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Formulation & development of fast dissolving film of Resperidone

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Abstract

Risperidone, an Antipsychotic drugs. Risperidone undergoes first pass metabolism on oral administration resulting in reduced bioavailability (60%). Thus the objective of the present study was to formulate and evaluate Fast Dissolving Film of Risperidone to overcome the limitation of bioavailability and increase patient's compliance. In the present study Fast Dissolving Film were prepared by solvent-casting method using hydrophilic polymer HPMC K4M and PEG 400 as plasticizer. The eighteen formulations were prepared by the application of heat drying technique and evaluated for the fast dissolving films specification and characteristics. It was found that, the films has potential to modify drug release rate and possess good stability and less fragile property. The F9 batch of dried Fast Dissolving Film has shown promising drug release within 10 min (95.11%) and tensile strength.

Keywords: Risperidone; Fast Dissolving Film; Solvent Casting Method; Orodispersible; HPMC K4M

1. Introduction

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, films that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast dissolving films are also called as sublingual films, melt in mouth films, Orodispersible films, rapid melts, porous films, quick dissolving etc. Fast dissolving films are those when put under tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect (1).

1.1. Mechanism of Sublingual Absorption

The main mechanism for the absorption of the drug into oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. For these formulation small volume of saliva is sufficient for disintegrate the whole formulation. In strategies of permeability, the sublingual area of oral cavity is more permeable than buccal (cheek) area. The difference in permeability is based upon relative thickness, blood supply, and degree of keratinization of these membranes. In addition to this, the difference in permeability is also based upon physicochemical properties of drug (3).

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The absorption potential of the oral mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the molecular weight of the substances. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional to layer thickness. The extent of drug absorption follows, sublingual >buccal>gingival>palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent (2).

- Absorption by Osmosis Process
- Salivary Gland

The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are parotid, submandibular and sublingual, which lies on the floor of the mouth. The acidic taste leads to the stimulation of salivary output, serving to avoid potential harm to acid sensitive tooth enamel by bathing the mouth in copious neutralizing fluids (4).

The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighbouring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the submental branches of the facial artery. The sublingual artery stems from the lingual artery the body's main blood supply to the tongue and the floor of the mouth which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere (5,7).

2. Experimental

2.1. Material

Risperidone was obtained as gift sample from by TOCRIS a biotechne brand R&D Cipla, Vikroli(Mumbai 400083), India. The HPMC K4M was purchased from TITEN BIOTECH LTD. Bhiwandi-301 019, Rajasthan, India. PEG400 was purchased from Oxford Laboratory, Mumbai, India. Ethanol was received from RESEARCH-LAB FINE CHEM INDUSTRIES, Mumbai 400 002 (INDIA). All other materials used were of analytical grade.

2.2. Compatibility Studies

A compatibility study for Risperidone was carried out with potential formulation excipients. PEG 400, HPMC K4M, complex. These samples were subjected to compatibility studies and stored for 30 days at elevated temperature and humidity conditions of 40 ± 2 ^{0}C / 75 ± 5 % RH.

After 30days

- IR spectra of these stored samples was obtained.
- The assay of drug was performed using U.V. Spectrophotometer.

3. Formulation of Fast Dissolving Film of Risperidone

The composition of Risperidone Fast Dissolving films is given in Table.1 & 2

Table 1 Composition of Risperidone Fast Dissolving Films

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Risperidone (mg)	158	158	158	158	158	158	158	158	158
2	HPMC K4M (gm)	1.5	1.5	1.5	1.8	1.9	2.0	2.1	2.1	2.1
3	PEG 400 (ml)	1	1	1	1	1	1	1	1	1
4	Ethanol (ml)	30	25	20	30	25	20	30	25	20
5	Water (ml)	20	25	30	20	30	20	25	20	30

