



Preparation and Evaluation of Risperidone Oro-dispersible Tablets

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ABSTRACT

The demand for Orodispersible tablets (ODTs) has been growing during the last decade especially for elderly and children who have swallowing difficulties. Risperidone is an atypical antipsychotic drug which is extensively metabolized due to the hepatic metabolism. Although the formulation of Risperidone into oro-dispersible dosage form will improve the release and bioavailability, the bitter taste of the drug will be a great problem. In the current work, the aim was masking the taste by complexation technique, with a formulation into oro-dispersible tablets by sublimation and lypholization. The inclusion complex of Risperidone with 2HP-β-CD (1:1 molar ratio) was prepared by solvent evaporation method. Phase solubility showed stability constant $39.13M^{-1}$. The prepared complex was evaluated for taste masking and characterized by using Infrared, differential scanning calorimetry, X-ray diffraction, scanning electron microscope and *in-vitro* drug release. Risperidone ODTs were successfully prepared by either of sublimation method using camphor as subliming or lypholization technique which involved addition of disintegration accelerators. The prepared tablets were evaluated for weight variation, friability, hardness, *in-vitro* disintegration, wetting time, drug content and *in-vitro* dissolution. The formulations R15 prepared by lypholization using 1% of tween 20 as disintegration accelerator is a promising novel formula for Risperidone where 100% of the labeled dose was dissolved within 3 minutes.

Keywords: Orodispersible tablets, Risperidone, 2-HP-β-CD, Complexation, Bitter taste, sublimation and lypholization.

INTRODUCTION

Cyclodextrins and their derivatives are well known by the ability to mask bitter taste of drugs¹ and enhance their bioavailability² through the formation of inclusion complexes. The oro-dispersible tablet (ODT), is one of the most widely employed commercial products^{3,4} that are useful in patients who may face difficulty in swallowing.⁵⁻⁷ According to European Pharmacopoeia, the ODTs should disperse/disintegrate in less than three minutes.⁵ The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to reduction of first pass metabolism.

A benzisoxazole derivative, Risperidone, is a well known atypical antipsychotic drug that used in the treatment of schizophrenia, mania in bipolar disorders and other psychotic problems.⁹ It mainly acts on 5-hydroxytryptamine (5-HT) and dopamine D2 receptors.⁸⁻¹¹ The bitter taste of the drug may cause patient's noncompliance if it is incorporated directly into an oro-dispersible dosage form; wasting the main objective behind formulation of such a dosage form.¹²⁻¹⁴ Thus our goals in the present study will be first to mask the bitter taste of Risperidone and then to formulate ODTs with acceptable taste improving patient compliance.

MATERIALS AND METHODS

Materials

Risperidone kindly supplied by (EIPICO Company, Cairo, Egypt); Kleptose® HPB:2-hydroxypropyl beta cyclodextrin

(Roquette Pharma, France); Ac-di-sol: crosscarmellose sodium (FMC corporation, Philadelphia, USA); Magnesium stearate (Prolabo, France); and granular mannitol (spray-dried NF, Fast Flo; Foremost Farms, Baraboo, WI); Aspartame, Camphor, Polyethylene glycol (PEG 6000, PEG 4000, PEG 4000), Ethyl Alcohol 95%, Tween 80 and Tween 20 (El-Nasr pharmaceutical chemical company, Cairo, Egypt). Gelatine, Glycine and Polyvinyl pyrrolidone (Povidone K90 and k25) (Fluka AG, Buchs, Switzerland).

