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FORMULATION AND DEVELOPMENT OF TADALAFIL 20 MG TABLETS FOR ENHANCEMENT OF DISSOLUTION RATE

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ABSTRACT

The aim of this study was to develop and evaluate a new formulation for an immediate release Tadalafil 20 mg tablets to enhance dissolution rate according to USP37 NLT 40% (Q) of the labeled amount of Tadalafil is dissolved in 10 minutes and NLT 80% (Q) of the labeled amount of Tadalafil is dissolved in 30 minutes. Tadalafil a PDE-5 inhibitor, belongs to BCS II. It is poorly soluble in water and hence requires enhancement in dissolution rate for increasing its oral bioavailability. Formulations were prepared by wet granulation method. Tadalafil 20 mg tablets were formulated with various materials used to enhance dissolution rate. In F1, F2 and F3 was used Croscarmellose sodium as superdisintegrants; F4, F5 and F6 used Kleptose lincaps to improve the solubility and F7 to F10 was used Ludipress as diluent and disintegrant. In this study a formulation F10 was developed by increase batch size subjected to the official monograph requirements like: appearance, thickness, diameter, hardness, friability, disintegration, assay, content uniformity and dissolution rate. The results obtained were: 101.12%, 101.66% for assay and content uniformity respectively and the dissolution results after 10 minutes were 84.83% and after 30 minutes 98.53%.Whereas the results of the innovator products were 84.92% after 10 minutes and 94.23% after 30 minutes. Similarity factor (f2) values of the dissolution profiles of F10 compared with that of the innovator was 55. The results obtained indicate the compliance of F10 with the new standards set by USP37 for Tadalafil 20mg tablets.

KEYWORDS: Dissolution rate, Tadalafil, Tablet, Similarity factor.

INTRODUCTION

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).[1] Pyrazino[1¢,2¢:1,6] pyrido[3,4-b]indole-1,4-dione, 6-(1,3- benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R -12aR)-; (6R,12aR)-2,3,6,7,12, 12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl] pyrazino[1¢,2¢:1,6] pyrido[3,4-b]indole-1,4-dione.[2]

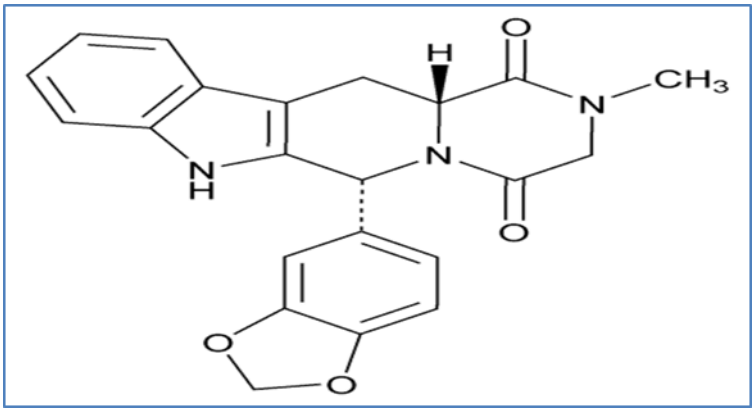

Figure 1. Structure of Tadalafil.

Tadalafil is white or almost white powder. Freely soluble in dimethyl sulfoxide; slightly soluble in methylene chloride; practically insoluble in water.[2] Tadalafil a PDE-5 inhibitor, belongs to BCS class II. It is poorly soluble in water and requires enhancement in solubility and dissolution rate for increasing its oral bioavailability.[1,3]

Solubility and dissolution rate are the factors considered to play a key role in the two first phases of the time course of drug distribution (LADME), i.e. liberation and absorption, significantly affecting bioavailability.[4]

The objective of the present study is to develop formulation for enhancement of the dissolution rate of Tadalafil 20 mg BCS class II in tablets dosage form according to USP37 (2014) NLT 40% (Q) of the labeled amount of Tadalafil is dissolved in 10 min and NLT 80% (Q) of the labeled amount of Tadalafil is dissolved in 30 min and evaluate the new formula. The new formula compare dissolution profiles with innovator.