Table 2 Composition of Risperidone Fast Dissolving Films

Sr. No.	Ingredients	F10	F11	F12	F13	F14	F15	F16	F17	F18
1	Risperidone (mg)	158	158	158	158	158	158	158	158	158
2	Pectin (gm)	1.5	1.5	1.5	1.8	1.9	2.0	2.1	2.1	2.1
3	PEG400 (ml)	1	1	1	1	1	1	1	1	1
4	Ethanol (ml)	30	25	20	30	25	20	30	25	20
5	Water (ml)	20	25	30	20	30	20	25	20	30

3.1. Preparation of Fast Dissolving Film

Weight accurate amount of polymer and socked in respective solvents for overnight. Risperidone was dissolved in required quantity of solvent. Mix the solution and add PEG 400 as a plasticizer. Heat the solution and keep standing for half an hour to get the proper viscosity. (Stir the solution continuously while heating). Sonicate the solution for 15 mins to remove the air bubbles. Then keep the solution overnight and next day casting procedure was carried out. Next day, lubricate the Petridish with help of castor oil. Pour the solution in Petridish and keep it overnight for proper drying. After complete drying of film, film was removed with the help of cutter. Wrap the film with aluminium foil and store in normal room temperature (6).

Figure 1 Fast Dissolving Sublingual Film Image of Batch F9

3.2. Evaluation of Fast Dissolving Films

3.2.1. Thickness

As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers (9). All the film formulations were found to have thickness in the range of 0.05mm to 0.15 mm. Result were shown in table 3.

3.2.2. Weight Variation

Three films each of 4 cm^2 were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 49 mg to 66mg. Surface pH. The surface pH of the films was ranging from 6.67 to 6.93. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity. In Final optimized batch, 3%, 3.6% and 4.2% HPMC K4M concentration were tried using different proportion blend of ethanol and water mixture. Result concluded that all formulation having all desirable film characteristics. All formulations were giving 90% drug dissolution within 10 minutes (10).

3.2.3. Disintegration Time

It was observed that disintegration time varies from 19 to 30 sec for all the formulations. Disintegration time of Fast Dissolving Film containing HPMC K4M as polymer was affected by the thickness of the film. Disintegration time of the films was found to increase with increase in the amount of the polymer. Result were shown in table 4.

3.2.4. Folding Endurance

Folding endurance of film was increase with increase in the concentration of polymer. The number of time the film fold until it broke is reported. All the formulation contain different amount of polymers, hence the folding endurance gradually increase with the amount of polymers. The maximum folding endurance was occurred in F9 & F12 Batch. Result were shown in table 4.

3.2.5. Tensile Strength

The tensile strength was found to increase with increase with concentration of HPMC K4M. Formulation F9 was found maximum 53.95 mg. Result were shown in table 5.

3.2.6. Elongation

The percentage elongation of all the batches ranges from 5-20 mm elongation. It increased upon polymer as shown by the formulations. Formulation F9, F12 had highest percentage elongation. Result were shown in table 5.

3.2.7. Drug Content

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory showing drug content as per labeled amount. Result were shown in table 5.

3.2.8. Dissolution Study

In-vitro drug release profiles of the formulations in pH 7.2 artificial saliva show differences depending on their composition as given in table1 & 2. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Risperidone within 10 min. The formulations F1 to F18 showed approximately 95 to 99% drug release within 10 minutes. It was also observed that HPMC K4M & Pectin was able to modulate the Risperidone release as lower amount of HPMC K4M as well as Pectin resulted in release of drug a faster rate. Result were shown in table 6 & 7.

4. Results and discussion

4.1. Drug-Polymers Compatibility Studies

4.1.1. Infrared Spectroscopy

Drug-excipients interaction study shown no interaction between Risperidone and selected polymers as there was no significant shift of peaks in IR spectrum.

Thus the Risperidone was found to be compatible with the selected excipients.

4.2. Evaluation of orally disintegrating films

4.2.1. Reformulation study

Color and Odour

Risperidone was observed and found to be white in color and odorless.