Methods

Phase Solubility Studies

A series of stoppered conical flasks containing excess quantity of Risperidone with distilled water was mixed with serial concentrations of 2-HP-β-CD (5 to 50 mM). The flasks were shaken for 3 days on a rotary flask shaker. The suspensions were then filtered through millipore filter paper and assayed for Risperidone using a UV spectrophotometer (Shimadzu, UV-1601) at 235 nm. The stability constants K_s were estimated from the straight line of the phase solubility diagrams according to Equation (1):

$$K_s = \frac{\text{Slope}}{\text{Intercept} (1 - \text{Slope})} \text{ reported by Higuchi and Connors.}^{15}$$

Where S_0 represents the drug solubility in absence of cyclodextrins. The complexation efficiency (CE)¹⁶ was calculated according to Equation (2):

$$CE = S_0 K_{1:1} = \left[\frac{\text{drug} - CD}{CD} \right] = \frac{\text{slope}}{1 - \text{slope}}$$



Where [drug-CD] is the concentration of the drug-cyclodextrin complex and [CD] is the concentration of the free cyclodextrin.

Preparation of Solid Complex

The inclusion complex of Risperidone with 2-HP- β -CD (at 1:1 molar ratio) was prepared using solvent evaporation technique.^{17,18} The mixture of the drug and cyclodextrin was dissolved in 10% ethanol (v/v). The solvent was vaporized at room temperature and then dried in the oven at 40° C for 6 hours. The resulting mass was pulverized using sieve no-80 and stored in desiccator.

Evaluation of Solid Complex

Infrared Spectroscopy

Infrared (IR) spectra of Risperidone, 2-HP- β -CD and complex were obtained by using a Bruker 640 IR spectrophotometer (Varian, Australia) with KBr pellets. The scanning range used was 4000 to 400 cm^{-1} .

X-ray Diffractometry

The X-ray diffraction pattern was recorded at room temperature using Scintag XGEN-4000 diffractometer. The samples were irradiated with Ni filtered Cu K_{α} radiation, at 45 Kv voltage and 40 mA current. The scanning rate employed was 2°/minute over a diffraction angle (2θ) range of 3 - 70°.

Differential Scanning Calorimetry

DSC studies were performed for Risperidone, 2-HP β -CD, the complex. The samples (3-4mg) were placed in aluminum pans and the experiments run in a calorimeter (Universal V2.3D TA Instruments) at a 10 °C/min heating rate over a temperature range of 25° to 300° C.²²

Scanning Electron Microscopy (SEM)

Shape and surface morphology characterization of Risperidone, 2-HP- β -CD and their complex were performed by scanning electron microscopy (SEM, JSM-6390 LV, JEOL, Tokyo, Japan) measured at the working distance of 15mm and an accelerated voltage of 20 kV.

In-vitro Drug Release

Release studies of samples were performed using USP paddle type II apparatus in 900 mL of dissolution medium (GSF pH 1.2). Temperature was maintained at 37 ± 0.5 °C, and rotation speed was 100 rpm. Five-milliliter aliquots were withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60, and 90 minutes. Samples were filtered through millipore filter paper and analyzed spectrophotometrically at 233 nm. The percentage of the labeled amount of drug released at each time point was calculated and a graph was plotted.

Assessment of the Taste in the Prepared Complex

Fixed weights of the prepared complex that equivalent to the dose of the drug (4mg) were subjected to six healthy human volunteers. Each volunteer was given pure

Risperidone as a control. After placing the formulation on the tongue for 1 minute bitterness was recorded against the control where; 0: no bitterness, 1: slight bitterness, 2: moderate bitterness and 3: strong bitter.^{20,21}

Formulation of Risperidone ODTs

Sublimation Method

Five ODTs of Risperidone (R1-R5) containing 18.2 mg of the prepared complex equivalent to drug dose (4 mg) were prepared using camphor as subliming agents (2.5-15% w/w). Accurately weighed ingredients, as shown in Table 1 were sifted through sieve no. 44, mixed and compressed into 100 mg tablets using single punch machine of 8 mm flat punch and die set. The prepared tablets were placed in an oven at 40 °C till constant weight is obtained.

