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RESEARCH ARTICLE

DISSOLUTION IMPROVEMENT OF TABLETS CONTAINING A POOR WATER-SOLUBLE TADALAFIL BY SOLUBILIZERS USING SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Tadalafil is a low solubility, low permeability (BCS class 4) drug prescribed for erectile dysfunction. Solubility enhancement is required to warrant the suitable formulation. This study aims to evaluate the various concentrations of povidone as a solubilizer using solvent evaporation technique to improve the dissolution of Tadalafil tablet.

Key words: Solvent evaporation technique, Solubilizer, Erectile dysfunction, Solubility enhancement, Granulation, Milling, Compression, Povidone.

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INTRODUCTION

The invention relates to Tadalafil compositions comprising tadalafil or its pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable excipient, wherein said composition comprises a tadalafil and povidone complex to improves the solubility and dissolution. The invention also relates to process of preparing a tadalafil/Povidone complex using solvent evaporation technique and compositions of tadalafil comprising the same. Povidone has been selected as a carrier to improve the solubility and enhance the dissolution of poorly soluble drugs like Tadalafil. Background of the Invention and related prior arts, Tadalafil is a cyclic guanosine monophosphate ("cGMP") specific phosphodiesterase type 5 ("PDE5") inhibitors. It is indicated for the treatment of erectile dysfunction in men and pulmonary hypertension. Tadalafil has a much longer duration of action because of its longer half-life (17.5 hr) than other PDE5 inhibitors like either sildenafil or vardenafil (4-5 hr). it is marketed in the US under the brand name of Cialis® and Adcirca® by Eli Lilly. Tadalafil is practically insoluble in water and very slightly soluble in ethanol. Because of its insoluble nature, conventional formulations of tadalafil exhibit very poor dissolution rate and bioavailability. Thus, it is required to increase the dissolution rate and bioavailability of the drug for faster and quicker onset of action. A number of techniques have been developed to increase the bioavailability of poorly soluble drugs like tadalafil which includes use of surfactants, particle size reduction, inclusion complexation and different solid dispersion methods. US5985326 relates to solid dispersions of poorly soluble drugs like tadalafil and its use in pharmaceutical compositions. US7182958 relates to composition comprising tadalafil wherein the bioavailability is enhanced by milling the active ingredient so that D_{90} of the active ingredient is less than 40 microns.

MATERIALS AND METHODS

Tadalafil (Aurobindo Pharma Limited), Povidone K-30 (BASF), Croscarmellose Sodium (JRS Pharma), Lactose Monohydrate, NF (Kerry Bio sceinces), Microcrystalline cellulose (JRS Pharma), Sodium Lauryl Sulfate (Spectra) and Magnesium Stearate (FACI asia/ Barrington), Acetone (Thomas). Tadalafil Tablets were prepared using solvent evaporation technique with Povidone (Solubilizer) and wet granulation technologies to improve the dissolution and later the final formula was subjected to Design of Experiment using Design of Expert to justify the povidone concentrations and the ratio of solvent used for solvent evaporation technique. Since, there was a Tadalafil API PSD patent (7182958) in orange book, (as D_{90} particles should be less than 40 microns), API particle size with D_{90} 60 microns was selected for the experimentation. Tadalafil and Povidone K-30 were dissolved in a solution of Acetone/Water (75:25) with continuous stirring until clear solution was formed. The said solution was then spray dried using Buchi 190 Mini Spray Dryer with nozzles and cyclones that were designed to generate and catch fine particles. Since these formulations utilized organic solvents, a Buchi 190 Mini Spray Dryer was used that was modified so that it was supplied with nitrogen as the gas source and equipped with an oxygen sensor and other safety equipment to minimize the possibility of explosion. The solution feed rate was 5 ml/minute, inlet temperature was adjusted to obtain the outlet temperature noted in each example, the top of the cyclone in some runs was jacketed and cooled to a temperature of about 30° C, the drying nitrogen flow rate was about 20 SCFM, and the atomizing nitrogen was supplied at 0.5 to 1.5 SCFM. The powders were further dried in the collector for 10-15 minutes (most often for 10 minutes) by maintaining approximately the outlet temperature and air volume after the feeding of the liquid formulation was completed. The resultant mass further dried in Vacuum Tray Drier to remove the excessive solvents. The dried material was milled to fine powder using Comminuting Mill with 0.5 MM screen.

