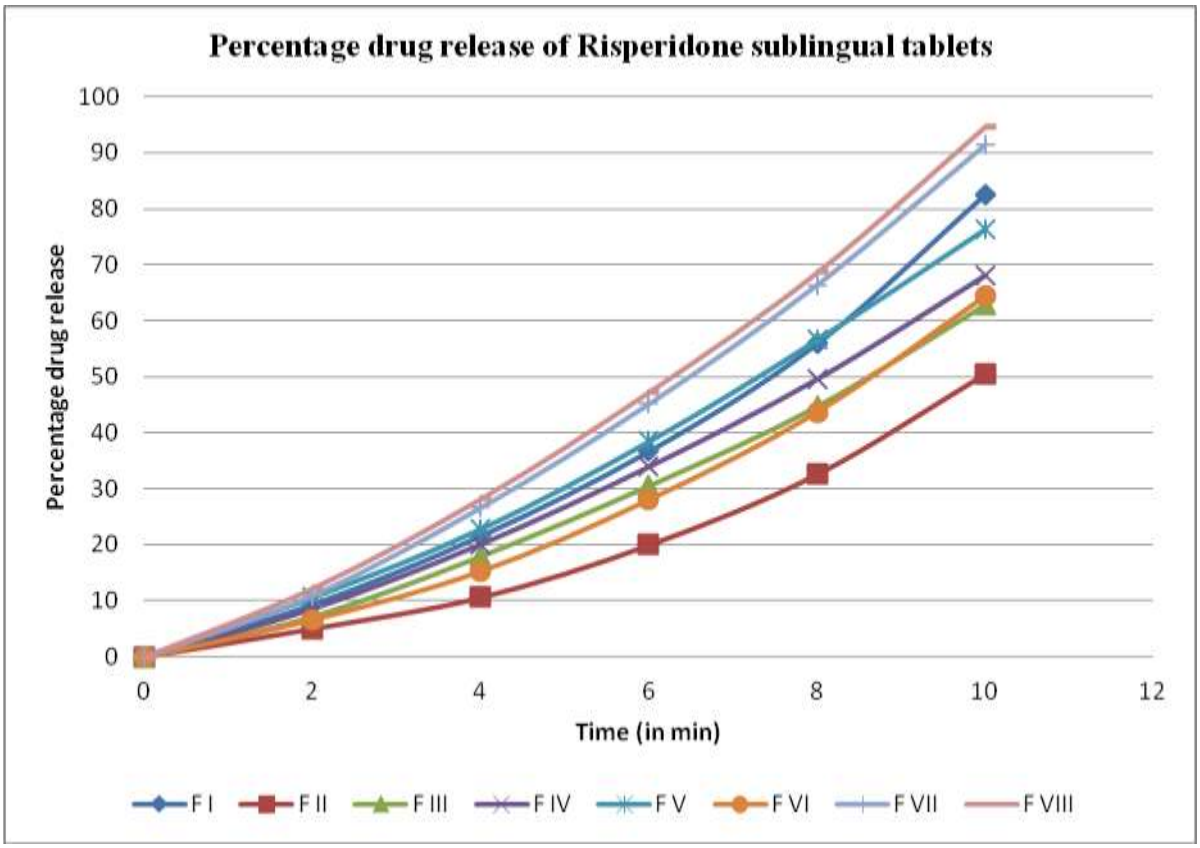

FIG.15. In Vitro drug release Profile of the Risperidone sublingual Tablets

DISCUSSION

The release of Risperidone Sublingual tabletswas studied in phosphate buffer 6.8 upto 10 minutes. The formulation F-VIII comes out as a best formulation.

The drug release of formulation F-I, F-II, F-III, F-IV, F-V, F-VI, F-VII, FVIII was found to be 82.53±1.66%, 50.51±1.73%, 62.92±1.38%, 68.14±2.03% , 76.42±0.52%, 64.36±1.24%, 91.35±0.98% at 10 minutes.

The acceptable limit of in vitro dissolution is NLT 80% of drug release at 10 minutes. All the formulations are passed the in vitro dissolution studies. The higher dissolution rates was observed in F-VII and F-VIII using MCC and Cross carmellose sodium as due to rapid disintegration and fine dispersion of particles after disintegration.

The formulation F-VIII prepared using PEG 8000, Mannitol, Sucrose as excipients shows higher drug release with direct compressible vehicle (Micro Crystalline Cellulose) which facilitates faster water uptake, faster disintegration, easy breakdown of the particles and rapid dissolution.