Lyophilization Method

Ten ODTs of Risperidone (R6-R15) were prepared using gelatin (0.25%, 5% and 1% w/v) to form the matrix, mannitol and glycine (0.886% w/v) to protect collapsing.²³

First gelatin was liquefied in distilled water at 40 °C to obtain the desired concentration. An accurately weighed amount of Risperidone, mannitol and glycine were mixed with the prepared aqueous solution of gelatin using a magnetic stirrer. One milliliter of the previous mixture was then poured in each pocket of a PVC blister pack of with 16mm diameter and 3 mm depth resulting in a tablet of 4 mg Risperidone.

The blister packs were then kept into a freezer at -22 °C for 48 h. The frozen tablets were transferred to a lyophilizer for 24 h.

The best of these tablets were taken forward to the next step which involved the addition of (1% w/v) disintegrants including: PEG 400, PEG 4000, PEG 6000, PVP K25, PVP K90, Tween 20 and Tween 80, as shown in Table 2. The prepared ODTs were dried at room temperature.

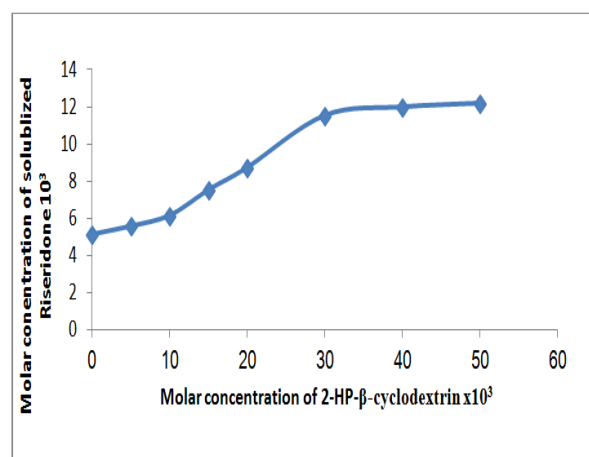


Figure 1: Phase solubility diagram for Risperidone inclusion complex with 2-HP β -CD in phosphate buffer pH 6.8.

Table 1: Composition of Risperidone ODTs prepared by Sublimation.

Formula Number	Camphor % (w/w)	Risperidone	Ac-Di-Sol	Aspartame	Magnesium stearate	Mannitol
R1	2.5	4 mg	8%	1%	1 %	Up to 100 mg
R2	5					
R3	7.5					
R4	10					
R5	15					

Table 2: Composition of Risperidone ODTs prepared by lypholization.

Formula Number	Matrix former (%w/v)	Disintegrant (%w/v)
R6	0.25	-
R7	0.5	-
R8	1	-
R9	0.5	1% PVP K90
R10	0.5	1% PVP K25
R11	0.5	1% PEG 6000
R12	0.5	1% PEG 4000
R13	0.5	1% PEG 400
R14	0.5	1% Tween 80
R15	0.5	1% Tween 20

*all tablets containing 8.86 (% w/v) mannitol, 0.886 (%w/v) glycine and 18.2 mg of the prepared complex.

Evaluation of Risperidone ODTs

All the prepared ODTs of formulae (R1:R5) were tested for weight variation, mechanical properties, *in-vitro* disintegration, wetting time, Risperidone content and *in-vitro* dissolution.

Weight variation tests were evaluated using twenty tablets of each formula randomly, and individually weighed. Not more than two tablets deviate from the average weight by more than 5%, and none deviate by more than twice that percentage.^{24,25} Friability was tested using friabilator, Pharma test, (Erweka type, GmbH, Germany) carried out according to British pharmacopoeia²⁵, while hardness was investigated using Erweka hardness tester (M6d, Drish leuniger, Pharmaton). For the *in-vitro* disintegration time test; the tablets were inserted in each of the six cells of the disintegrator, USP Disintegration tester apparatus (Hanson Research, USA); using 900 ml simulated saliva fluid (SSF) pH=6.75 kept at 37 ± 1 °C with a constant frequency of 30 ± 2 cycles/min.^{27,28} For wetting time test five rounded filter papers of 10 cm diameter are located in a petridish with the same diameter. Ten milliliters of eosin solution is putted into petridish. Then each tablet is carefully placed on the petridish and the time required for the dye to colour the tablet's upper surface was recorded.