Wet granulation Process

The spray dried and milled part of Tadalafil/Povidone mixture, Lactose Monohydrate and Microcrystalline Cellulose was granulated in Rapid Mixer Granulator suing Granulation solution of Sodium lauryl sulfate dissolved in sufficient quantity of water. The wet mass was kneaded sufficiently to get desired granules.

Table 1. Composition of Tadalafil/Povidone complex for solvent evaporation technique

S.No	Ingredient	Quantity per tablet in milligrams	Quantity for 3000 tablets in grams
	Materials for Solvent Evaporation		
1	Tadalafil	20.00	60.00
2	Povidone K-30	40.00	120.00
3.	Acetone/water ratio	75:25 (Ratio)	Sufficient quantity to dissolve the mixture

Table 2. Composition of Tadalafil tablet for wet granulation process[4]. (Trial-1)

S.No	Ingredient	Quantity per tablet in milligrams	Quantity for 2000 tablets in grams
	Intragranular part		
1	Tadalafil/Povidone mixture	60.00	120.00
2	Lactose Monohydrate, NF	160.00	320.00
3.	Microcrystalline cellulose, NF (PH 101)	40.00	80.00
	Granulation solution		
4.	Sodium lauryl sulfate	2.00	4.00
5.	Purified water	Sufficient quantity	Sufficient quantity
	Extragranular part		
6.	Microcrystalline Cellulose (PH 102)	80.00	160.00
7.	Croscarmellose sodium, NF	15.00	30.00
8.	Magnesium Stearate, NF	3.0	6.00
	Total weight	360.00	720.00

Table 3. Comparisons of dissolutions of the RLD and Trial batches in 0.1NHCl, using paddle in 1000 ml at 50 rpm (Average of 6 units)

Time points in minutes	RLD	Trial-1	Trial-2
10	45.0	43.2	25.6
15	52.5	50.9	27.2
20	65.0	64.1	28.3
30	83.5	82.6	30.2
45	90.0	89.2	31.0

Table 4. Summary of DOE experiments

	Batch Number	Trial-3	Trial-4	Trial-5	Trial-6	Trial-7
S.No	Ingredient	Quantity per tablet in milligrams				
	Intragranular part					
1.	Tadalafil/Povidone mixture	20.00+ 40.00	20.00+ 50.00	20.00+ 30.00	20.00+ 30.00	20.00+ 50.00
2.	Acetone/Water ratio	75:25	65:35	65:35	85:15	85:15
3.	Lactose Monohydrate, NF	160.00	150.00	170.00	170.00	150.00
4.	Microcrystalline cellulose, NF (PH 101)	40.00	40.00	40.00	40.00	40.00
	Granulation solution					
5.	Sodium lauryl sulfate	2.00	2.00	2.00	2.00	2.00
6.	Purified water	Sufficient quantity				
	Extra granular part					
7.	Microcrystalline Cellulose (PH 102)	80.00	80.00	80.00	80.00	80.00
8.	Croscarmellose sodium, NF	15.00	15.00	15.00	15.00	15.00
9.	Magnesium Stearate, NF	3.0	3.0	3.0	3.0	3.0
	Total weight	360.00	360.00	360.00	360.00	360.00

Table 5. Compilation of dissolution results (Dissolution in 0.1N HCl media using 1000 ml, paddle, 50 rpm