By the above results, Formulation VIII was observed as optimized formulation based onrapid disintegration time, wetting time, in vitro dispersion time and dissolution profile.

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1.4.2..5.Kinetics studies.

Table:28.Drug- release Kinetics Studies.

Time (min)	Log time	Square root of time	Cumulative % drug release	Cumulative % drug remaining	Log Cumulative % drug release	Log Cumulative %drug remaining	Cube root Of % drug remaining
0	∞	0	0	100	∞	2	4.6415
2	0.3010	1.4142	7.2	92.8	0.8257	1.9675	7.6163
4	0.6020	2	22.9	77.1	1.3598	1.8870	6.7191
6	0.7781	2.4494	42.32	57.68	1.6265	1.7610	5.4610
8	0.9030	2.8284	66.31	33.69	1.8215	1.5275	3.5640
10	1	3.1622	94.26	5.74	1.9743	0.7589	0.4370

Fig.19.A Plot for Korsmeyer peppas kinetics of Risperidone sublingual tablet.

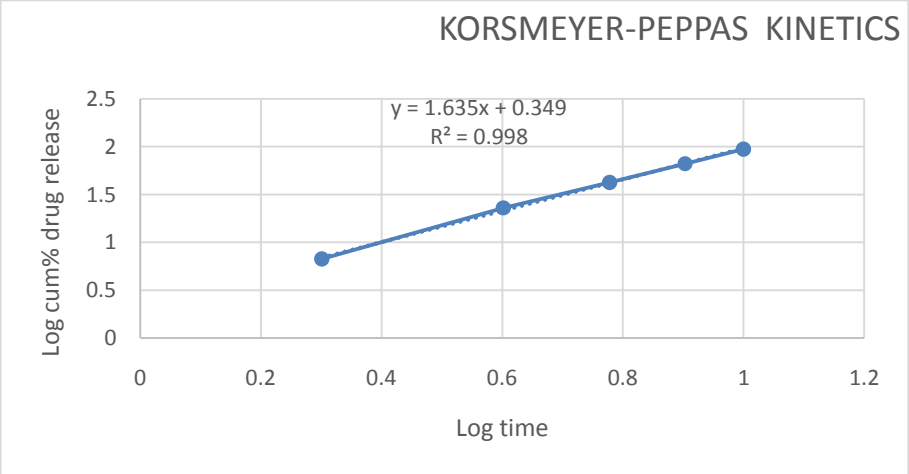

Table:29.R^2 values of various kinetics models :

Kinetics models	Co-efficient of determination (R) Of optimized formulation
First order	0.7597
Zero order	0.9657
Higuchi	0.7876
Korsmeyer and peppas	**0.9987**
Hisson crowell	0.5194

The data from in-vitro released of optimized formulation was fit into various kinetic models to find out the mechanism of drug release.
Good linearity was observed with the Korsmeyer and peppas ($\mathbf{R^{2=0.9987)}}$ plot model**.**

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III. SUMMARY AND CONCLUSION

The present study demonstrated that Risperidone Sublingual tablets can be successfully formulated using a direct compression method. The formulation and evaluation of risperidone Sublingual tablets were successfully carried out, and the results showed that the formulated Sublingual tablets had excellent characteristics such as rapid disintegration time, acceptable drug content, and a similar dissolution profile to the marketed risperidone tablets. The use of low melting point excipients such as MCC, Mannitol, PEG 8000, PEG 400, Gelatin powder and croscarmellose sodium in the formulation played a significant role in achieving rapid disintegration. Moreover, the use of mannitol, lactose, and sucrose as a for super compression and softening helped in maintaining the structural integrity of the Sublingual tablets. Therefore, Risperidone Sublingual tablets could be a potential alternative to conventional tablets for the treatment of mental illnesses, especially for patients who have difficulty swallowing conventional tablets.

From the experimental results the following points can be summarized,

- In the pre-formulation study Risperidoneshowed similar color, taste and odor as perthe I.P specification.
- The results of drug excipients compatibility study showed that the excipients selected for the formulation were compatible with the API and suitable for formulation development.
- FT- IR spectral studies of pure drug and drug with excipients showed that there was no interaction between the drug and excipients used in the formulation.
- The results of micromeritic properties indicate that the flow property of formulation F-VIII showed better flow property compared with other formulations.
- All formulations possessed uniform thickness. The prepared tablets also possessed good mechanical strength with sufficient hardness.
- All formulations of Risperidone Sublingual tablets passed the weight variation of the tablet. All formulations of Risperidone Sublingual tablets showed less than 1% weight loss and passed the friability test.