The content of Risperidone in the prepared tablets was determined by accurately weighing ten tablets of each formula individually. Each tablet was crushed and

dissolved in 8 ml methanol in a 10-ml volumetric flask. The solution was filtered and the Risperidone content was analyzed spectrophotometrically (Shimadzu, UV-1601) at 235 nm.

The *in-vitro* dissolution of all prepared formulations R1-R15 was investigated using USP type II dissolution apparatus at 50 rpm with temperature of 37 ± 0.5 °C and 900 ml of SSF. Aliquot of 5 ml was withdrawn at specific time intervals and it was filtered and checked by UV at 235.

RESULTS AND DISCUSSION

Phase Solubility Studies

The phase solubility diagram of Risperidone with 2-HP- β -CD is shown in Figure 1. The correlation coefficient value (R^2) is 0.9295 and K_s was found to be $39.13M^{-1}$. Therefore the solubility curve of 2-HP- β -CD is considered of the Ap type, indicating that the solubility of Risperidone increased linearly with the addition of 2-HP- β -CD.² This is mainly due to the formation of inclusion complexes.¹⁸ The initial ascending portions of the curve can be attributed to the formation of complex which has higher solubility than the drug alone. When the solubility limit of the formed complex increases, the ascending linear portion begins to leveling off forming a plateau. The shape of the solubility curve can indicate that a 1:1 molar ratio is most probable for the formation of inclusion complex. Also this result agreed to Shukla.²⁸

Characterization of Prepared Inclusion Complex

Infrared Spectroscopy

Risperidone spectrum shows its main bands at 1350.71 cm^{-1} , 1129.25 cm^{-1} and 1651.6 cm^{-1} corresponds to C-N, C-F and C=O stretching; respectively.²⁹ The IR spectrum of CD shows bands at $3500\text{--}3300\text{ cm}^{-1}$ corresponding to the free -OH stretching vibration.

The spectrum of the physical mixture was the superposition of pure components, indicating the absence of interaction in the physical mixture, Figure 2A. This result was in good agreement with the work of Fernandes³⁰ who found no change in the carbonyl broadening of nicardipine in the physical mixtures prepared with cyclodextrins.

The restriction of the drug in cyclodextrin cavities explains the change in the intensity of its aromatic band³¹, and the overlapping between carbonyl band of the drug at 1651 cm^{-1} and the band corresponding to the

hydrated bonds within cyclodextrin at $1650\text{-}1640\text{ cm}^{-1,32}$, as shown in the IR spectrum of complex.

X-ray Powder Diffractometry Studies

X-ray diffractograms revealed the crystalline nature of Risperidone, which contained a number of sharp peaks with two prominent peaks of high intensity at $2\theta = 14.21^\circ$ and $2\theta = 21.25^\circ$, while the diffractograms of 2-HP- β -CD exhibited its amorphous structure as shown in Figure 2B. The complex is also amorphous in nature similar to the

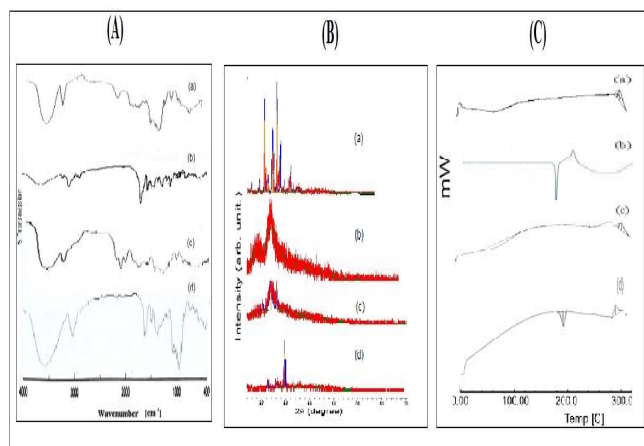


Figure 2: A): IR spectra of Risperidone/2-HP- β -CD binary solid system: (a) Pure Risperidone; (b) Pure HP- β -CD; (c) 1:1 M complex by solvent evaporation; (d) Physical mixture.