Identification by Melting point

The melting point of Risperidone was taken in triplicate and mean value was found to be 169-171ºC.

Solubility

Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and dilute acid solutions.

Thickness

As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers. All the film formulations were found to have thickness in the range of 0.05mm to 0.15 mm. Result were shown in table 3.

Weight Variation

Three films each of 4 cm2 were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 49 mg to 66mg. Surface pH. The surface pH of the films was ranging from 6.67 to 6.93. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity. In Final optimized batch, 3%, 3.6% and 4.2% HPMC K4M concentration were tried using different proportion blend of ethanol and water mixture. Result concluded that all formulation having all desirable film characteristics. All formulations were giving 90% drug dissolution within 10 minutes. However, with economic aspect of formulation HPMC K4M with lower concentration and lower amount of ethanol preferable for optimized batch. Result were shown in table 3.

Table 3 Evaluation Parameter of Sublingual Film Batch F1 to F18

Formulation Code	Thickness (mm) with S.D.	Weight (mg)/4cm2S.D.	Surface pH with S.D.
F1	0.053±0.0057	49.33±0.472	6.86±0.057
F2	0.066±0.0000	51.33±0.472	6.90±0.100
F3	0.088±0.0057	53.33±0.472	6.96±0.057
F4	0.093±0.0057	55.33±0.472	7.06±0.057
F5	0.100±0.0057	58.00±0.472	7.00±0.100
F6	0.113±0.0057	60.33+0.472	7.10±0.100
F7	0.126±0.0057	62.33±0.472	7.03±0.152
F8	0.140±0.0000	64.66±0.472	7.06±0.057
F9	0.150±0.0000	66.66±0.472	7.16±0.057
F10	0.146±0.0000	65.30±0.472	7.04±0.057
F11	0.148±0.0000	64.18±0.472	7.02±0.150
F12	0.148±0.0050	65.96±0.472	7.14±0.057
F13	0.142±0.0057	62.40±0.472	6.98±0.057
F14	0.137±0.0000	60.33±0.472	6.94±0.100
F15	0.129±0.0057	59.72±0.472	6.90±0.100
F16	0.117±0.0057	57.80±0.472	6.88±0.057
F17	0.100±0.0057	56.82±0.472	6.86±0.057
F18	0.90±0.0000	52.00±0.472	6.80±0.057

4.2.2. Disintegration Time

It was observed that disintegration time varies from 19 to 30 sec for all the formulations. Disintegration time of Fast Dissolving Film containing HPMC K4M as polymer was affected by the thickness of the film. Disintegration time of the films was found to increase with increase in the amount of the polymer. Result were shown in table 4.

4.2.3. Folding Endurance

Folding endurance of film was increase with increase in the concentration of polymer. The number of time the film fold until it broke is reported. All the formulation contain different amount of polymers, hence the folding endurance

gradually increase with the amount of polymers. The maximum folding endurance was occurred in F9 & F12 Batch. Result were shown in table 4.

Table 4 Evaluation Parameter of Sublingual Film Batch F1 to F18

Formulation Code	Disintegration Time in sec (starts) with S.D.	Folding Endurance (no. of times to break) with S.D.
F1	19.00±1.73	201±3.60
F2	18.33±1.54	212±2.08
F3	17.66±0.57	220±5.00
F4	22.33±0.57	229±7.50
F5	23.66±0.57	241±9.07
F6	25.33±0.57	249±6.55
F7	27.66±0.57	264±8.38
F8	29.00±0.00	273±2.88
F9	30.00±0.00	278±1.52
F10	28.73±0.00	276±1.52
F11	28.86±0.00	232±7.50
F12	29.68±0.00	279±1.52
F13	25.48±0.57	260±8.32
F14	23.73±0.57	255±6.55
F15	22.69±0.57	247±6.52
F16	17.82±0.00	238±7.50
F17	18.76±0.00	220±5.00
F18	18.64±0.00	238±7.49

Tensile Strength

The tensile strength was found to increase with increase with concentration of HPMC K4M. Formulation F9 was found maximum 53.95 mg. Result were shown in table 5.