Time points in minutes	RLD	Trial-3	Trial-4	Trial-5	Trial-6	Trial-7
10	45.0	43.5	41.2	34	38.3	43
15	52.5	50.6	48.5	44.2	45.1	50.1
20	65.0	64.9	59.2	56.9	61.1	64.8
30	83.5	83.0	76.5	75.2	78.7	82.5
45	90.0	89.5	82.4	79	89.5	90

The wet granules were dried at 60°C in Rapid dryer to get the desired LOD. The dried granules were milled using Comminuting Mill. The Milled granules were blended using extra granular part microcrystalline cellulose and Croscarmellose sodium and then lubricate with magnesium stearate. The final blend was compressed to tablets to evaluate for dissolution. A comparative batch (Trail-2) was taken with the above composition of Trail-1, using normal wet granulation process and was compressed into tablets to evaluate for dissolution. The dissolution profiles of Trial-1 & trial-2 were compared to study the effect of solvent evaporation technique on formulation.

RESULTS AND DISCUSSION

As per the Office of Generic Drugs data base, the official media for dissolution testing the tablets was 0.5% Sodium Lauryl Sulfate dissolved in water (official media). The official media was unable to discriminate the differences, when there was quantitative change in the formulation. Hence 0.1N HCl without the addition of SLS media was chosen as discriminating media for further study of dissolutions. The results from the table 3 shows that Tadalafil has improved its solubility and dissolution in formulation (Trial-1) when Tadalafil API was complexed with Povidone using solvent

evaporation technique. The amount of Povidone and the ratio of acetone/water used in the formulation was justified by optimizing their concentration and ratios to evaluate for dissolution. In our study, the results (Table 5) reveal that the trials with Acetone/water ratio of 65:35 were observed on lower side when compared to the RLD, where as Trial 7 (50 mg of Povidone and higher concentrations of Acetone) exhibits comparable dissolution profiles when compared with RLD. However higher concentrations of Povidone have given process related issues during spray drying.

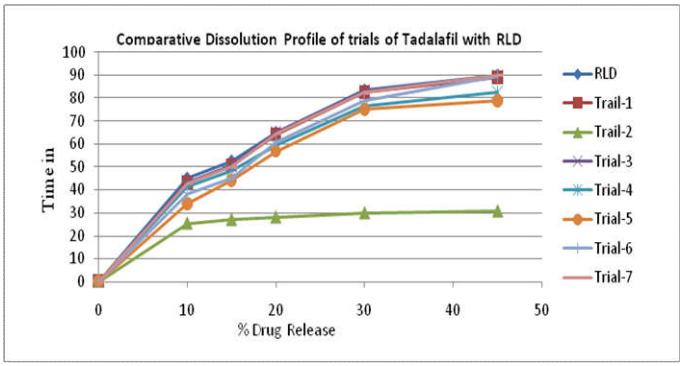

Figure 1. Graphical representation of Dissolution of Trial batches and RLD

The data clearly reveals that Povidone, selected as a solubilizer has enhanced the Tadalafil solubility and in further has improved the dissolution profiles using Solvent evaporation technique.

Conclusion

In the present study, a satisfactory attempt has been made to formulate Tadalafil Tablets using solvent evaporation and followed by wet granulation technologies. From the experimental study result, it was concluded that optimized Trial-1 shows complete release of drug from the formulation when compared with the RLD. An attempt has been made in optimization the Povidone concentration and Acetone/water ratio using solvent evaporation technique on the final formulation and had concluded and justified the selected concentrations in the dosage form. Finally, Tadalafil solubility and dissolution has been enhanced by varying the concentrations of Povidone using solvent evaporation technique and wet granulation process.

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REFERENCES

Dissolution Improvement of tablets containing a poorly water soluble Tadalafil by solubilizer (Government Pharmaceutical Organization)
Tadalafil compositions WO2012085927A2
Processes for spray drying solutions of hydrophobic drugs and compositions thereof US 5985248 A
FDA label CIALIS
Hand book of Pharmaceutical excipients

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