Dissolution Rate

The speed at which a drug substance dissolves in a medium is called its dissolution rate. Dissolution rate data, when considered along with data on a drug's solubility, dissolution constant, and partition coefficient, can provide an indication of the drug's absorption

potential. For a chemical entity, its acid, base, or salt forms, as well as its physical form (e.g., particle size), may result in substantial differences in the dissolution rate.[5]

MATERIALS AND METHODS

Materials: Material used for formulation were Tadalafil (Rakshit, India), Microcrystalline Cellulose 200 and Croscarmellose sodium (GRS, Germany), Kleptose lincaps (Roquette, France), Ludipress (Basf, Germany), Magnesium stearate (Peter Greven, Germany), and Opadry II yellow (Colorcon, U.K)

All of these substances were a gift sample from Azal pharma Sudan.

Reagents: Reagents used were of the analytical grade, Sodium dodecyl sulfate (Basf, Germany), Methanol, Acetonitrile and Trifluoroacetic acid (Scharlau, Spain). Reference Tadalafil powder (working standard).

All of these substances were a gift sample from Azal pharma Sudan.

Table 1: Innovator Tadalafil 20 Mg Tablets Used For Comparison.

No.	Name	Manufacturer	Batch NO.	Mfg.	Exp.
1	Innovator	Eli Lilly	C486406	03/2015	02/2018

Instruments: Formulation and Analysis of Tadalafil were carried out on Oven (Dhaihan Labtech, Korea), Compression Machine (Shanghi- Yali, China), Dissolution Tester, Disintegration Tester, Friability Tester and Hardness Tester (Pharma Test), Blister Packing Machine and coating Machine (Jiangnan, China), HPLC (shimadzu Prominence, Japan) and UV -Vis Spectrophotometer (shimadzu UV-1800, Japan), Balance (Sartorius ED2245, ED153-CW, GW-6202, Germany).

Preformulation Study of Drug: Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The tablet manufacturability and performance are dependent, among other things, on the physicochemical properties of the drug substance. The characterization of the physicochemical and mechanical properties of the active pharmaceutical ingredient (API) is referred to as preformulation. Preformulation also includes the evaluation of the compatibility of the API with potential excipients. During the drug development process, a general

evaluation of physicochemical properties of a chemical compound is performed, with a goal of ascertaining its drug ability,[6,7]

Preparation of Tadalafil 20mg: the formula was prepared by using wet granulation method. Microcrystalline Cellulose 200 was used as filler. Croscarmellose sodium as disintegrant, Kleptose linecaps (Maltodextrin) as a binder and diluent in both direct-compression and wet-granulation or agglomeration Processes. Maltodextrin appears to have no adverse effect on the rate of dissolution of tablet and capsule formulations. It has been used as a carrier in a spray-dried redispersible oil-in-water emulsion to improve the bioavailability of poorly soluble drugs.[8] Kleptose linecaps is a novel excipient from Roquette Frères, Lestrem, France.[9]

Ludipress was used as diluent and disintegrant, it is a unique three-in-one system, combining the strengths of three excipients: lactose monohydrate 93% as carrier and filler, binding agent povidone K-30 3.5%, and crospovidone 3.5% one of the best disintegrant on the market. Together they form granulate with excellent flowability, low hygroscopicity, plus outstanding binding power. This enables you to quickly and easily create homogeneous mixtures with your active ingredient and fast active ingredient release.[10] Magnesium stearate was used as lubricants. Purified water was used as granulating fluid in wet granulation method. The tablet granules were compressed into tablets using 12 mm Almond punches. Opadry II yellow was used film-coated for formula (F10) only. In each formula 100 tablets were compressed except formula (F10) increase batch size to 1200 tablets. (Table 2).

Table 2: Formulae Tadalafil 20mg Tablets.

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ingredient	**mg**									
Tadalafil	20	20	20	20	20	20	20	20	20	20
Microcrystalline Cellulose 200	262	262	262	----	----	----	----	----	----	----
Croscarmellose sodium	15	15	15	----	----	----	----	----	----	----
Kleptose lincaps (Maltodextrin)	----	----	----	20	30	40	----	----	----	----
Ludipress	----	----	----	257	247	237	277	277	277	277
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Opadry II yellow	----	----	----	----	----	----	----	----	----	8
Total weight	300	300	300	300	300	300	300	300	300	308

Evaluation of Tablet

Thickness in mm: The thickness of tablet is important for uniformity of tablet size and must be controlled to facilitate packaging.[3,11] 10 tablets were taken randomly and tested by the Hardness/ Thickness tester. The average of measured thickness results in mm, was calculated.

Diameter in mm: 10 tablets were taken randomly and tested by the Hardness/ Diameter tester and the average was calculated.

Hardness in Kp: 10 tablets were taken randomly and tested individually by using hardness tester, and the average was calculated.