Elongation

The percentage elongation of all the batches ranges from 5-20 mm elongation. It increased upon polymer as shown by the formulations. Formulation F9 F12 had highest percentage elongation. Result were shown in table 5.

Drug Content

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory showing drug content as per labeled amount. Result were shown in table 5.

Table 5 Evaluation Parameter of Sublingual Film Batch F1 to F18

Formulation Code	Tensile Strength (mg) with S.D.	Elongation (mm) with S.D.	Drug Content (%) with S.D.
F1	51.83±0.015	5.33±0.57	92.13±0.32
F2	51.53±0.011	5.66±0.57	94.30±0.10
F3	52.92±0.025	6.66±0.57	93.63±0.35
F4	52.72±0.037	8.33±0.57	93.53±0.23
F5	53.52±0.025	10.00±0.00	93.40±0.45
F6	53.02±0.068	10.66±0.57	93.16±0.28
F7	53.22±0.026	13.00±0.00	94.60±0.30
F8	53.59±0.136	13.66±0.57	94.33±0.28
F9	53.95±0.050	14.66±0.57	95.11±0.90
F10	53.02±0.015	14.29±0.57	94.86±0.78
F11	52.68±0.021	13.56±0.00	94.47±0.31
F12	53.92±0.025	14.80±0.57	94.98±0.23
F13	52.47±0.011	11.98±0.57	93.76±0.24
F14	52.26±0.026	10.47±0.57	93.27±0.21
F15	51.87±0.015	9.04±0.00	93.04±0.20
F16	51.68±0.014	8.35±0.57	92.32±0.18
F17	51.48±0.011	6.40±0.00	92.57±0.18
F18	51.18±0.09	6.37±0.57	92.20±0.14

4.2.4. Dissolution Study

Table 6 Percentage CDR of Formulation F1 to F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	37.22 ±0.12	35.33 ±0.48	50±0. 44	47.22 ±0.21	45.55 ±0.22	40.55 ±0.95	38.88 ±0.76	66.66 ±0.23	67.22 ±0.96
4	47.59 ±0.34	48.71 ±0.53	61.61 ±0.48	61.58 ±0.32	59.9 ±0.32	55.4 ±0.84	50.38 ±0.56	72.33 ±0.85	72.33 ±0.23
6	59.17 ±0.10	60.31 ±0.28	72.77 ±0.24	67.15 ±0.44	63.27 ±0.50	62.06 ±0.74	61.44 ±0.73	80.27 ±0.66	84.72 ±0.21
8	70.31 ±0.14	71.46 ±0.25	80.16 ±0.57	79.52 ±0.21	78.89 ±0.59	69.34 ±0.73	72.05 ±0.12	86.61 ±0.56	91.11 ±0.15
10	84.33 ±0.28	86.6 ±023	92.61 ±0.28	91.97 ±0.59	91.33 ±0.87	88.35 ±0.58	87.75 ±0.88	93.27 ±0.42	95.11 ±0.36

In-vitro drug release profiles of the formulations in pH 7.2 artificial saliva show differences depending on their composition as given in table. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Risperidone within 10 min. The formulations F1 to F18 showed approximately 95 to 99% drug release within 10 minutes. It was also observed that HPMC K4M & Pectin was able to modulate the Risperidone

release as lower amount of HPMC K4M as well as Pectin resulted in release of drug a faster rate. Result were shown in table 6 & 7.