B): X-RDP of Risperidone/2HP- β -CD solid systems: (a) Pure Risperidone; (b) Pure 2-HP- β -CD; (c) 1:1 M complex by solvent evaporation; (d) Physical mixture.

C): DSC thermograms of Risperidone, HP- β -CD, and their complex in 1:1 molar ratio: (a) Pure Risperidone; (b) Pure HP- β -CD; (c) 1:1 M complex by solvent evaporation; (d) Physical mixture.

2HP- β -CD, as it has same diffused XRPD pattern, confirming the formation of inclusion complex.^{33,34}

Differential Scanning Calorimetry

The endothermic peak of Risperidone at 170.68°C was totally disappeared in the prepared complex as shown in Figure 2C.

These results are in accordance with those obtained by Veiga³⁵ during the investigation of tolbutamide- β -cyclodextrin complex formation.

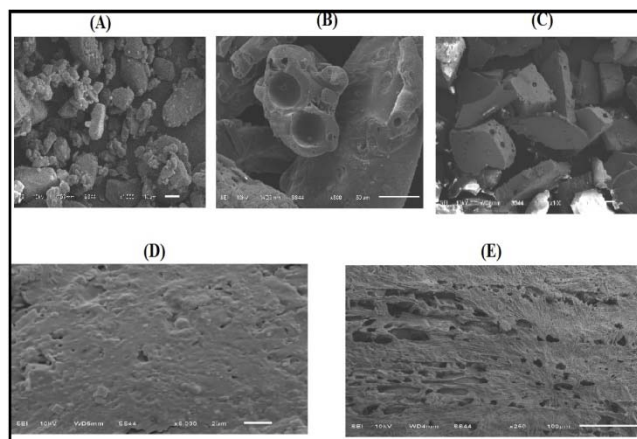


Figure 3: Scanning electron micrograph of Risperidone, HP- β -CD, and their complex in 1:1 molar ratio:

(a) Pure Risperidone;

(b) Pure HP- β -CD;

(c) 1:1 M complex by solvent evaporation;

(d) Surface view of ODTs (R5) showing the porous structure of the tablet due to camphor sublimation.

(e) Surface view ODTs (R15) showing the high porous structure of the tablet due to water lyophilization.

Table 3: Evaluation of Risperidone ODTs.