Friability test: 20 tablets were taken randomly and carefully dedusted prior to testing. The tablet sample was accurately weighed, and placed in the drum. The drum was rotated 100 times, then the tablets were removed and dedusted as before, and accurately weighed. A maximum loss of mass not more than 1.0%.[12]

Weight variation: 20 tablets were weighed individually and the average mass, was calculated.

Disintegration test: A sample of 6 tablets were randomly selected and introduced to Disintegration tester one tablets in each tube. Water was used as disintegration medium and maintained at 37C the apparatus was operate for 30 minutes. After 30 minutes all of tablets must have disintegrated completely.

Uniformity of Dosage Units: Uniformity of Dosage Units were carried out according to USP37.

Assay: Assay was carried out according to USP37.

Dissolution test: Dissolution testing were carried out according to USP37.

Dissolution profile: Dissolution profiles were compared according to USP37. Approximately 10 ml of sample was withdrawn and filtered from each vessel at 5, 10, 15, 20, 30, 45, and 60 minutes and substituted with 10 ml of fresh medium.

Data analysis: Dissolution profiles were evaluated by using Similarity factor, similarity factor f2 as described by the US FDA and presented in the following equation:

$$f2 = 50 \bullet \log \{[1 + (1/n)\Sigma t=1n (Rt - Tt)2]-0.5 \bullet 100\}$$

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent of dissolution between the two curves. Where n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t. Two dissolution profiles are considered similar when the f2 value is ≥ 50. Difference factor (f1): Difference factor can be mathematically computed by using:

$$f1= \{[t+1 n |Rt-Tt|]/ [t+1nRt]\} *100$$

The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves[13, 14].

RESULTS

Table 3: Dissolution of Innovator film coated tablets and pure API according to USP37

Dissolution limit USP37	USP37 Limit	Pure API	Innovator
After 10 min NLT 40%(Q)	40%	54.46%	84.92%
After 30 min NLT 80%(Q)	80%	71.07%	94.23%

Table 4: Physicochemical Properties Of Tadalafil 20mg Tablets Formulation F1-F9.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (KP)	Disintegration (min)	Friability (%)	% Dissolved(x) 10min	% Dissolved(x) 30 min
F1	12.26	4.65	19.41	0:20	0.11	54.26	77.21
F2	12.21	4.57	22	2:00	0.14	52.76	70.31
F3	12.25	4.48	18	0:25	0.34	51.1	75.9
F4	12.33	4.65	5.23	0:20	0.41	44.39	80.52
F5	12.27	4.49	6.47	1:15	0.34	48	73.44
F6	12.25	4.54	7.01	2:00	0.42	46.27	74.87
F7	12.26	4.61	5.98	2:00	0.44	69.81	95.71
F8	12.33	4.52	6.25	2:00	0.54	68.75	95.36
F9	12.36	4.55	6.12	2:00	0.43	69.25	95.51

Formulation (F10): was increased the batch size (1200 tablets) and coated with suitable material (Opadry II yellow) then tested according to USP37 before compression (Table 5), before coating (Table 6),after coating(Table 7) and dissolution profile similarity factor compared with Innovator.

Table 5: Assay For Mixture Before Compression.

Test	F10
Assay (%)	100.56

Table 6: Physicochemical Properties Evaluation Results Of F10 (Befor Coating).

No	Test	F10
1	Appearance	White color, almond, convex surfaces tablet
2	Thickness (mm)	4.36
3	Diameter (mm)	12.27
4	Hardness (Kp)	10.2
5	Friability (%)	0.1
6	Disintegration (min)	02:58
7	Weight variation (mg)	302
8	Assay (semi finish) (%)	100.27
9	Uniformity of Dosage Units (%)	101.98
10	Dissolution After 10 min NLT 40%	78.89
11	Dissolution After 30 min NLT 80%	94.04

Table 7: Physicochemical Properties Evaluation Results Of F10 (After Coating).

No	Test	F10
1	Appearance	Yellow color, almond, convex surfaces, film coated tablets
2	Thickness (mm)	4.4
3	Diameter (mm)	12.39
4	Hardness (Kp)	10.84
5	Disintegration (min)	03:25
6	Assay (%)	101.12
7	Uniformity of Dosage Units (%)	101.66
8	Dissolution After 10 min NLT 40%	84.83
9	Dissolution After 30 min NLT 80%	98.53

Table 8: Dissolution Profile of Formulation F10 And Innovator.