Table 7 Percentage CDR of Formulation F10 to F18

F10	F11	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0	0
42.45 ±0.89	57.23 ±0.64	65.11 ±0.63	40.87 ±0.34	42.23 ±0.13	47.22 ±0.87	45.11 ±0.89	46.87 ±0.63	38.88 ±0.52
58.87 ±0.51	69.34 ±0.52	71.87 ±0.86	59.94 ±0.87	58.96 ±0.18	61.58 ±0.54	60.87 ±0.42	59.47 ±0.58	52.38 ±0.45
62.89 ±0.93	77.78 ±0.56	82.64 ±0.67	64.78 ±0.46	63.43 ±0.65	68.15 ±0.65	72.95 ±0.78	71.94 ±0.96	61.54 ±0.56
72.34 ±0.58	84.76 ±0.36	89.76 ±0.42	70.67 ±0.14	73.85 ±0.38	77.52 ±0.25	79.45 ±0.82	78.65 ±0.59	74.25 ±0.23
84.42 ±0.37	89.32 ±0.88	94.57 ±0.28	82.98 ±0.54	84.86 ±0.54	88.97 ±0.36	87.6 ±0.73	85.9 ±0.79	87.55 ±0.12

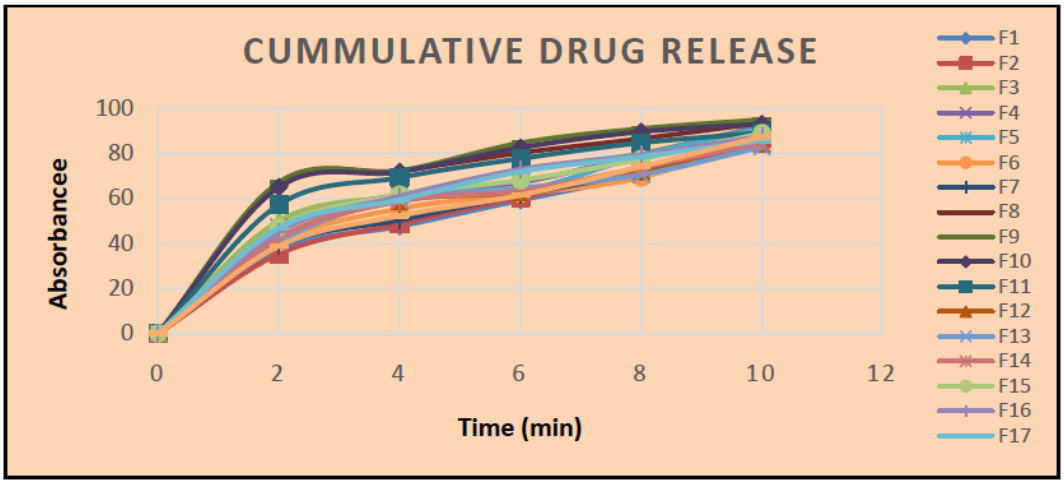

Figure 2 *In-vitro* Dissolution Profile of Formulation Batch F1 to F18

5. Conclusion

Risperidone is used in the treatment of psychiatric disorder, mania and schizophrenia. Quick onset of action is desirable in acute treatment of these disorders. Oral delivery of Risperidone having many problems like poor bioavailability, extreme first pass hepatic metabolism, alteration of drug effect by various in vivo factors and poor patient compliance. So, fast dissolving sublingual film is promising approach for this drug candidate.

The fast dissolving sublingual film of Risperidone was prepared by the solvent casting method using HPMC K4M and PEG-400 as plasticizers. The prepared film was evaluated for different parameters and the results was found to be promising ensuring safe, and effective dosage form, which can be reproduced with a robust manufacturing process.

From the results obtained by this study it can be concluded that Risperidone given in form of fast dissolving sublingual film should be advantageous for patients suffering from psychosis, providing better patient compliance and effective mode of treatment in a disguised manner. From the present investigation, it can be conclude that fast dissolving sublingual film formulation can be a potential novel drug dosage form for paediatric, geriatric and also for general population.

Compliance with ethical standards

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Disclosure of conflict of interest

We declare that we have no conflict of interest.

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