Formula	Weight variation (mg)	Thickness (cm)	Mean Diameter (cm)	Hardness (kg/cm^2)	Drug content (%)	Friability (%)	In-vitro disintegration time (sec.)	Wetting Time (sec)
R1	100.01 ± 0.03	0.22 ± 0.02	0.80 ± 0.03	2.91 ± 0.82	98 ± 1.22	$0.04\% \pm 0.03$	21	30
R2	100.1 ± 0.02	0.22 ± 0.09	0.81 ± 0.03	2.22 ± 0.62	101 ± 1.89	$0.05\% \pm 0.04$	17	29
R3	100.01 ± 0.04	0.23 ± 0.04	0.80 ± 0.01	2.03 ± 0.84	99 ± 1.37	$0.05\% \pm 0.04$	16	25
R4	99.78 ± 0.04	0.22 ± 0.03	0.80 ± 0.05	1.99 ± 0.34	98 ± 1.91	$0.06\% \pm 0.03$	12	15
R5	98.91 ± 0.04	0.22 ± 0.08	0.81 ± 0.04	1.90 ± 0.30	99 ± 1.21	$0.13\% \pm 0.15$	9	15
R6	--	--	--	--	--	$2.31\% \pm 0.08$	--	--
R7	--	--	--	--	--	$0.78\% \pm 0.04$	--	--
R8	--	--	--	--	--	$0.87\% \pm 0.03$	--	--
R9	113.72 ± 0.45	0.19 ± 0.023	1.60 ± 0.08	--	99 ± 2.15	$0.74\% \pm 0.09$	4	6
R10	114.02 ± 0.47	0.20 ± 0.029	1.60 ± 0.04	--	100 ± 2.15	$0.77\% \pm 0.10$	2	6
R11	113.91 ± 0.30	0.19 ± 0.039	1.61 ± 0.05	--	100 ± 1.97	$0.90\% \pm 0.09$	6	5
R12	113.23 ± 0.30	0.19 ± 0.021	1.60 ± 0.04	--	99 ± 2.05	$0.6\% \pm 0.12$	3	4
R13	114.06 ± 0.08	0.20 ± 0.017	1.63 ± 0.08	--	100 ± 2.02	$0.91\% \pm 0.09$	2	5
R14	114.04 ± 0.84	0.20 ± 0.003	1.60 ± 0.09	--	100 ± 1.97	$0.74\% \pm 0.19$	2	6
R15	113.89 ± 0.13	0.19 ± 0.064	1.60 ± 0.09	--	99 ± 1.15	$0.90\% \pm 0.12$	2	4

Scanning Electron Microscopy

The SEM micrographs revealed the complete disappearance of drug particles due to their inclusion in the cyclodextrin cavities proving complete removal of drug bitter taste, Figure 3.

In-vitro Drug Release

It was confirmed that more than 85% of the drug released from the complex at the end of one hour which shows suitability data for tablet formulation as shown in Figure 4A.

Assessment of the Taste of the Prepared Complex

The bitterness of the drug is associated to presence of free drug in the salivary fluid of the mouth¹⁹. The percentage of *in-vitro* amount released was 11.04% which is insufficient to impart bitter taste. The *in-vivo* score was zero indicating that the bitter taste of Risperidone was masked after complexation.

Evaluation of Risperidone taste-masked RDTs

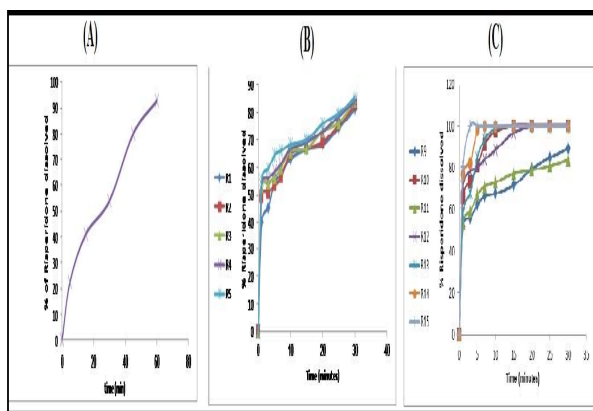


Figure 4: A) *In-Vitro* drug release of prepared complex. B): Dissolution profile of Risperidone from its ODTs (R1, R2, R3, R4 and R5) prepared by sublimation method. C): Dissolution profile of Risperidone from its ODTs (R9, R10, R11, R12, R13, R14 and R15) prepared by lyophilization method.

The compiled data in Table 3 revealed that: All the prepared Risperidone taste-masked ODTs from all formulae were found to conform to pharmacopoeial limits.^{36,37}

Scanning electron micrographs of the surface of ODTs R5 and R15 shown in Figures (4B, 4C).

Due to highly porous surface of the prepared lyophilized tablets water in the oral cavity penetrates rapidly which makes the tablets disintegrate and dissolve in shorter time.²¹

CONCLUSION

This study demonstrated that the development of Risperidone lyophilized ODTs containing 2-HP- β -CD, as a complex is a promising formula resulted in successful masking of the bitter taste of the drug and significantly

higher dissolution in comparing with those tablets prepared by sublimation method.

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