Time (min)	F10 % Released	Innovator% Released
5	31.97	44.6
10	69.77	84.92
15	86.45	90.27
20	89.95	92.02
30	95.34	94.23
45	97.04	93.66
60	96.07	98.07
f1	7	
f2	55	

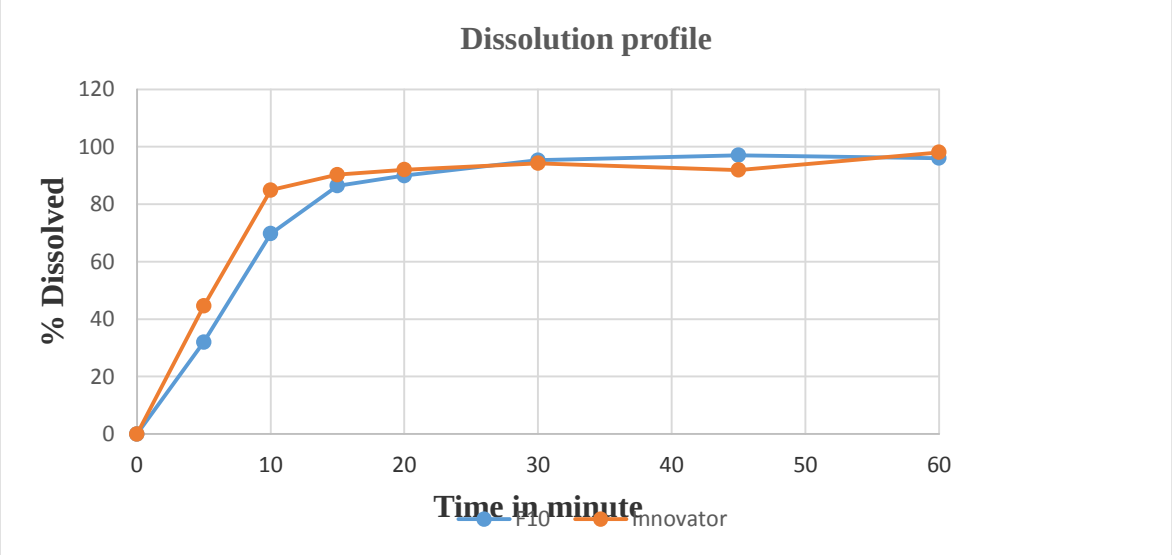

Figure 2: Dissolution Profiles of Formulation F10 And Innovator.

DISCUSSION

The aim of the study was to formulate Tadalafil 20 mg tablet with similar in vitro release dissolution profile to innovator product. According to USP37 NLT 40% (Q) of the labeled amount of Tadalafil is dissolved in 10 min and NLT 80% (Q) of the labeled amount of Tadalafil is dissolved in 30 min.

Tadalafil 20 mg tablets were formulated with various materials (Microcrystalline Cellulose 200, Croscarmellose sodium, Kleptose lincaps, Ludipress and Magnesium stearate) (Table 2).

The results of dissolution test for pure API Tadalafil powder was (54.46%) after 10 minutes and after 30 minutes was (71.07%). The results of dissolution test for innovator product was (84.92%) after 10 minutes and after 30 minutes was (94.23%).

Formulations (F1, F2 and F3) were prepared with Croscarmellose sodium the result of dissolution was not improve. Formulations (F4, F5 and F6) used Kleptose lincaps in different concentration but there was no significant change in dissolution rate. Formulations (F7, F8 and F9) used Ludipress with Tadalafil the results of dissolution test after 10 minutes was (69.81%, 68.75%, and 69.25%) and after 30 minutes was (95.71%, 95.36% and 95.51%) respectively (Table 4). Formulation (F10) was formulated by increase the batch size (1200 tablets) and coated with suitable material (Opadry II yellow) then tested according to USP37 before compression (Table 4), before coating (Table 6),after coating (Table 7) and dissolution profile similarity factor compared with innovator product.

Dissolution profile of the tablets prepared from formula (F10) was compared with innovator product by applying similarity factor (f2) and difference factor (f1) which were shown (Table 8) (Figure 2).

Formulation (F10) which contain Tadalafil and Ludipress (a co-processed excipient containing Lactose monohydrate, Povidone K-30 and crospovidone) which showed reasonable results compared to the pure drug and the innovator product.

Finally it can be concluded that, although the filler (Ludipress) is a new co-processed excipient which is higher in cost than other excipient, the formulation (F10) overall production cost is much lower and the method is cost effective.

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